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The chemistry of zerumbone. Part 5: Structural transformation of the dimethylamine derivatives

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Abstract—Zerumbone (**1**) and its 6,7-epoxide (**2**) react with ammonia and dimethylamine regio- and stereospecifically, affording monoamines **3**, **4**, **7** and **8**. All adducts have the same relative configuration at C2 and C3. The conjugate amination is thermodynamically controlled to arrive at a single diastereomer. At 15°C **7** reacts with cyanide to give aminonitrile **10** as the single product, while at 30°C, acyclic aminonitrile **11** is also formed. The reaction with **8** affords at 0°C bicyclic aminonitrile **12** of the asteriscane skeleton, while at 30°C or higher temperature, mixtures of **12** and tricyclic nitriles **13** and **13′** are obtained. Refluxing of **7**, **8** and **10** in aqueous acetonitrile promotes scission of the zerumbone ring by retro-Mannich reaction to provide acyclic aldehydes **16**–**18**, respectively. The dimethylamino group of **7**, **8** and **10** is eliminated stereospecifically by Cope- and base-catalyzed eliminations to regenerate the zerumbone skeleton in the products **1**, **2** and **21**. Cope elimination of **12** results in a mixture of **13** and **13′** by deaminative transannular etherification.

1. Introduction

Zerumbone **1**[1,2a–c] is a crystalline sesquiterpene abundantly available from the wild ginger, *Zingiber zerumbet* Smith. Despite its unique structure, with a cross-conjugated ketone in an 11-membered ring, as well as interesting biological activity, only limited chemical[3a–h] and pharmaceutical[4a–j] studies have been reported.

Zerumbone **1** presents an unusual and increasingly rare opportunity to investigate the chemistry of strained, reactive natural products. Historically, the study of natural products has enriched organic chemistry enormously. Examples from terpenes alone include the information and useful by-products acquired from the investigation of the resin acids, menthol, and carvone, our knowledge of rearrangements gained from the reactions of camphor, pinene, caryophyllene, longifolene, and chrysanthemic acid, and the occurrence of transannular reactions in the chemistry of the germacrenes.[5a–e] Today, when structures can be determined on milligrams without ever performing a reaction, the opportunity to fully explore the chemistry of interesting substrates available in almost unlimited supply is rare. For the purpose of practical utilization of **1** as a new natural resource, we have initiated an investigation of its fundamental behavior and chemical reactions. In previous papers, we have found that **1** fully justifies thorough investigation. The conjugated double bonds permit introduction of additional and varied functionality by conjugate addition. Many kinds of derivatives were synthesized from **1** in moderate to high yield with high regio- and stereoselectivity.[6–10]

Of the nucleophiles examined so far, methanol, cyanide, and benzenethiol and selenol add mainly to C3 of **1** and **2** at mild conditions, and afford stereospecific addition products. Hydroxide and acetate have not provided conjugate addition products under similar mild conditions, although retro-aldol reaction may be occurring. The subjects of the present report are the conjugate addition of ammonia and dimethylamine, and further structural transformation of the addition products (Scheme 1).

Keywords: zerumbone; sesquiterpene; retro-Mannich; asteriscane; transannular; Cope elimination.

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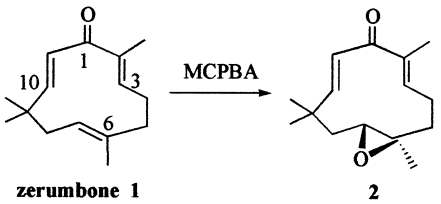


Scheme 1.

2. Results and discussion

2.1. Conjugate addition of amines

Common primary and secondary amines reacted with **1** and **2** at room or lower temperature to give conjugate addition products at C3, and sometimes at C3 and C10 of the substrates. Imine adducts were not observed in these reactions, although oxime[3b,11] is obtained with hydroxylamine. Among amines tested, ammonia and dimethylamine were typical and studied in detail in this paper.

In a tightly sealed container, **1** was stirred with excess concentrated aqueous ammonia in acetonitrile at room temperature to provide monoamine **3** (Scheme 2). The same reaction with **2** gave crystalline **4**. These were then acetylated to amides **5** and **6**, respectively, for further analysis. The reaction of **1** and **2** with dimethylamine afforded crystalline monoamines **7** and **8**, respectively. These conjugate aminations gave a single diastereomer of each monoamine, and no diamine and no another diastereomer of products were observed.

The stereochemistry of **4**, **5**, **7** and **8** was determined unambiguously by X-ray diffraction (Fig. 1). Their relative configurations at C2 and C3 are the same, and show that the all amino adducts were obtained as *syn* adducts. The configuration is, however, opposite to that of the benzenethiol and benzeneselenol adducts.[7]

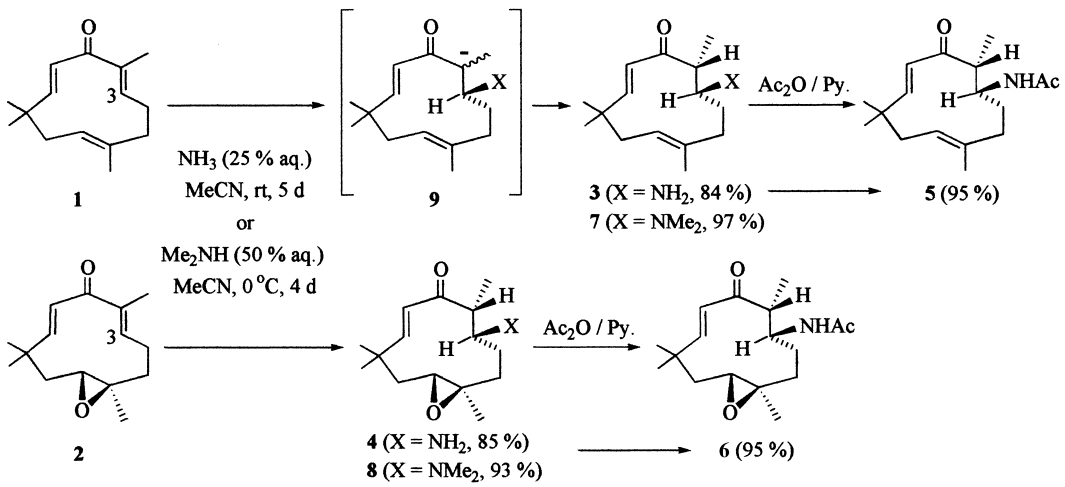
NMR spectra taken during the early stages of the reaction of ammonia with **1** showed that the addition product was a diastereomer mixture, *syn*-adduct **3** and anti-adduct (76:24 for 5 h detected by ^{1}H NMR). The mixture finally equilibrated to the single diastereomer **3**. The spectral changes were observed faster in the other aminations. Moreover, monoamine **3** was somewhat unstable and gradually reverted to **1**, but not to its [2*Z*]-isomer. This result implies that the conjugate addition is thermodynamically controlled in an equilibrium between two diastereomers of **3** and **1** via carbanion **9** (or the corresponding enolate), and finally affords **3** of the X-ray structure as the more stable product. The opposite stereochemistry of zerumbonethiol and zerumboneselenol adducts must then be the result of kinetically controlled additions.

The all [*E*] configuration of **1** seems more stable than the [2*Z*]-isomer, since the reverse reaction of **3** gives **1** in the equilibrium. The relative orientation of the amino group and epoxide oxygen in **4** and **8** shows that amination occurred from the same face as the epoxide in **2**. Steric repulsion of the C6 methyl group of **2** is the provable reason, since the methyl stands almost perpendicular to the face of the zerumbone ring, as can be seen in its X-ray structure.[3c]

2.2. Conjugate addition of cyanide

Since cyanide appears to have a particular affinity for **1** and **2**,[2c] it was tested with **7** and **8** so as to introduce a new functional group and to check the reactivity of the remaining conjugated double bond at C10. The reaction provided different products depending on the substrate and the temperature. At 0°C no reaction occurred with **7**, but at 15°C it afforded a single diastereomer of aminonitrile **10** and no another diastereomer of product was observed, and at 30°C a mixture of **10** and acyclic aminonitrile **11** was formed in equal amounts (Scheme 3). The striking ring scission which occurs at 30°C is a retro-Mannich reaction, and will be discussed below. No further addition of cyanide to C9 of **11** was observed, even using excess cyanide. The configuration of **10** at C10 has not been determined, while the relative structure at C2 and C3 appears unchanged by the reaction conditions.

Cyanation of epoxyamine **8** at 0°C gave bicyclic aminonitrile **12** as a single diastereomer and no another diastereomer of product was observed, while at 30°C the product was a mixture of **12** and the tricyclic nitriles **13** and **13′**. The structures having the asteriscane skeleton[12] were



Scheme 2.

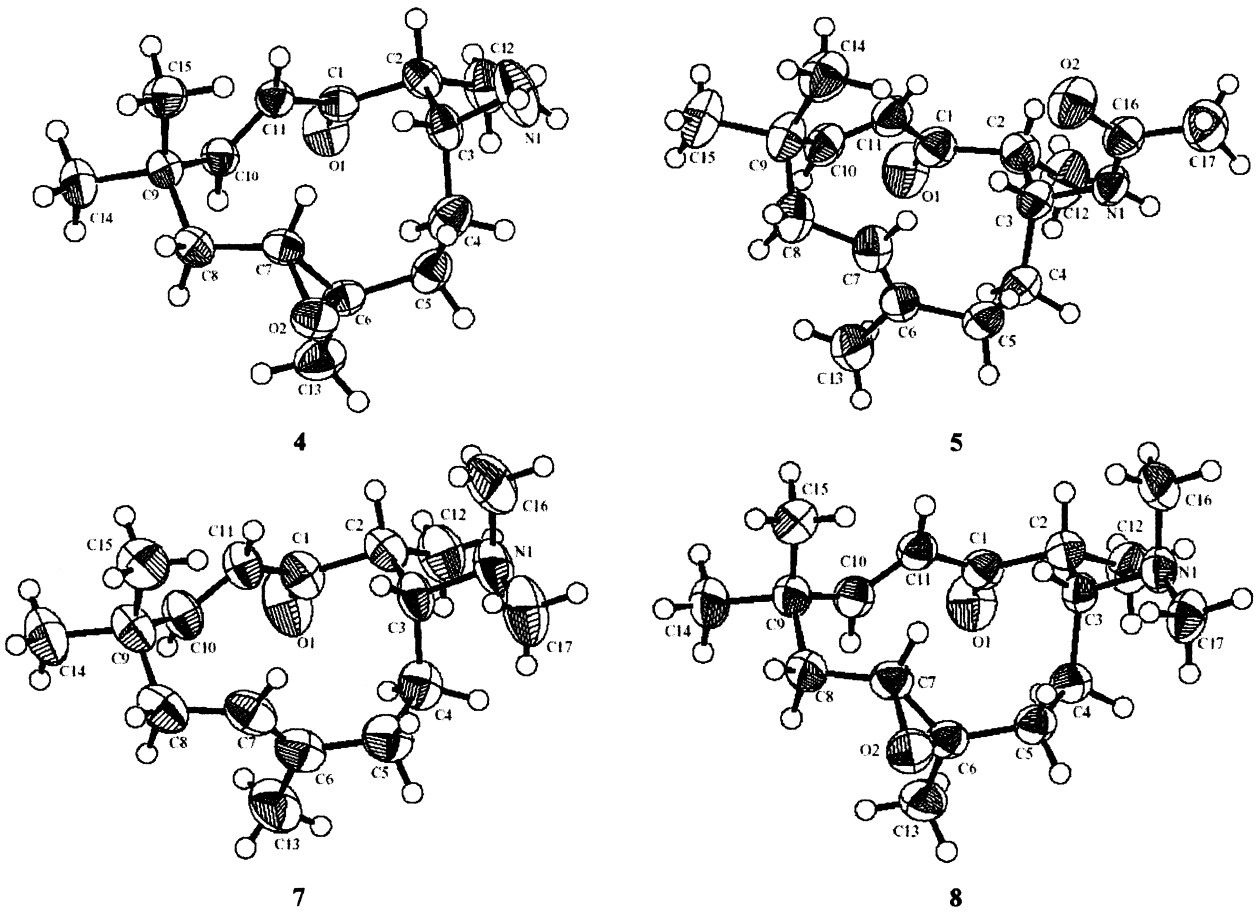


Figure 1. ORTEP drawings of the crystal structures of amine derivatives **4**, **5**, **7** and **8**.

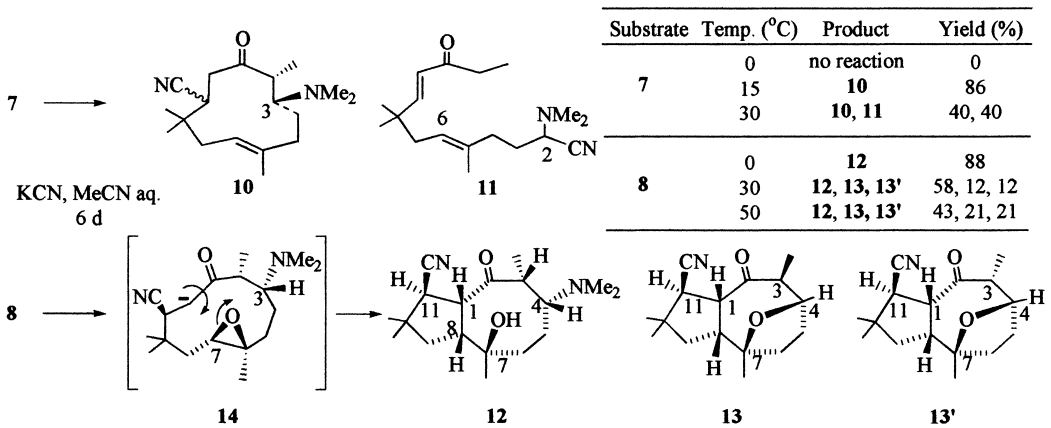
determined by NOE analysis and X-ray diffraction (Fig. 2). Another diastereomer of **13** was previously obtained from the benzeneselenol adduct.[6] The results suggest that some multi-functional asteriscanes can be synthesized from **1** by these simple reactions.

This transformation is initiated by conjugate addition of cyanide to C10 of **8** (Scheme 3). The carbanion on C11 of **14** attacks the C7 carbon of the epoxide ring from the back side by transannular displacement to provide alcohol **12**. The formation of the diastereomeric mixture of **13** and **13′** is shown in Scheme 3.

2.3. Retro-Mannich reaction

When amine **7** was refluxed in aqueous acetonitrile, acyclic ketoaldehyde **16** was obtained almost quantitatively. The same type of reaction occurred with **8** and **10** to afford **17** and **18**, respectively. This thermal deaminative ring-cleavage can be described as a retro-Mannich reaction. Hydrolysis of the intermediate iminium ion **19** gives an unstable hemiaminal, which is rapidly hydrolyzed to the corresponding aldehydes (Scheme 4).

The aldehyde **16** was transformed with potassium cyanide to



Substrate	Temp. (°C)	Product	Yield (%)
7	0	no reaction	0
	15	**10**	86
	30	**10, 11**	40, 40
8	0	**12**	88
	30	**12, 13, 13'**	58, 12, 12
	50	**12, 13, 13'**	43, 21, 21

Scheme 3.

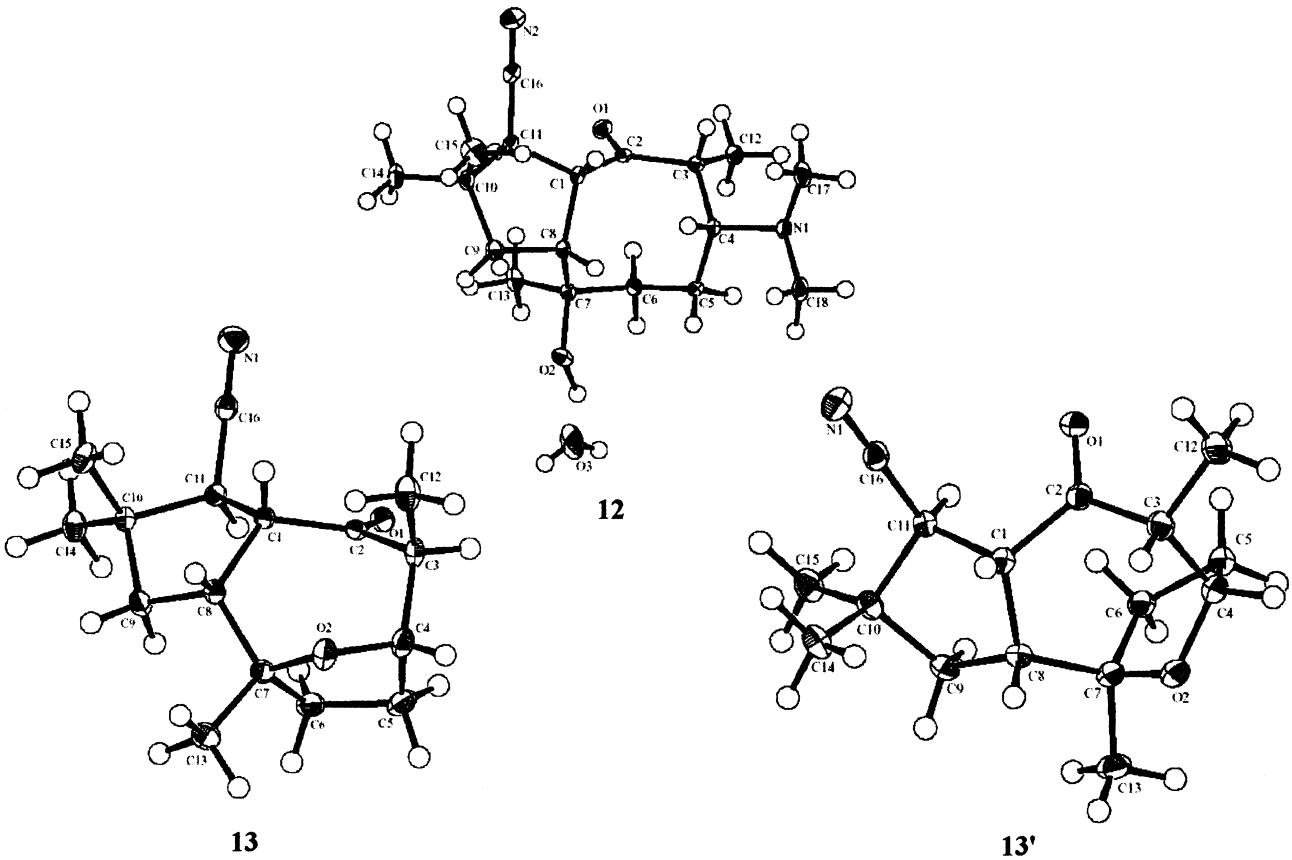
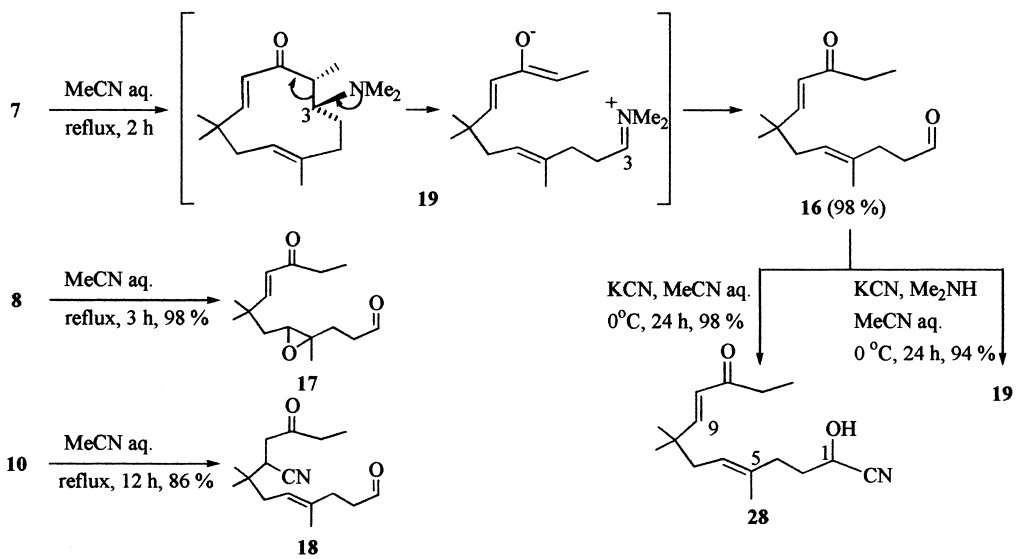


Figure 2. ORTEP drawings of the crystal structures of asterisianes **12**, **13** and **13'**.

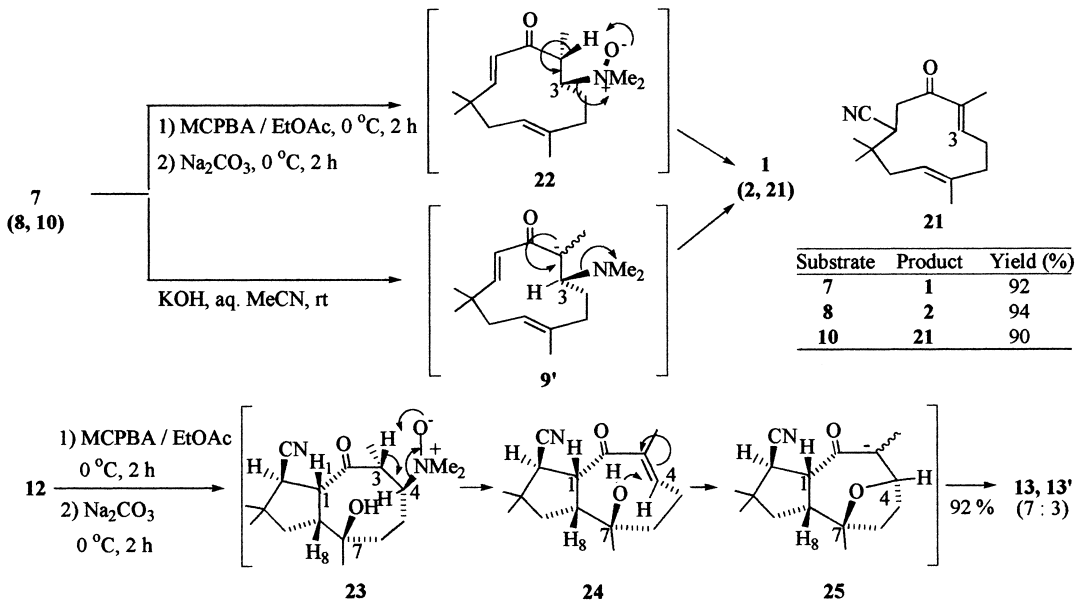
cyanohydrin **20**, while in the presence of dimethylamine, **11** was afforded in high yield. Even using excess cyanide, neither reaction provided any conjugate addition to C8 of the aldehyde.

2.4. Cope and base-catalyzed elimination

The dimethylamino group of **7** was easily eliminated by treatment with *m*-chloroperbenzoic acid (MCPBA) at 0°C to regenerate **1** in high yield (Scheme 5). The same reaction occurred with **8** and **10**, yielding **2** and **21**, respectively. No epoxidation of the remaining double bond was observed. The [2*E*]-geometry of **21** was determined by X-ray diffraction (Fig. 3). These reactions appear to be Cope eliminations, wherein the amine oxide **22** initially formed by oxidation with MCPBA undergoes thermal *syn*-elimination to afford the [2*E*] alkene. In earlier work[7] we reported a similar thermal elimination of zeurmboneselenol adduct.



Scheme 4.



Scheme 5.

In this case the C2 hydrogen and the leaving selenoyl group on C3 had a *trans* relationship, and then the predominant product of *syn*-elimination was the [2*Z*] isomer.

Attempted conjugate addition of hydroxide to **7** at room temperature led instead to elimination to again afford **1**. The same reaction occurred with **8** and **10** to give **2** and **21**, respectively. All the products had exclusively the [2*E*] configuration. The hydroxide-catalyzed elimination of dimethylamine is best described as an E1cB mechanism and equilibration through carbanion intermediate **9′** (Scheme 5).

The reaction of **12** with MCPBA at 0°C afforded a mixture of **13** and **13′**, which appear to result from initial Cope elimination followed by base catalyzed conjugate addition of the C7 hydroxyl group. Amineoxide **23** was observed as an intermediate in ^{1}H NMR spectra of the reaction of **12** with MCPBA. It was unstable and was rapidly transformed to the mixture of **13** and **13′** by washing with sodium carbonate.

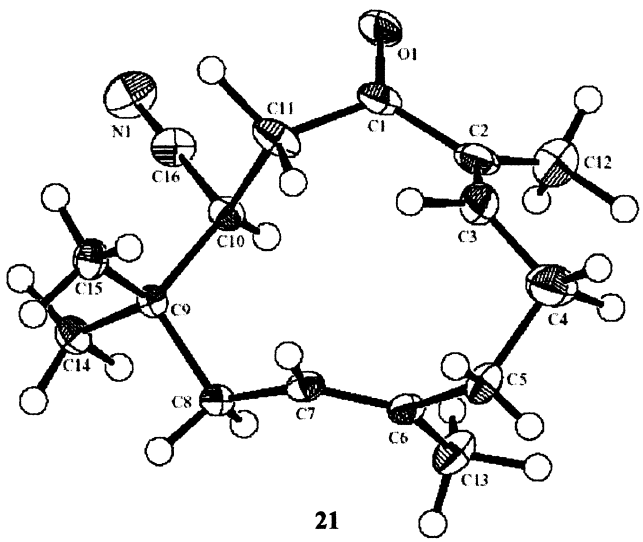


Figure 3. ORTEP drawing of the crystal structure of **21**.

In this reaction, the initially formed amineoxide **23** undergoes *syn*-elimination to generate alcohol **24**, which has a newly formed conjugated double bond at C3. The hydroxyl group on C7 of **24** undergoes intramolecular conjugate addition to the double bond, and provides carbanion intermediate **25**, which finally affords by protonation the diastereomeric mixture of **13** and **13′**. Their ratio seems to depend on the base used in the reaction. The internal etherification was also observed in the reaction of **8** with cyanide (Scheme 3). The reaction involves the base-catalyzed elimination of **12** followed by conjugate addition as in the case of **24**.

These elimination reactions show that dimethylamine can be a good protecting group for the C2 double bond of **1** and **2**. The amine adducts also permit selective scission of the C2–C3 bond by retro-Mannich reaction giving an acyclic product, which we have not yet been able to reach by the more obvious retro-aldol reaction.

3. Conclusion

Addition of amines occurs selectively at the less hindered conjugated double bond of zerumbone, leading to mono-amine derivatives. These have been found to undergo ready ring cleavage by a reverse Mannich reaction, providing a useful alternative to retroaldol ring scission. On treatment with cyanide, the dimethylamine adduct of zerumbone oxide undergoes transannular cyclization to the natural asteriscane skeleton, providing a new synthetic route to this family. Finally, the amino group serves as a valuable protecting group for the C2 double bond, since it can be readily eliminated.

4. Experimental

4.1. General methods

Melting points (mp) are uncorrected. NMR spectra were obtained at 270 and 500 MHz for protons, and 68 and 125 MHz for ^{13}C in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard unless otherwise noted. Chemical shifts δ were reported in ppm from TMS. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were obtained by direct injection. The X-ray diffraction and CCDC numbers appear in the section on compound data. Chemicals were commercially available reagent grade, and used without further purification. The preparation and properties of **1** and **2** have been described in earlier papers.[2c,9]

4.1.1. Preparation of 3 and 4. A mixture of **1** (0.65 g, 3.0 mmol) in acetonitrile (10 mL) and ammonia (25% in water, 10 mL) was stirred for 5 days at room temperature in a tightly sealed container using a silicone stopper. The solution was concentrated on a rotary evaporator under reduced pressure, and the residue was taken up in EtOAc (15 mL). The organic solution was successively washed with water (3×5 mL) and brine (2 mL), and dried over anhydrous Na_2SO_4. The solvent was removed to yield a crystalline solid, which was recrystallized from hexane to give adduct **3**. The procedure was applied to **2** for 4 days to furnish **4**. Acetylation of **3** and **4** with acetic anhydride and pyridine followed standard procedures to give amides **5** and **6**, respectively.

Compound (2*R**,3*R**)-[6*E*,10*E*]-3-*amino*-2,6,9,9-*tetramethylcycloundec*-6,10-*dien*-1-*one* (**3**). Yield 0.59 g, 84%; IR (neat) 1692, 1628 cm^{-1}; ^1H NMR: δ ppm 1.00 (d, 3H, *J*=6.5 Hz, CH_3 on C2), 1.03–1.07 (m, 2H, C4), 1.14 (s, 3H, CH_3 on C9), 1.18 (s, 3H, CH_3 on C9), 1.40 (s, 3H, CH_3 on C6), 1.83–1.92 (m, 2H, C5 and C8), 2.05–2.10 (m, 1H, C5), 2.24 (t, 1H, *J*=11.6 Hz, C8), 2.68 (dq, 1H, *J*=3.0, 6.5 Hz, C2), 3.30–3.34 (m, 1H, C3), 5.08 (dd, 1H, *J*=4.3, 11.6 Hz, C7), 6.11 (d, 1H, *J*=16.2 Hz, C11), 6.20 (d, 1H, *J*=16.2 Hz, C10); ^{13}C NMR: δ ppm 6.0 (CH_3 on C2), 16.5 (CH_3 on C6), 22.9 (CH_3 on C9), 29.0 (CH_3 on C9), 30.6 (C4), 38.0 (C5), 39.9 (C9), 41.3 (C8), 53.1 (C3), 55.3 (C2), 122.0 (C7), 128.1 (C11), 138.0 (C6), 151.7 (C10), 202.0 (C1); HRMS *m*/*z* calcd mass for $C_{15}H_{25}NO$ 235.1936, found 235.1925.

Compound (2*R**,3*R**,6*R**,7*R**)-[10*E*]-3-*amino*-6,7-*epoxy*-2,6,9,9-*tetramethylcycloundec*-10-*en*-1-*one* (**4**). From **2**, crystallized from hexane, yield 85%; mp 142–143°C; IR (KBr): 1695, 1634 cm^{-1}; ^1H NMR: δ ppm 1.00–1.01 (m, 1H, C4), 1.01 (d, *J*=7.0 Hz, CH_3 on C2), 1.04–1.06 (m, 1H, C5), 1.08–1.14 (m, 1H, C4), 1.13 (s, CH_3 on C6), 1.16 (s, CH_3 on C9), 1.27 (s, CH_3 on C9), 1.36–1.41 (m, 1H, C8), 1.90–1.92 (m, 1H, C8), 2.10–2.14 (m, 1H, C5), 2.68–2.71 (m, 2H, C2 and C7), 3.21–3.23 (m, 1H, C3), 6.28 (d, *J*=16.0 Hz, 1H, C10), 6.34 (d, *J*=16.0 Hz, 1H, C11); ^{13}C NMR: δ ppm 5.8 (CH_3 on C2), 16.9 (CH_3 on C6), 23.3 (CH_3 on C9), 27.8 (C4), 29.6 (CH_3 on C9), 36.2 (C9), 36.9 (C5), 40.4 (C8), 53.9 (C2), 54.6 (C3), 60.5 (C7), 61.8 (C6), 127.9 (C11), 150.5 (C10), 202.9 (C1); HRMS: *m*/*z* calcd mass for $C_{15}H_{25}NO_2$ 251.1885, found 251.1888.

Crystallographic study of **4**. A colorless prismatic crystal, crystal size 0.40×0.50×0.70 mm^3, monoclinic, space group $P2_1/n$ (no. 14), *a*=10.268(1), *b*=7.448(1), *c*=19.321(1) Å, β=90.425(9)°, *V*=1477.5(3) $Å^3$, *Z*=4, D_{calcd}=1.130 g/cm^3, μ(Cu Kα)=5.82 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 20.0°C by a ω–2θ scan technique. The structure was solved by direct methods (SIR92)[13] and expanded using Fourier techniques (DIRDIF94).[14] All calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 2236 observed reflections ($I>1.50\sigma(I)$) and 264 variable parameters and gave R=0.056 and R_w=0.086. The value of the goodness of fit indicator was 1.06 (Summary of Data CCDC 183922).

4.1.2. (2*R,3*R**)-[6*E*,10*E*]-3-(*N*-Acetylamino)-2,6,9,9-tetramethylcycloundec-6,10-dien-1-one (5).** Crystallized from EtOAc, yield 95% from **3**; mp 192–193°C; IR (KBr): 3302, 1693, 1632, 1547 cm^{-1}; ^1H NMR: δ ppm 0.96 (d, *J*=7.0 Hz, CH_3 on C2), 1.00–1.05 (m, 1H, C4), 1.15–1.21 (m, 1H, C4), 1.18 (s, CH_3 on C9), 1.23 (s, 3H, CH_3 on C9), 1.41 (s, 3H, CH_3 on C6), 1.76 (t, *J*=12.5 Hz, 1H, C5), 1.90 (dd, *J*=4.0, 12.5 Hz, 1H, C8), 1.96–2.00 (m, 1H, C5), 2.04 (s, 3H, CH_3 of NHAc), 2.25 (t, *J*=12.5 Hz, 1H, C8), 2.94–2.98 (m, 1H, C2), 4.56 (dt, *J*=2.5, 8.0 Hz, 1H, C3), 5.20 (dd, *J*=4.0, 12.5 Hz, 1H, C7), 5.69 (d, *J*=8.0 Hz, NH, C3), 6.18 (d, *J*=16.0 Hz, 1H, C10), 6.45 (d, *J*=16.0 Hz, 1H, C11); ^{13}C NMR: δ ppm 6.8 (CH_3 on C2), 16.4 (CH_3 on C6), 23.0 (CH_3 on C9), 23.3 (CH_3, NHAc), 27.8 (C4), 28.9 (CH_3, C9), 37.0 (C5), 40.0 (C9), 41.6 (C8), 50.7 (C3), 50.8 (C2), 123.4 (C7), 128.5 (C11), 136.4 (C6), 151.8 (C10), 170.1 (C=O, NHAc), 202.0 (C1); HRMS: *m*/*z* calcd mass for $C_{17}H_{27}NO_2$ 277.2042, found 277.2068.

Crystallographic study of **5**. A colorless prismatic crystal, crystal size 0.20×0.30×0.70 mm^3, monoclinic, space group $P2_1/a$ (no. 14), *a*=9.809(1), *b*=22.007(3), *c*=15.644(2) Å, β=94.78(1)°, *V*=3365.3(6) $Å^3$, *Z*=8, D_{calcd}=1.095 g/cm^3, μ(Cu Kα)=5.54 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 20.0°C by a ω–2θ scan technique. The structure was solved by direct methods (SIR92)[13] and expanded using Fourier techniques (DIRDIF94).[14] All calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 4490 observed reflections ($I>1.50\sigma(I)$) and 565 variable parameters and gave R=0.056 and R_w=0.089. The value of the goodness of fit indicator was 1.24 (Summary of Data CCDC 183923).

4.1.3. (2*R,3*R**,6*R**,7*R**)-[10*E*]-3-(*N*-Acetylamino)-6,7-epoxy-2,6,9,9-tetramethylcyclo-undec-10-en-1-one (6).** Crystallized from EtOAc, 95% from **4**; mp 207–208°C; IR (KBr): 3072, 1697, 1632, 1551 cm^{-1}; ^1H NMR: δ ppm 0.89–0.97 (m, 1H, C5), 0.96 (d, *J*=7.0 Hz, CH_3, C2), 1.03–1.07 (m, 1H, C4), 1.13 (s, CH_3, C9), 1.16 (s, CH_3, C9), 1.23–1.32 (m, 1H, C4), 1.35 (s, CH_3, C6), 1.38–1.43 (m, 1H, C8), 1.91–1.95 (m, 1H, C8), 1.99–2.03 (m, 1H, C5), 2.01 (s, CH_3, NHAc, C3), 2.86 (dd, *J*=1.6, 11.2 Hz, 1H, C7), 2.98–3.01 (m, 1H, C2), 4.47 (dt, *J*=3.0, 9.0 Hz, 1H,

C3), 6.00–6.03 (m, 1H, NHAc, C3), 6.29 (d, J=15.9 Hz, 1H, C11), 6.60 (d, J=15.9 Hz, 1H, C10); ^{13}C NMR: δ ppm 6.6 (CH_3, C2), 16.9 (CH_3, C9), 23.2 (CH_3, NHAc, C3), 23.4 (CH_3, C6), 24.7 (C4), 29.5 (CH_3, C9), 36.0 (C5), 36.3 (C9), 40.8 (C8), 49.7 (C2), 52.0 (C3), 60.3 (C7), 61.3 (C6), 128.4 (C10), 150.6 (C11), 170.3 (C=O, NHAc), 202.8 (C1); HRMS: m/z calcd mass for $C_{17}H_{27}NO_3$ 293.1991, found 293.2012.

4.1.4. (2*R* *,3*R* *)-[6*E*,10*E*]-3-(*N*,*N*-Dimethylamino)-2,6,9,9-tetramethylcycloundec-6,10-dien-1-one (7). From **1** (4.4 g, 20 mmol), dimethylamine (50% in water, 60 mL) and acetonitrile (50 mL); crystallized in hexane, yield 5.1 g, 97%; mp 62–64°C; IR (KBr): 1690, 1624 cm^{-1}; ^{1}H NMR: δ ppm 0.96–0.99 (m, 1H, C4), 1.02 (d, J=6.5 Hz, CH_3 on C2), 1.14 (s, CH_3 on C9), 1.19 (s, CH_3 on C9), 1.36 (s, CH_3 on C6), 1.40–1.45 (m, 1H, C4), 1.85–1.90 (m, 2H, C5 and C8), 2.07–2.11 (m, 1H, C5), 2.20 (t, J=12.5 Hz, 1H, C8), 2.37 (s, 6H, $N(CH_3)_2$, C3), 2.69- 2.71 (m, 1H, C3), 2.94–2.98 (m, 1H, C2), 5.05–5.09 (m, 1H, C7), 6.06 (d, J=16.0 Hz, 1H C11), 6.26 (d, J=16.0 Hz, 1H, C10); ^{13}C NMR: δ ppm 8.1 (CH_3, C2), 16.2 (CH_3, C6), 22.7 (CH_3, C9), 25.7 (C4), 28.8 (CH_3, C9), 39.2 (C5), 40.2 (C9), 41.5 (C8), 43.5 ($N(CH_3)_2$, C3), 47.6 (C2), 65.8 (C3), 122.3 (C7), 127.7 (C11), 138.3 (C6), 151.7 (C10), 202.5 (C1). Anal. calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.79; H, 11.09; N, 5.35.

Crystallographic study of **7**. A colorless prismatic crystal, crystal size 0.70×0.40×0.08 mm^3, monoclinic, space group $P2_1/c$ (no. 14), a=7.779(2), b=9.952(1), c=21.357(1) Å, β=94.01(1)°, V=1649.4(5) Å^3, Z=4, D_{calcd}=1.061 g/cm^3, μ(Cu Kα)=4.91 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 20.0°C by a ω–2θ scan technique. The structure was solved by direct methods (SIR92)[13] and expanded using Fourier techniques (DIRDIF94).[14] All calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 1772 observed reflections (I>1.50σ(I)) and 216 variable parameters and gave R=0.086 and R_w=0.121. The value of the goodness of fit indicator was 1.86 (Summary of Data CCDC 183924).

4.1.5. (2*R* *,3*R* *,6*R* *,7*R* *)-[10*E*]-3-(*N*,*N*-Dimethylamino)-6,7-epoxy-2,6,9,9-tetramethylcycloundec-10-en-1-one (8). From **2**, crystallized from EtOAc, yield 93%; mp 104–106°C; IR (KBr): 1693, 1630 cm^{-1}; ^{1}H NMR: δ ppm 0.92–0.98 (m, 2H, C4 and 5), 1.02 (d, J=6.5 Hz, CH_3 on C2), 1.09 (s, CH_3 on C6), 1.17 (s, CH_3 on C9), 1.29 (s, CH_3 on C9), 1.34–1.39 (m, 1H, C8), 1.44–1.56 (m, 1H, C4), 1.91–1.96 (m, 1H, C8), 2.10–2.18 (m, 1H, C5), 2.31 (s, 6H, $N(CH_3)_2$, C3), 2.45–2.49 (m, 1H, C3), 2.68 (dd, J=2.2, 11.2 Hz, 2H, C7), 2.92–3.01 (m, 1H, C2), 6.29 (d, J=15.7 Hz, 1H, C11), 6.43 (d, J=15.7 Hz, 1H, C10); ^{13}C NMR: δ ppm 7.5 (CH_3 on C2), 16.2 (CH_3 on C6), 23.1 (CH_3 on C9), 23.7 (C4), 29.5 (CH_3 on C9), 36.2 (C9), 38.9 (C5), 40.5 (C8), 43.7 ($N(CH_3)_2$, C3), 48.4 (C2), 61.6 (C6), 61.7 (C7), 67.9 (C3), 126.8 (C11), 151.6 (C10), 202.9 (C1). Anal. calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.00; H, 10.54; N, 5.02.

Crystallographic study of **8**. A colorless plate crystal, crystal size 0.50×0.04×0.80 mm^3, monoclinic, space group $P2_1/n$ (no. 14), a=10.835(2), b=7.590(3), c=20.496(3) Å, β=98.28(2)°, V=1668.0(8) Å^3, Z=4, D_{calcd}=1.113 g/cm^3, μ(Cu Kα)=5.59 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 20.0°C by a ω–2θ scan technique. The structure was solved by direct methods (SIR92)[13] and expanded using Fourier techniques (DIRDIF94).[14] All calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 2153 observed reflections (I>1.50σ(I)) and 297 variable parameters and gave R=0.057 and R_w=0.083. The value of the goodness of fit indicator was 1.20 (Summary of Data CCDC 183925).

4.2. Reaction of 7 and 8 with potassium cyanide

Potassium cyanide (0.78 g, 12 mmol) was added at 15°C to a stirring solution of **7** (0.79 g, 3.0 mmol) in acetonitrile (10 mL) and water (2 mL). The solution was stirred at 15°C for 6 days, and then concentrated on a rotary evaporator under reduced pressure. The residue was dissolved in EtOAc (10 mL), washed with water (3×3 mL) and brine (3 mL), and dried over anhydrous Na_2SO_4. The solvent was removed to yield dry **10** as a crystalline solid in a 80% yield. The same procedure at 30°C gave a 1:1 mixture of **10** and **11**. The mixture was subjected to column chromatography over silica gel using hexane and EtOAc (2:1) as an eluent to afford **10** and **11** in yields of 0.35 g (40%) and 0.35 g (40%), respectively.

The procedure was followed at 0°C to convert **8** (0.84 g, 3.0 mmol) to **12**, which was recrystallized from EtOAc (0.81 g, 88%) as a single diastereomer. The reaction at 50°C a 2:1:1 mixture of **12**, **13** and **13′**. The mixture was subjected to column chromatography over silica gel using hexane and EtOAc (2:1) as an eluent to afford **12**, **13** and **13′** in yields of 0.37 g (40%), 0.16 g (21%) and 0.16 g (21%), respectively.

4.2.1. [2*R* *,3*R* *,10(*R* or *S*)*]-[6*E*]-10-Cyano-3-(*N*,*N*-dimethylamino)-2,6,9,9-tetramethyl-cycloundec-6-en-1-one (10). Crystallized from hexane–EtOAc mixture, yield 0.75 g, 86%; mp 100–102°C; IR (KBr): 2237, 1705 cm^{-1}; ^{1}H NMR: δ ppm 1.01 (d, J=6.5 Hz, CH_3 on C2), 1.17 (s, CH_3 on C9), 1.26 (s, CH_3 on C9), 1.42 (s, CH_3 on C6), 1.45–1.56 (m, 2H, C4), 1.76–1.85 (m, 2H, C5 and C8), 2.02–2.09 (m, 1H, C5), 2.14–2.24 (m, 1H, C8), 2.30–2.32 (m, 1H, C3), 2.34 (s, 6H, $N(CH_3)_2$, C3), 2.43 (dd, J=4.1, 19.8 Hz, 1H, C11), 2.88 (dq, J=1.9, 6.5 Hz, 1H, C2), 3.31 (t, J=4.1 Hz, 1H, C10), 3.54 (dq, J=4.1, 19.8 Hz, 1H, C11), 5.12–5.16 (m, 1H, C7); ^{13}C NMR: δ ppm 9.0 (CH_3 on C2), 16.1 (CH_3 on C6), 21.2 (CH_3 on C9), 26.1 (C4), 32.1 (CH_3 on C9), 33.2 (C10), 36.0 (C9), 40.1 (C5), 41.5 (C8), 41.6 (C11), 43.4 ($N(CH_3)_2$, C2), 46.2 (C2), 68.1 (C3), 121.3 (C7), 122.4 (CN, C10), 137.4 (C6), 205.4 (C1); HRMS: m/z calcd mass for $C_{18}H_{30}N_2O$ 290.2358, found 290.2368.

4.2.2. [5*E*,9*E*]-2-(*N*,*N*-Dimethylamino)-5,8,8-trimethyl-11-oxo-tridec-5,9-diene-1-nitrile (11). Colorless oil, yield 0.35 g, 40%; IR (neat): 2210, 1697, 1674, 1626 cm^{-1}; ^{1}H NMR: δ ppm 1.06 (s, 6H, 2 CH_3, C8), 1.10 (t, J=7.3 Hz, 3H,

C13), 1.60 (s, CH_3, C5), 1.76–1.86 (m, 2H, C3), 2.08 (d, J=7.3 Hz, 2H, C7), 2.14–2.20 (m, 2H, C4), 2.30 (s, 6H, $N(CH_3)_2$, C2), 2.57 (q, J=7.3 Hz, 2H, C12), 3.41 (t, J=7.8 Hz, 1H, C2), 5.17 (t, J=7.3 Hz, 1H, C6), 6.00 (d, J=16.2 Hz, 1H, C10), 6.78 (d, J=16.2 Hz, 1H, C9); ^{13}C NMR: δ ppm 8.1(C13), 15.9 (CH_3, C5), 26.2 (2 CH_3, C8), 29.7 (C3), 33.4 (C12), 35.8 (C4), 37.5 (C8), 40.1 (C7), 41.7 (N(CH_3)2, C2), 57.9 (C2), 116.5 (C1), 122.1 (C6), 126.1 (C10), 135.3, (C5), 155.5 (C9), 201.1 (C11); HRMS: m/z calcd mass for $C_{18}H_{30}N_2O$ 290.2358, found 290.2338.

4.2.3. (1*S* *,3*R* *,4*R* *,7*R* *,8*R* *,11*S* *)-Bicyclo[6.3.0]-11-cyano-4-(*N*,*N*-dimethylamino)-7-hydroxy-3,7,10,10-tetramethylundecan-2-one (12). Crystallized from EtOAc, yield 88%; mp 163–164°C; IR (KBr) 3460, 3354, 2233, 1699 cm^{-1}; ^{1}H NMR: δ ppm 1.01 (s, 3H, CH_3 on C7), 1.15 (d, 3H, J=6.5 Hz, CH_3 on C3), 1.20 (s, 3H, CH_3 on C10), 1.26 (s, 3H, CH_3 on C10), 1.37–1.43 (m, 1H, C5), 1.54–1.60 (m, 2H, C6), 1.78–1.96 (m, 2H, C9), 2.05–2.07 (m, 1H, C5), 2.32 (s, 6H, $N(CH_3)_2$ on C4), 2.68–2.72 (m, 1H, C3), 2.89–2.95 (m, 1H, C4), 2.95–3.02 (m, 1H, C8), 3.02 (d, 1H, J=12.2 Hz, C11), 3.47 (t, 1H, J=12.2 Hz, C1); ^{13}C NMR: δ ppm 7.7 (CH_3 on C3), 24.3 (CH_3 on C7), 25.3 (C5), 26.0 (CH_3 on C10), 27.8 (CH_3 on C10), 39.3 (C10), 40.6 (C6), 41.5 (C9), 42.9 (C11), 44.1 ($N(CH_3)_2$ on C4), 48.5 (C8), 50.2 (C3), 55.5 (C1), 64.3 (C4), 74.0 (C7), 119.4 (CN at C11), 210.0 (C2); HRMS m/z calcd mass for $C_{18}H_{30}N_2O_2$ 306.2307, found 306.2320 (excluding one molecule of H_2O, while X-ray crystal contains it).

Crystallographic study of **12**. A colorless prism crystal, crystal size 0.24×0.41×0.04 mm^3, triclinic, space group P-1 (no. 2), a=7.5895(11), b=9.912(2), c=12.534(2) Å, α=104.515(8)°, β=93.851(7)°, γ=90.660(7)°, V=910.3(2) Å^3, Z=2, D_{calcd}=1.184 g/cm^3, μ(Mo Kα)=0.80 cm^{-1}, was used for data collection. The intensity data were measured on a Rigaku Mercury CCD detector using Mo Kα radiation at a temperature of −180±1°C. The structure was solved by direct methods (SIR97)[15] and expanded using Fourier techniques (DIRDIF99).[16] All calculations were performed using the Crystal Structure crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 3963 reflections (all data) and 324 variable parameters and gave $R1$=0.050 (I>2.0σ(I)) and $wR2$=0.162 (all data). The value of the goodness of fit indicator was 1.01 (Summary of Data CCDC 183926).

4.2.4. (1*S* *,3*S* *,4*S* *,7*R* *,8*R* *,11*S* *)-Tricyclo[6.3.1^{4,7}.0]-11-cyano-3,7,10,10-tetramethyl-4,7-oxyundecan-2-one (13). Mp 191–192°C; IR (KBr) 2237, 1686 cm^{-1}; ^{1}H NMR: δ ppm 1.04–1.14 (m, 1H, C9), 1.17 (s, 3H, CH_3 on C10), 1.22 (s, 3H, CH_3 on C10), 1.27 (s, 3H, CH_3 on C7), 1.33 (d, 3H, J=7.3 Hz, CH_3 on C3), 1.36–1.41 (m, 1H, C6), 1.49–1.58 (m, 1H, C6), 1.64–1.72 (m, 1H, C9), 1.74–1.82 (m, 1H, C5), 2.03–2.14 (m, 1H, C5), 2.61 (dq, 1H, J=2.2, 7.3 Hz, C3), 2.81–2.93 (m, 1H, C8), 3.06 (d, 1H, J=10.5 Hz, C11), 3.47 (dd, 1H, J=10.5, 11.9 Hz, C1), 4.11 (dd, 1H, J=2.2, 7.3 Hz, H at C4); ^{13}C NMR: δ ppm 15.6 (CH_3 on C3), 24.0 (CH_3 on C10), 27.7 (CH_3 on C10), 29.4 (CH_3 on C7), 30.7 (C5), 30.9 (C6), 41.4 (C10), 42.2 (C11), 44.0 (C9), 47.7 (C8), 54.2 (C1), 55.8 (C3), 79.9 (C4), 85.3 (C7), 119.8 (CN at C11), 210.1 (C2); HRMS m/z calcd mass for $C_{16}H_{23}NO_2$ 261.1729, found 261.1715.

Crystallographic study of **13**. A colorless prism crystal, crystal size 0.20×0.40×0.10 mm^3, monoclinic, space group $P2_1/n$ (no. 14), a=8.162(1), b=17.276(3), c=11.132(2) Å, β=114.850(7)°, V=1424.4(4) Å^3, Z=4, D_{calcd}=1.219 g/cm^3, μ(Mo Kα)=0.79 cm^{-1}, was used for data collection. The intensity data were measured on a Rigaku Mercury CCD detector using Mo Kα radiation at a temperature of −180±1°C. The structure was solved by direct methods (SIR97)[15] and expanded using Fourier techniques (DIRDIF99).[16] All calculations were performed using the Crystal Structure crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 3199 reflections (all data) and 265 variable parameters and gave $R1$=0.039 (I>2.0σ(I)) and $wR2$=0.103 (all data). The value of the goodness of fit indicator was 1.01 (Summary of Data CCDC 183927).

4.2.5. (1*R* *,3*S* *,4*S* *,7*R* *,8*R* *,11*S* *)-Tricyclo[6.3.1^{4,7}.0]-11-cyano-3,7,10,10-tetramethyl-4,7-oxyundecan-2-one (13′). Mp 170–172°C; IR (KBr) 2232, 1693 cm^{-1}; ^{1}H NMR: δ ppm 1.01 (d, 3H, J=6.8 Hz, CH_3 on C3), 1.05–1.10 (m, 1H, C9), 1.16 (s, 3H, CH_3 on C10), 1.22 (s, 3H, CH_3 on C7), 1.26 (s, 3H, CH_3 on C10), 1.29–1.36 (m, 1H, C6), 1.46–1.55 (m, 1H, C6), 1.64–1.68 (m, 1H, C9), 1.71–1.79 (m, 1H, C5), 1.86–1.95 (m, 1H, C5), 2.90–3.01 (m, 2H, C3 and C8), 3.13 (d, J=10.3 Hz, 1H, C11), 3.34–3.42 (m, 1H, C1), 4.17 (dd, 1H, J=4.3, 7.0 Hz, t C4); ^{13}C NMR: δ ppm 11.8 (CH_3 on C3), 23.5 (CH_3 on C10), 26.4 (C5), 27.1 (CH_3 on C10), 29.0 (CH_3 on C7), 30.6 (C6), 40.8 (C10), 41.7 (C11), 43.5 (C9), 47.7 (C8), 53.2 (C3), 58.2 (C1), 80.5 (C4), 85.3 (C7), 119.9 (CN on C11), 208.6 (C2); HRMS m/z calcd mass for $C_{16}H_{23}NO_2$ 261.1729, found 261.1723.

Crystallographic study of **13′**. A colorless prism crystal, crystal size 0.30×0.30×0.06 mm^3, triclinic, space group P-1 (no. 2), a=8.561(6), b=9.486(7), c=9.584(6) Å, α=74.62(2)°, β=71.41(2)°, γ=88.43(2)°, V=709.9(8) Å^3, Z=2, D_{calcd}=1.223 g/cm^3, μ(Mo Kα)=0.80 cm^{-1}, was used for data collection. The intensity data were measured on a Rigaku Mercury CCD detector using Mo Kα radiation at a temperature of −180±1°C. The structure was solved by direct methods (SIR97)[14] and expanded using Fourier techniques (DIRDIF99).[15] All calculations were performed using the Crystal Structure crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 3095 reflections (all data) and 264 variable parameters and gave $R1$=0.044 (I>2.0σ(I)) and $wR2$=0.124 (all data). The value of the goodness of fit indicator was 1.04 (Summary of Data CCDC 183928).

4.3. Retro-Mannich reaction of 7, 8 and 10

A solution of **7** (1.0 g, 3.8 mmol) in acetonitrile (50 mL) and water (5 mL) was stirred under reflux for 2 h and concentrated on a rotary evaporator under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with water (3×3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated to yield ketoaldehyde **16**. The

same procedure was applied to **8** and **10** to afford **17** and **18**, respectively.

4.3.1. [4*E*,8*E*]-4,7,7-Trimethyl-10-oxododeca-4,8-dienal (16). Yield 0.88 g, 98%, colorless oil; IR (neat): 1724, 1697, 1674, 1626 cm^{-1}; ^1H NMR: δ ppm 1.04 (s, 6H, $2CH_3$, C7), 1.10 (t, J=7.5 Hz, 3H, C12), 1.60 (s, CH_3, C4), 2.06 (d, J=7.5 Hz, 2H, C6), 2.34 (t, J=7.5 Hz, 2H, C3), 2.50–2.53 (m, 2H, C2), 2.58 (q, J=7.5 Hz, 2H, C11), 5.13 (t, J=7.5 Hz, 1H, C5), 5.99, (d, J=15.0 Hz, 1H, C9), 6.77 (d, J=15.0 Hz, 1H, C8), 9.74 (t, J=1.6 Hz, 1H, C1); ^{13}C NMR: δ ppm 8.1 (C12), 16.2 (CH_3, C4), 26.1 ($2CH_3$, C7), 32.0 (C3), 33.4 (C11), 37.5 (C7), 40.1 (C6), 42.1 (C2), 121.1 (C5), 126.1 (C9), 135.6 (C4), 155.4 (C8), 201.4 (C10), 202.2 (C1); HRMS: m/z calcd mass for $C_{15}H_{24}O_2$ 236.1776, found 236.1777.

4.3.2. [8*E*]-4,5-Epoxy-4,7,7-trimethyl-10-oxododec-8-en-1-al (17). Refluxed for 3 h, yield 98%; IR (neat): 1674, 1626 cm^{-1}; ^1H NMR: δ ppm 1.11 (t, J=7.3 Hz, CH_3, C12), 1.15 (s, CH_3, C7), 1.17 (s, CH_3, C7), 1.24 (s, CH_3, C4), 1.53–1.71 (m, 2H, C6), 1.79–1.93 (m, 2H, C3), 2.50–2.55 (m, 2H, C2), 2.60 (q, J=7.3 Hz, 2H, C11), 2.68–2.71 (m, 1H, C5), 6.08 (d, J=16.2 Hz, 1H, C9), 6.82 (d, J=16.2 Hz, 1H, C8), 9.76 (t, J=1.3 Hz, 1H, C1); ^{13}C NMR: δ ppm 8.0 (CH_3, C12), 16.9 (CH_3, C4), 26.3 (CH_3, C7), 27.0 (CH_3, C7), 30.2 (C3), 33.7 (C11), 36.3 (C7), 39.0 (C2), 40.5 (C6), 59.1 (C4), 60.0 (C5), 126.4 (C9), 154.3 (C8), 201.1 (C1), 201.2 (C10); HRMS: m/z calcd mass for $C_{15}H_{24}O_3$ (M+H) 253.1804, found 253.1827.

4.3.3. [4*E*]-8-Cyano-4,7,7-trimethyl-10-oxododec-4-en-1-al (18). Refluxed for 12 h, yield 86%; IR (neat): 2237, 1717, 1682 cm^{-1}; ^1H NMR: δ ppm 0.97 (s, CH_3, C7), 1.03 (s, CH_3, C7), 1.10 (t, J=7.3 Hz, CH_3, C12), 1.65 (s, CH_3, C4), 1.99–2.18 (m, 2H, C6), 2.37 (t, J=7.3 Hz, 2H, C3), 2.51 (q, J=7.3 Hz, 2H, C11), 2.53–2.60 (m, 2H, C2), 2.62–2.83 (m, 2H, C9), 2.98–3.03 (m, 1H, C8), 5.19 (t, J=8.1 Hz, 1H, C5), 9.77 (t, J=1.8 Hz, 1H, C1); ^{13}C NMR: δ ppm 7.6 (C12), 16.4 (CH_3, C4), 24.2 (CH_3, C7), 24.7 (CH_3, C7), 32.1 (C3), 35.9 (C8), 36.1 (C7), 36.2 (C11), 38.1 (C6), 39.9 (C9), 42.1 (C2), 119.8 (C5), 121.0 (CN, C8), 137.0 (C4), 202.2 (C1), 207.1 (C10); HRMS: m/z calcd mass for $C_{16}H_{25}NO_2$ 263.1885, found 263.1884.

4.4. Reaction of 16 with potassium cyanide

Potassium cyanide (0.97 g, 15 mmol) was added to a mixture of **16** (0.88 g, 3.7 mmol) and cation-exchange resin (DOWEX 50W-X2, 10 mL) in acetonitrile (20 mL) and water (5 mL). The mixture was stirred for 24 h at 0°C, and filtrated. The filtrate was concentrated on a rotary evaporator under reduced pressure. The residue was taken up in EtOAc (20 mL), washed with water (3×3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated to yield cyanohydrin **20**.

4.4.1. [5*E*,9*E*]-2-Hydroxy-5,8,8-trimethyl-11-oxotridec-5,9-dienenitrile (20). Colorless oil, yield 0.95 g, 98%; IR (neat): 3440, 2480, 1672, 1624 cm^{-1}; ^1H NMR: δ ppm 1.04 (s, 6H, $2CH_3$, C8), 1.10 (t, J=7.3 Hz, 3H, C13), 1.60 (s, CH_3, C5), 1.93–1.98 (m, 2H, C3), 2.08 (d, J=7.3 Hz, 2H, C7), 2.19–2.23 (m, 2H, C4), 2.60 (q, J=7.3 Hz, 2H, C12), 4.41 (t, J=6.8 Hz, 1H, C2), 5.19 (t, J=7.3 Hz, 1H, C6), 6.02 (d, J=16.2 Hz, 1H, C10), 6.80 (d, J=16.2 Hz, 1H, C9); ^{13}C NMR: δ ppm 8.6 (C13), 16.3 (CH_3, C5), 26.6 (CH_3, C8), 33.5 (C3), 34.1 (C12), 35.2 (C4), 38.0 (C8), 40.7 (C7), 60.9 (C2), 120.5 (C1), 122.7 (C6), 126.5 (C10), 135.6 (C5), 156.4 (C9), 203.0 (C11); HRMS: m/z calcd mass for $C_{16}H_{25}NO_2$ 263.1885, found 263.1866.

4.5. Reaction of 16 with potassium cyanide in the presence of dimethylamine

Potassium cyanide (0.47 g, 7.2 mmol) was added to a solution of **16** (0.43 g, 1.8 mmol) and dimethylamine (50% in water, 4 mL) in acetonitrile (10 mL). The solution was stirred for 24 h at 0°C, and then concentrated on a rotary evaporator under reduced pressure. The residue was taken up in EtOAc (10 mL). The solution was washed with water (3×3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated to yield aminonitrile **11** (0.49 g, 94%) as a colorless oil.

4.6. Deaminations with MCPBA and potassium hydroxide

A solution of **7** (0.26 g, 1.0 mmol) and MCPBA (0.24 g, 1.4 mmol) in EtOAc (10 mL) was stirred at 0°C for 2 h, and concentrated at reduced pressure. The residue was stirred with sodium carbonate (1N, 5 mL) in acetonitrile (5 mL) for 2 h at room temperature, then diluted with water (5 mL) and extracted with EtOAc (3×5 mL). The organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield **1** as a crystalline solid (0.20 g, 92%). The procedure was applied to **8** and **10** to afford **2** and **21** in yields of 94 and 90%, respectively.

On a similar scale, **7**, **8** and **10** were treated with potassium hydroxide (70 mg, 1.2 mmol) in aqueous acetonitrile at room temperature to afford **1**, **2** and **21**, respectively, in over 90% yield. The NMR and IR spectra of **1** and **2** formed by the reaction were identical with those of authentic material.

4.6.1. [2*E*,6*E*]-10-Cyano-2,6,9,9-tetramethylcycloundec-2,6-dien-1-one (21). From **10**, yield 90%; mp 97–99°C; IR (KBr): 2233, 1663 cm^{-1}; ^1H NMR: δ ppm 1.08 (s, CH_3, C9), 1.20 (s, CH_3, C9), 1.59 (s, CH_3, C6), 1.78 (s, CH_3, C2), 2.09–2.12 (m, 2H, C8), 2.27–2.30 (m, 1H, C4), 2.32–2.39 (m, 1H, C5), 2.41–2.46 (m, 1H, C4), 2.48–2.52 (m, 1H, C5), 2.56–2.61 (m, 1H, C11), 2.73–2.78 (m, 1H, C10), 2.95–3.00 (m, 1H, C11), 5.13 (t, J=7.0 Hz, 1H C7), 5.99–6.02 (m, 1H, C3); ^{13}C NMR δ ppm 12.4 (CH_3, C2), 15.8 (CH_3, C6), 24.5 (C5), 25.7 (CH_3, C9), 28.2 (CH_3, C9), 36.7 (C10), 37.3 (C9), 39.1 (C11), 39.6 (C4), 40.1 (C8), 120.2 (CN at C10), 122.9 (C7), 134.8 (C2), 137.0 (C6), 143.6 (C3), 202.7 (C1); HRMS: m/z calcd mass for $C_{16}H_{23}NO$ 245.1780, found 245.1782.

Crystallographic study of **21**. A colorless prism crystal, crystal size 0.50×0.20×0.30 mm^3, orthorhombic, space group $Pca2_1$ (no. 29), a=14.559(1), b=11.4306(9), c=17.464(2) Å, V=2906.2(7) $Å^3$, Z=8, D_{calcd}=1.121 g/cm^3, μ(Mo Kα)=0.69 cm^{-1}, was used for data collection. The intensity data were measured on a Rigaku/MSC

Mercury CCD diffractometer using Mo Kα radiation at a temperature of −180°C. The structure was solved by direct methods (SIR92)[13] and expanded using Fourier techniques (DIRDIF94).[14] All calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 6350 reflections (all data) and 445 variable parameters and gave $R1=0.070$ ($I>2.0\sigma(I)$) and $wR2=0.198$ (all data). The value of the goodness of fit indicator was 1.30 (Summary of Data CCDC 183929).

4.7. Reaction of 12 with MCPBA

MCPBA (0.21 g, 1.2 mmol) was added to a stirred solution of **12** (0.31 g, 1.00 mmol in EtOAc, 3 mL), and the solution was stirred 2 h at 0°C, and concentrated at reduced pressure. The ^{1}H NMR spectrum of the residue showed no starting material, but a single product consistent with amine oxide **23**, along with *m*-chlorobenzoic acid and MCPBA. The residue was stirred with sodium carbonate (1N, 5 mL) in acetonitrile (5 mL) for 2 h at room temperature, then diluted with water (5 mL) and extracted with EtOAc (3×5 mL). The organic layer was dried over Na_2SO_4 and concentrated. Crystallization in EtOAc yielded a 7:3 mixture of **13** and **13′** (0.24 g, 92%). The ratio of diastereomer mixture was shown by ^{1}H NMR.

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References

1. In this article, the nomenclature of zerumbone (**1**) is based on the IUPAC rules; thus **1** is (2*E*,6*E*,10*E*)-2,6,9,9-tetramethyl-cycloundeca-2,6,10-trien-1-one.
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