Selective conjugate addition to zerumbone and transannular cyclization of its derivatives

Kouichi Ohe,*[a] Koji Miki,[a] Shin-ichi Yanagi,[a] Takumi Tanaka,[a] Seiji Sawada[b] and Sakae Uemura *[a]

[a] *Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*
[b] *Kyoto University of Education, Fushimi-ku, Kyoto 612-0863, Japan*

Some chemical transformations of zerumbone (**1**) isolated from rhizomes of *Zingiber zerumbet* Smith have been described. Regioselective addition of benzenethiol and benzeneselenol to the $\Delta^{1,2}$ double bond of **1** occurs in the presence of tetra-*n*-butylammonium fluoride (TBAF) as a catalyst to give 1-phenylthio and 1-phenylseleno adducts **2a** and **2b**, respectively, with moderate diastereoselectivity. In the presence of $BF_3 \cdot OEt_2$ the reaction of **2a** and **2b** with trimethylsilyl cyanide proceeds in 1,4-addition fashion to give the corresponding 5-cyano silyl enolates **3a** and **3b**, respectively. Desilylation of **3a** and **3b** with HF·pyridine provides (8*E*)-5-cyano-2,6,6,9-tetramethyl-1-phenylthiocycloundec-8-en-3-one (**5a**) and (8*E*)-5-cyano-2,6,6,9-tetramethyl-1-phenylselenocycloundec-8-en-3-one (**5b**) as a single diastereoisomer, respectively. Treatment of **2a** and **2b** with $TiCl_4$ affords compounds with a bicyclo[5.3.0]decane skeleton, **6a** and **6b**, respectively, as *trans*-fused isodaucane derivatives *via* a transannular reaction between C-4 and C-9 of **2** followed by rearrangement. Palladium-mediated transannular reaction between C-4 and C-9 of **3b** yields **7b** with a bicyclo[5.4.0]undec-8-ene skeleton. Brønsted acid-catalyzed transannular reactions between C-3 and C-8 of **5a** and **5b** afford compounds with bicyclo[5.4.0]undecane skeletons **8a** and **8b**. A lithium enolate of (1*Z*)-5-cyano-8,9-epoxyzerumbone **10/10′** derived from **5b** gives compounds with tricyclic skeletons, **11** and **12**, by a transannular reaction between C-4 and C-8. Compounds **11** and **12** involve the carbon skeleton of 5,8-fused bicyclic natural sesquiterpene, asteriscane. Some molecular structures of key intermediates and products have been characterized by X-ray crystallography.
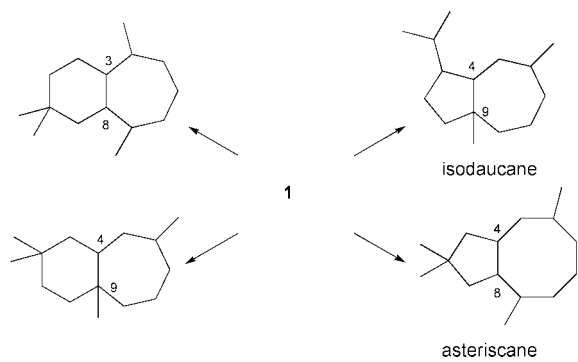
Introduction

Transannular cyclizations are of much importance in the synthesis of polycyclic complex molecules.[1] They occur frequently in medium, *i.e.* 8-, 9-, 10-, and 11-membered, rings where favored conformations allow opposite sides of the rings to come close to each other for bond formation. Transannular cyclizations involving carbocations generated from cyclodeca- and cycloundeca-polyenes have been the subject of extensive research, largely in connection with our understanding of the biosynthesis of a wide range of polycyclic sesquiterpenes.[2] Among the 10- and 11-membered sesquiterpenes, germacrene[3] and humulene[4] are known as the key precursors to eudesmane, guaiane, eremophilane, pseudoguianane, caryophyllane, proto-illudane, hirustane, capnellane, and pentalenane *etc.*, and extensive studies on their transannular reactivity have demonstrated the suitability for transformation into such natural products. On the other hand, annulation of zerumbone (**1**)[5] as the 3-keto form of humulene, which has a unique cross-conjugated dienone unit, has been restricted to a few examples as shown in Scheme 1. Chhabra and co-workers reported the acid-catalyzed transannular cyclization between C-3 and C-8 of **1** leading to bicyclo[5.4.0]undecane skeletons.[6] Luu *et al.* reported that the Nazarov-type cyclization between C-1 and C-5 of zerumbone 8,9-epoxide, one component of *Zingiber zerumbet*, afforded bicyclo[6.3.0]undecane and bicyclo-[5.3.0]decane skeletons.[7] Recently, we have reported the formation of bicyclo[7.1.0]decane skeletons *via* Favorskii-like ring-contractive transannular reaction between C-1 and C-4 of the 1,2-dibromozerumbone derivative.[8] In line with our continuing study into transformations of **1** we wish to report
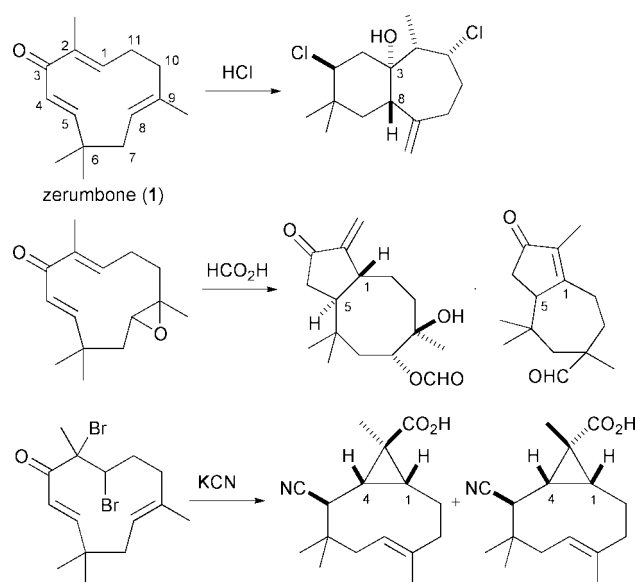
Scheme 1

herein reactions of **1** involving new types of transannular cyclizations which provide several polycyclic compounds such as 6,7-, 5,7-, and 5,8-carbocycles, as illustrated in Scheme 2. The 5,7- and 5,8-bicyclic products involve the representative structural unit of natural sesquiterpenes, *i.e.*, isodaucane[9] and asteriscane.[10]
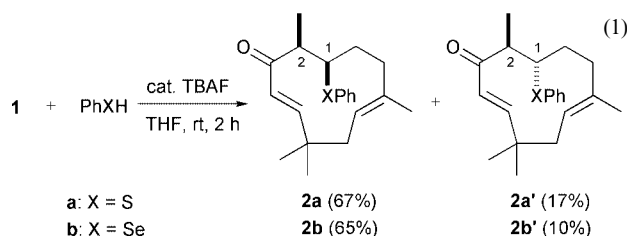
Scheme 2

Fig. 1 Molecular structure of **4a** as determined by X-ray diffraction.

Results and discussion

Introduction of functional groups into zerumbone. Conjugate addition reactions

As previously reported, conjugate addition of CN⁻ or MeO⁻ to zerumbone (**1**) is facile.[8] Other conjugate additions to **1** have since been examined. Thus, when the reaction of **1** with benzenethiol was carried out in tetrahydrofuran (THF) at room temperature in the presence of tetra-*n*-butylammonium fluoride (TBAF),[11] addition took place at C-1 to give a mixture of (4*E*,8*E*)-2,6,6,9-tetramethyl-1-phenylthiocycloundeca-4,8-dien-3-one (**2a**) and its diastereoisomer **2a′** in 67 and 17% isolated yields, respectively [eqn. (1)]. The relative stereo-

chemistry at the C-1 and C-2 centers was deduced by X-ray crystallography of a derivative of **2a** (*vide infra*). The reaction with benzeneselenol under the same reaction conditions gave a mixture of (4*E*,8*E*)-2,6,6,9-tetramethyl-1-phenylseleno-cycloundeca-4,8-dien-3-one (**2b**) and its diastereoisomer **2b′** in 65 and 10% yields, respectively. No adducts derived from addition to C-5 were observed in these reactions. Next, we examined Michael-type additions of organomagnesium reagents to **2**. The reaction of **2b** with ethylmagnesium bromide in the presence of CuBr·SMe₂ and trimethylsilyl chloride[12] afforded (8*E*)-5-ethyl-2,6,6,9-tetramethyl-1-phenylselenocyclo-undec-8-en-3-one as a single diastereoisomer in 42% yield after hydrolysis. However, the reaction of **2b** with other organo-magnesium reagents such as trimethylsilylethynylmagnesium bromide and 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide formed no adducts at C-5 under the same reaction conditions. Next we examined the addition of trimethylsilyl cyanide (TMSCN) as a carbon nucleophile. In the event, the conjugate addition of TMSCN to the remaining conjugated bond of **2b** was successfully achieved in the presence of 10 mol% of BF₃·OEt₂[13] under reflux in CHCl₃, providing 5-cyano-2,6,6,9-tetramethyl-1-phenylseleno-3-(trimethylsilyloxy)cycloundeca-3,8-diene (**3b**) in 64% yield as a 10:1 mixture of (*E*)- and (*Z*)-silyl enolates [eqn. (2)]. The introduction of other functionalities at C-5 of **2** was not successful.

Stereochemistry of 2

When **3a**, obtained from the reaction of **2a** with TMSCN, was treated with aqueous HF in MeCN at room temperature for 4 h, (8*E*)-5-cyano-2,6,6,9-tetramethyl-1-phenylthiocycloundec-
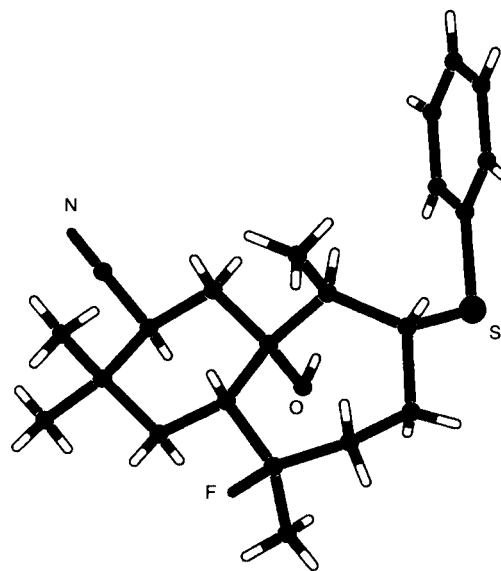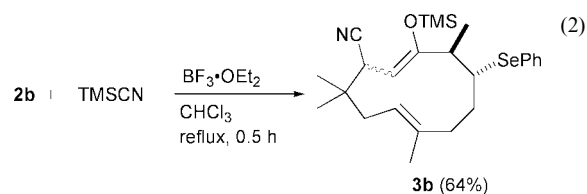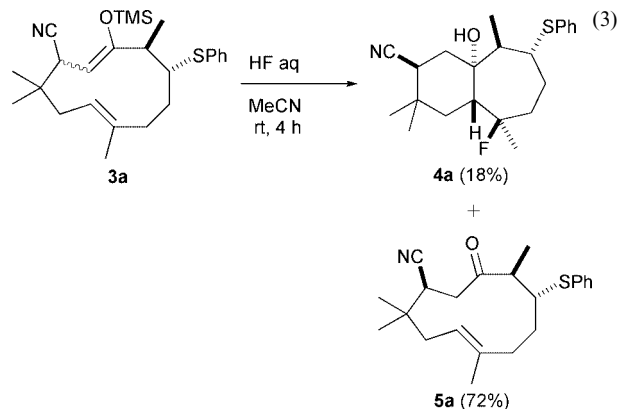

8-en-3-one (**5a**) was obtained as a major product (72% yield) together with a compound having a bicyclo[5.4.0]undecane skeleton **4a** in 18% yield [eqn. (3)]. The structure of **4a** was

unambiguously established by X-ray diffraction analysis. The X-ray structure indicates that **4a** has an axial methyl at C-2 and an equatorial phenylthio group at C-1 of a seven-membered carbocycle as shown in Fig. 1. A *trans* stereochemistry at ring junctures is also clarified by the X-ray analysis. The config-urations of all the stereogenic centers except for the C-1 carbon are consistent with the stereochemistry of a similar bicyclo-[6.3.0]undecane skeleton reported in ref. 6. Hence, the *syn*-1,2-stereochemical relationship at C-1 and C-2 of **2a** and **2b** is correct as illustrated in eqn. (1).

Transannular cyclization of 2 followed by rearrangement leading to the compounds having a 5,7-bicyclic skeleton

Parker *et al.* have reported that the treatment of humulene with aqueous sulfuric acid in acetone afforded a bicyclo[5.3.0]deca-1,8-diene, *via* the initial formation of humulol (Scheme 3).[14] This stimulated us to investigate the acid-promoted trans-annular cyclization of zerumbone derivatives. When the reaction of **2a** with HCl gas was carried out in CH₂Cl₂
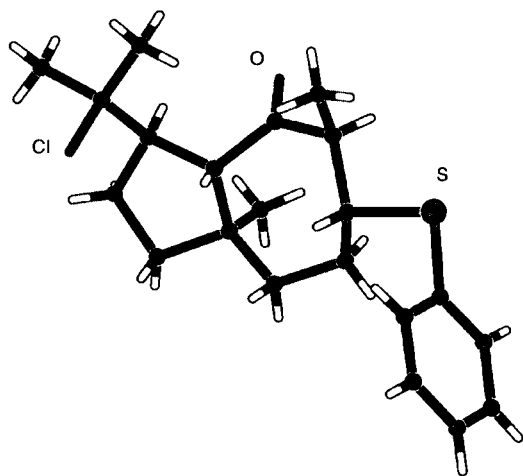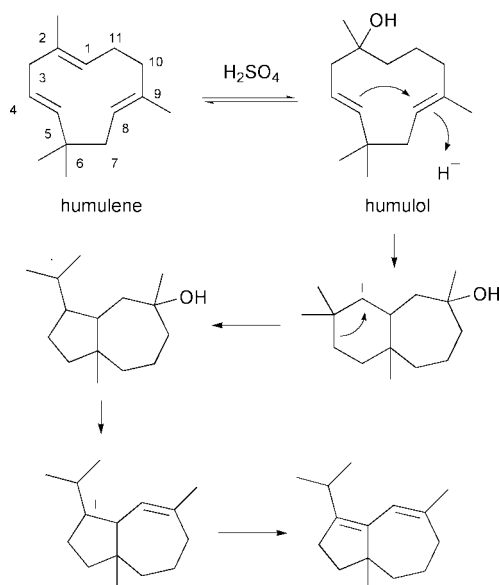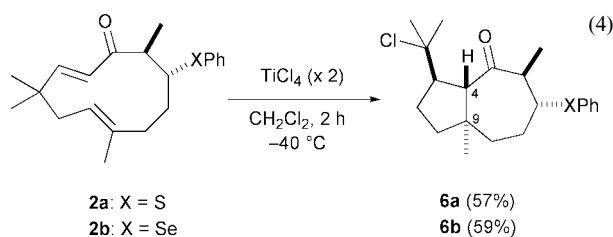
Fig. 2 Molecular structure of **6a**.

Scheme 3

Scheme 4

at −78 °C, a complex mixture was obtained, its IR spectra indicating the absence of the carbonyl group. We supposed that transannular cyclization similarly gave 6,7-bicyclic skeletons as shown in eqn. (3).[15] Next, we attempted the reaction of **2** with a Lewis acid. The reaction of **2a** with two equivalents of TiCl$_4$ in CH$_2$Cl$_2$ at −40 °C afforded a bicyclo[5.3.0]decane skeleton **6a** in 57% yield as shown in eqn. (4). The structure of **6a** was determined by X-ray diffrac-

tion analysis (Fig. 2). The X-ray structure shows that the 5,7-bicyclic skeleton is formed *via* transannular cyclization between C-4 and C-9 followed by rearrangement. The structure of **6a** is similar to the isodaucane sesquiterpenes except for *trans* angular stereochemistry. The most plausible pathway to **6a** is shown in Scheme 4. The proposed initial coordination of TiCl$_4$ with the $\Delta^{8,9}$ double bond generates a cationic site at C-9 which then acts as the trigger for the subsequent cyclization
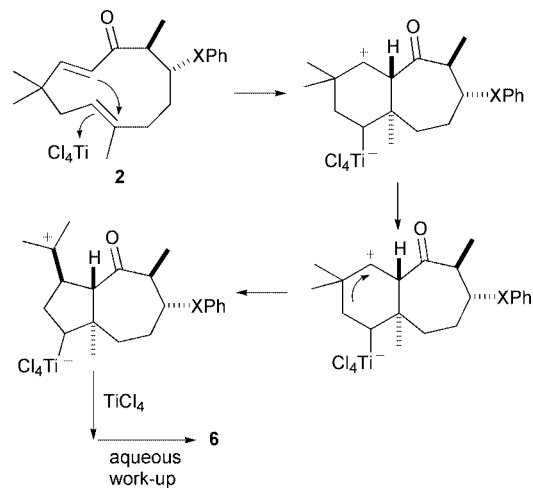
step involving participation by the $\Delta^{4,5}$ double bond to provide a 6,7-bicyclic skeleton. The subsequent migration of an adjacent bond to the cationic center in the 6,7-bicyclic intermediate gives a 5,7-bicyclic skeleton with a more stable exocyclic tertiary carbocation. Finally, incorporation of a chloride anion from TiCl$_4$ or solvent followed by protonolysis of the titanate provides the 5,7-bicyclic compound **6**.

Transannular cyclization of 3 and 5 leading to the compounds having a 6,7-bicyclic skeleton

We examined the transannular cyclization of zerumbone derivatives such as **3** and **5**. We envisioned transannular cyclization between C-4 and C-8 of **3b** with a divalent palladium complex[16] leading to a compound having a 5,8-bicyclic sesquiterpene skeleton, *i.e.* asteriscane. The reaction of **3b** with a stoichiometric amount of Pd(OAc)$_2$ in MeCN at 50 °C,
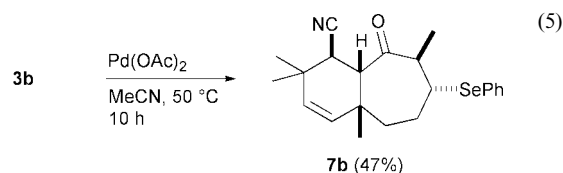
however, gave **7b** with the bicyclo[5.4.0]undec-8-ene structure in 47% yield [eqn. (5)]. This result shows that an expected oxy-π-allylpalladium species undergoes the carbopalladation in 6-*endo* fashion rather than 5-*exo* fashion to give a 6,7-bicyclic alkylpalladium intermediate leading to **7b** (Scheme 5). The *cis*
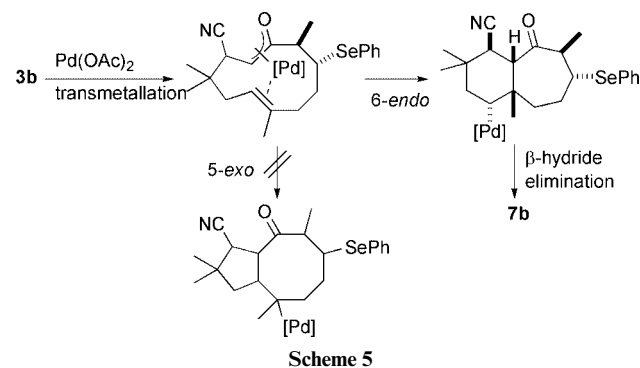
Scheme 5

stereochemistry at the ring juncture of **7b** was deduced by NOE analysis.[17]

Next, we investigated the transannular reaction of **5**. We supposed that the minor product **4a** shown in eqn. (3) would be produced by formation of **5a**, and then we tried to find an
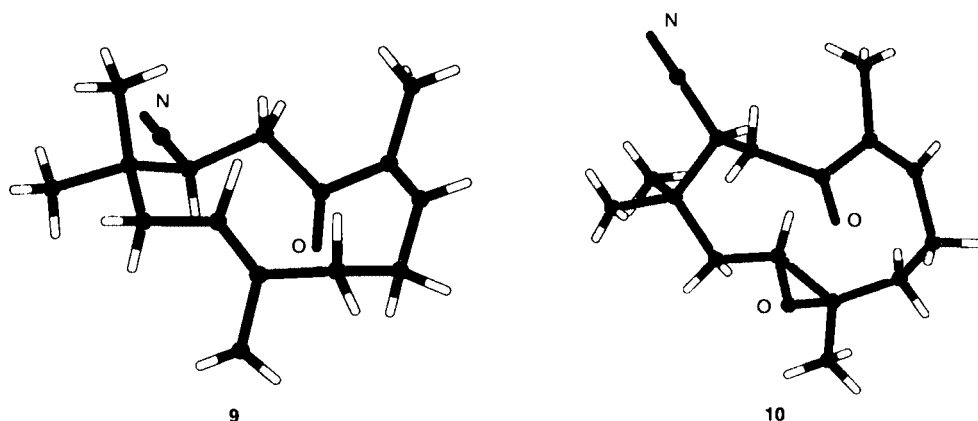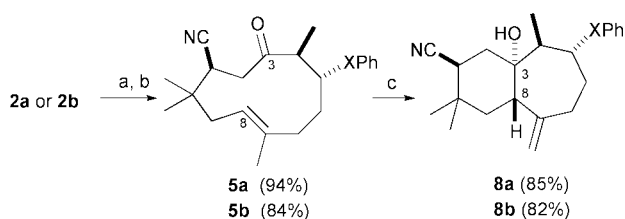
Fig. 3 Molecular structures of **9** and **10**.

effective route for desilylation of **3** leading to **5**. The reaction of **2a** and **2b** with TMSCN followed by treatment with HF·pyridine complex selectively gave **5a** and **5b**, in 94 and 84% yields for the two steps, respectively (Scheme 6). As expected, **5a** and **5b**


Scheme 6 *Reagents and conditions*: (a) TMSCN, BF₃·OEt₂, CHCl₃, reflux, 0.5 h; (b) HF·py, MeCN, rt, 2 h; (c) HCl aq., CHCl₃, rt, 1.5 h.

were converted to compounds with a 6,7-bicyclic skeleton, **8a** and **8b**, by the acid-catalyzed transannular reaction between C-3 and C-8 of **5**. All spectral data supported the structure of **8** having an *exo* methylene, which is similar to that of **4a**.

Transannular cyclization leading to compounds with a 5,8-bicyclic skeleton

As mentioned above the palladium-promoted transannular reaction of **3b** was found to produce a compound with a 6,7-bicyclic and not a 5,8-bicyclic skeleton. During the course of our study on the transformation of zerumbone derivatives, we found that (1*Z*)-5-cyanozerumbone **9** was obtained by selen-oxide elimination of **5b** (Scheme 7). This selenoxide elimination was almost regioselective with only traces of (8*E*,11*E*)-5-cyano-2,6,6,9-tetramethylcycloundeca-8,11-dien-3-one (unconjugated
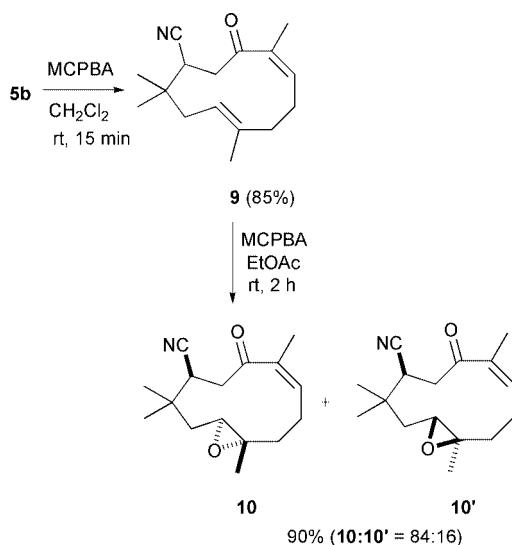
Scheme 7

product) being obtained. This stereochemical outcome strongly supported the *syn*-vicinity of hydrogen and PhSe at C-1 and C-2 of **5b**. The X-ray structure of **4a** (Fig. 1) also supported the orientation and stereochemistry of the elimination (*vide supra*). The structure of **9** was also established by X-ray crystallographic analysis (Fig. 3); the X-ray structure of **9** clearly shows that the two double bonds $\Delta^{1,2}$ and $\Delta^{8,9}$ adopt a parallel arrangement in the solid-state structure. Then, we carried out epoxidation of the $\Delta^{8,9}$ double bond of **9** expecting stereo-selective epoxidation through the *Re*-face of the $\Delta^{8,9}$ double bond leading to the (8*R**,9*R**)-epoxide. Upon treatment of **9** with MCPBA in AcOEt, a mixture of 8,9-epoxides **10** and **10′** was produced in 90% yield in a ratio of 84:16 (Scheme 7). The structure of the major product **10** was unambiguously determined by X-ray crystallographic analysis as shown in Fig. 3. This compound contained the opposite epoxide configuration (8*S**,9*S**) to the expected one (8*R**,9*R**). Anticipating the transannular displacement of an epoxide by an enolate, as demonstrated in fusicoccadione from dolabelladione monoepoxide by Shin and Fenical,[18] we examined the bond-forming reaction between C-4 and C-8 of **10** and **10′** in order to obtain compounds with a 5,8-bicyclic skeleton. When the reaction of a mixture of **10** and **10′** with lithium

(6)
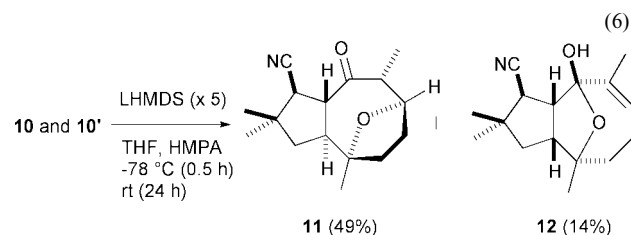
hexamethyldisilazanide (LHMDS) was carried out in THF at −78 °C, tricyclic products **11** and **12** were obtained in 49 and 14% yields, respectively [eqn. (6)]. The structures of these products were characterized by spectroscopic data and unambiguously determined by X-ray diffraction analysis (Fig. 4). The major product **11** was found to involve a 5,8-bicyclic skeleton in *trans* angular configuration, while the minor product **12** was found to involve a 5,8-bicyclic hemiketal structure with a *cis* angular configuration. Although the *trans* angular configuration in the major product we obtained is rare in natural sesquiterpenes, this result shows that the transannular reaction between C-4 and C-8 of zerumbone derivatives can provide the 5,8-bicyclic structure. The stereochemical configuration at C-9 of each product indicates that **11** and **12** might be produced from **10** and **10′**, respectively (Scheme 8). Therefore, we can expect the predominant formation of the 5,8-bicyclic structure with a *cis* angular configuration, provided that we can obtain the reverse stereoselectivity in the epoxidation of **9**.
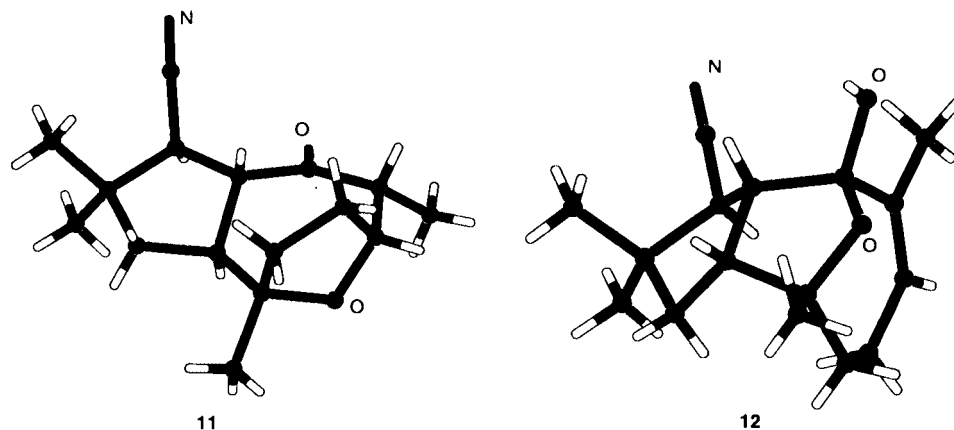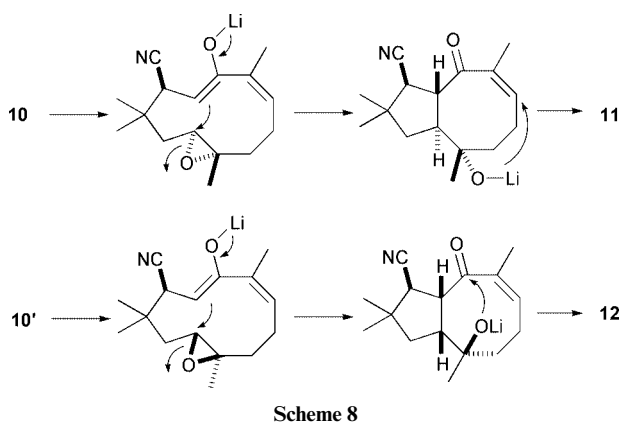
Fig. 4 Molecular structures of **11** and **12**.

Scheme 8

In conclusion, we have demonstrated that the stepwise chemical transformation of zerumbone using conjugate addition reactions of its penta-1,4-dien-3-one moiety afforded zerumbone derivatives bearing functionalities, which can be applied to transannular cyclization reactions that lead to more complex polycyclic sesquiterpene structures. Transannular cyclization of **3** or **5** induced by palladium or a Brønsted acid gives 6,7-bicyclic structures *via* bond formation between C-4 and C-9, or between C-3 and C-8. The Lewis acid-promoted transannular reaction of **2** followed by rearrangement produces a compound with a bicyclo[5.3.0]-decane structure. Intramolecular nucleophilic ring-opening of an epoxide with a lithium enolate is followed by transannular cyclization to give the novel polycyclic structures **11** and **12**.

Experimental

General

All reactions were performed in oven-dried or flame-dried glassware under an atmosphere of dry Ar or N_2 unless otherwise noted. Solvents and chemicals were obtained commercially and purified by standard procedures. ^{1}H NMR spectra were recorded on 270 or 400 MHz FT-NMR spectrometers, and ^{13}C NMR spectra were recorded on 67.5 or 100 MHz FT-NMR spectrometers. Chemical shifts are reported in ppm relative to TMS in the solvents specified. ^{1}H NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constant (Hz), relative intensity, and interpretation. ^{13}C NMR data are reported as follows: chemical shift in ppm (δ). Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed with silica gel 60 Merck F-254 plates. Column chromatography on SiO_2 was performed with Merck silica gel 60. Elemental analyses were performed at Microanalytical Center of Kyoto University.

Typical procedure for conjugate addition of PhXH (X = S, Se) to 1

(4*E*,8*E*)-2,6,6,9-Tetramethyl-1-phenylthiocycloundeca-4,8-dien-3-one (2a). To a solution of **1** (1.1 g, 5.0 mmol) and benzenethiol (0.56 g, 5.5 mmol) in dry tetrahydrofuran (THF) (5 ml) was added a solution of 1 M tetra-*n*-butylammonium fluoride (TBAF) in THF solution (0.5 ml, 0.5 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 2 h, poured into saturated aqueous $NaHCO_3$ solution (50 ml), and extracted with AcOEt (3 × 20 ml). The organic layer was dried over $MgSO_4$. The solvent was evaporated under vacuum and the residual solid was recrystallized from hexane–AcOEt (20 : 1) to afford a pure colorless crystalline solid **2a** (1.1 g, 3.4 mmol, 67% yield); mp 122.8–124.1 °C; ν_{max} (KBr)/cm^{-1} 1686 (C=O), 1622 (C=C); δ_H (400 MHz, CDCl$_3$) 1.12 (s, 3H), 1.14 (s, 3H), 1.28 (d, *J* 6.8 Hz, 3H), 1.43 (m, 1H), 1.53 (s, 3H), 1.82 (m, 1H), 1.89–1.96 (m, 2H), 2.10 (dd, *J* 6.0, 13.0 Hz, 1H), 2.29 (t, *J* 12.7 Hz, 1H), 2.57 (dq, *J* 6.8, 6.8 Hz, 1H), 3.30 (dt, *J* 4.0, 8.4 Hz, 1H), 5.10 (dd, *J* 4.8, 11.8 Hz, 1H), 5.78 (d, *J* 16.6 Hz, 1H), 6.17 (d, *J* 16.6 Hz, 1H), 7.23–7.32 (m, 3H), 7.42–7.46 (m, 2H); δ_C (100 MHz, CDCl$_3$) 13.5, 16.7, 23.5, 29.1, 33.5, 38.8, 39.3, 41.6, 52.6, 54.1, 123.3, 124.9, 127.5, 128.9, 133.3, 135.2, 137.2, 153.5, 204.2. $C_{21}H_{28}OS$ requires C, 76.78; H, 8.59. Found: C, 76.52; H, 8.73%.

(4*E*,8*E*)-2,6,6,9-Tetramethyl-1-phenylselenocycloundeca-4,8-dien-3-one (2b). A crystalline colorless solid (65% yield); mp 109.8–111.5 °C; ν_{max} (KBr)/cm^{-1} 1686 (C=O), 1628 (C=C); δ_H (400 MHz, CDCl$_3$) 1.08 (s, 3H), 1.14 (s, 3H), 1.28 (d, *J* 6.8 Hz, 3H), 1.44–1.58 (m, 4H), 1.84–2.00 (m, 3H), 2.08 (br dd, *J* 10.0, 13.2 Hz, 1H), 2.28 (dd, *J* 7.2, 12.8 Hz, 1H), 2.55 (dq, *J* 6.8, 7.8 Hz, 1H), 3.25–3.34 (m, 1H), 5.05 (br dd, *J* 4.4, 11.6 Hz, 1H), 5.75 (d, *J* 16.0 Hz, 1H), 6.18 (d, *J* 16.0 Hz, 1H), 7.23–7.33 (m, 3H), 7.54–7.61 (m, 2H); δ_C (100 MHz, CDCl$_3$) 15.2, 16.8, 23.4, 29.1, 38.9, 39.3, 41.6, 49.6, 54.0, 123.3, 124.8, 127.9, 129.0, 129.2, 135.7, 137.1, 153.6, 204.7. $C_{21}H_{28}OSe$ requires C, 67.19; H, 7.52. Found: C, 67.16; H, 7.44%.

5-Cyano-2,6,6,9-tetramethyl-1-phenylseleno-3-(trimethylsilyloxy)cycloundeca-3,8-diene (3b)

To a solution of **2b** (0.38 g, 1.0 mmol) and trimethylsilyl cyanide (0.40 ml, 3.0 mmol) in dry CHCl$_3$ (0.5 ml) was added boron trifluoride–diethyl ether complex (BF$_3$·OEt$_2$) (13 µl, 0.10 mmol) at reflux under nitrogen and the mixture was stirred for 0.5 h. After the mixture was diluted with CHCl$_3$ (10 ml), the solution was washed with water (10 ml) and then by saturated aqueous NaHCO$_3$ solution (10 ml) and dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to short column chromatography on SiO_2 with hexane–AcOEt (10 : 1) as an eluent to give a colorless liquid of **3b** as a mixture

of two diastereoisomers (dr = 91:9) (0.31 g, 0.64 mmol, 64% yield); ν_{max} (neat)/cm^{-1} 2240 (CN), 1661 (C=C), 1580 (C=C); δ_H (400 MHz, CDCl$_3$) 0.21 (s, 9H), 1.07 (s, 3H), 1.21–1.23 (m, 6H), 1.56 (s, 3H), 1.72–2.08 (m, 7H), 2.68 (ddd, J 2.0, 6.0, 11.2 Hz, 1H), 3.41 (d, J 10.4 Hz, 1H), 4.46 (d, J 10.4 Hz, 1H), 5.11 (br dd, J 7.2, 8.0 Hz, 1H), 7.23–7.32 (m, 3H), 7.51–7.60 (m, 2H); δ_C (100 MHz, CDCl$_3$) 0.7, 18.1, 21.3, 21.9, 31.4, 32.7, 37.2, 37.4, 38.4, 41.7, 47.3, 55.9, 103.0, 120.4, 120.8, 127.6, 129.0, 130.1, 133.8, 135.0, 158.0. C$_{25}$H$_{37}$NOSeSi requires C, 63.27; H, 7.86; N, 2.95. Found: C, 63.02; H, 7.86; N, 2.84%.

10-Cyano-6-fluoro-2,6,9,9-tetramethyl-3-phenylthiobicyclo-[5.4.0]undecan-1-ol (4a)

To a solution of **2a** (0.66 g, 2.0 mmol) and trimethylsilyl cyanide (0.80 ml, 6.0 mmol) in dry CHCl$_3$ (1.0 ml) was added boron trifluoride–diethyl ether complex (BF$_3$·OEt$_2$) (26 μl, 0.20 mmol) under nitrogen. The reaction mixture was stirred at reflux temperature for 0.5 h. This solution was washed with water (20 ml) and extracted with Et$_2$O (2 × 20 ml). The combined organic layer was dried over Na$_2$SO$_4$ and then evaporated under vacuum to leave the crude phenylthio analog of **3b** (**3a**). It was added to 47% aqueous HF (1.0 ml) in MeCN (50 ml) at room temperature. The mixture was stirred for 4 h. The resulting mixture was poured into saturated aqueous NaHCO$_3$ solution (50 ml) and extracted with AcOEt (2 × 50 ml). The organic layer was dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (3:1) to give a colorless solid **4a** (0.13 g, 0.36 mmol, 18% yield); mp 64.5–67.3 °C; ν_{max} (KBr)/cm^{-1} 3452 (OH), 2241 (CN); δ_H (400 MHz, CDCl$_3$) 1.00 (s, 3H), 1.17 (s, 3H), 1.21 (d, J 8.0 Hz, 3H), 1.35 (s, 3H), 1.46 (dd, J 13.8, 3.8 Hz, 1H), 1.61–1.64 (m, 2H), 1.72–1.77 (m, 2H), 1.89–2.10 (m, 3H), 2.19–2.25 (m, 1H), 2.18 (q, J 8.0 Hz, 1H), 2.56 (br s, 1H), 2.82 (dd, J 12.8, 3.6 Hz, 1H), 3.42 (t, J 9.4 Hz, 1H), 7.26–7.30 (m, 2H), 7.32–7.39 (m, 3H); δ_C (100 MHz, CDCl$_3$) 19.7, 21.4, 26.2, 27.7, 30.7, 32.5, 35.6, 36.5, 41.2, 42.1, 44.5, 47.6, 51.0, 75.6, 76.2, 121.4, 127.5, 129.3, 131.7, 134.5. C$_{22}$H$_{30}$FNOS requires C, 70.36; H, 8.05; N, 3.73. Found: C, 70.46; H, 8.33; N, 3.46%.

Typical procedure for conjugate addition of TMSCN to 2

(8E)-5-Cyano-2,6,6,9-tetramethyl-1-phenylthiocycloundec-8-en-3-one (5a). To a solution of **2a** (0.99 g, 3.0 mmol) and trimethylsilyl cyanide (1.2 ml, 9.0 mmol) in dry CHCl$_3$ (3.0 ml) was added BF$_3$·Et$_2$O (38 μl, 0.30 mmol) at reflux under nitrogen. After the mixture was stirred for 0.5 h, the solution was added to a solution of hydrogen fluoride–pyridine (0.1 ml) in MeCN (40 ml) at room temperature. (**CAUTION**: HCN gas is generated.) After stirring for 2 h, the solution was washed with saturated aqueous NaHCO$_3$ solution (50 ml). The aqueous layer was extracted with AcOEt (2 × 20 ml). The combined organic layer was washed with brine (50 ml) and dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (10:1) to give a white solid of **5a** (1.0 g, 2.8 mmol, 94% yield); mp 83.8–86.0 °C; ν_{max} (neat)/cm^{-1} 2231 (CN), 1698 (C=O); δ_H (400 MHz, CDCl$_3$) 1.13 (s, 3H), 1.26 (s, 3H), 1.28 (d, J 6.8 Hz, 3H), 1.49 (s, 3H), 1.55–1.77 (m, 1H), 1.94–2.13 (m, 4H), 2.13–2.24 (m, 1H), 2.48 (dd, J 6.0, 17.6 Hz, 1H), 2.80–2.98 (m, 3H), 3.07–3.18 (m, 1H), 5.18 (t, J 10.8 Hz, 1H), 7.21–7.35 (m, 3H), 7.37–7.46 (m, 2H); δ_C (100 MHz, CDCl$_3$) 15.2, 16.5, 24.0, 30.0, 30.1, 34.7, 36.6, 36.9, 37.8, 39.6, 48.6, 52.2, 121.3, 121.8, 127.5, 129.1, 132.8, 134.6, 137.4, 206.6. C$_{22}$H$_{29}$NOS requires C, 74.32; H, 8.22; N, 3.94. Found: C, 74.05; H, 8.34; N, 3.71%.

(8E)-5-Cyano-2,6,6,9-tetramethyl-1-phenylselenocycloundec-8-en-3-one (5b). A colorless liquid (84% yield); ν_{max} (neat)/cm^{-1} 2240 (CN), 1712 (C=O); δ_H (400 MHz, CDCl$_3$) 1.11 (s, 3H),

1.21–1.28 (m, 6H), 1.46 (s, 3H), 1.73–1.86 (m, 1H), 1.90–2.20 (m, 5H), 2.43 (dd, J 7.6, 17.6 Hz, 1H), 2.80–2.97 (m, 3H), 3.07–3.20 (m, 1H), 5.15 (br t, J 7.2 Hz, 1H), 7.23–7.36 (m, 3H), 7.51–7.60 (m, 2H); δ_C (100 MHz, CDCl$_3$) 15.8, 16.3, 23.7, 29.9, 31.2, 34.6, 36.4, 37.3, 37.4, 39.6, 48.4, 48.9, 121.1, 121.7, 128.0, 128.7, 129.0, 135.3, 137.0, 206.7. C$_{22}$H$_{29}$NOSe requires C, 65.66; H, 7.26; N, 3.48. Found: C, 65.51; H, 7.41; N, 3.41%.

Typical procedure for TiCl$_4$-promoted transannular cyclization of 2

10-(1-Chloro-1-methylethyl)-3,7-dimethyl-4-phenylthiobi-cyclo[5.3.0]decan-2-one (6a). To a solution of **2a** (0.26 g, 0.80 mmol) in CH$_2$Cl$_2$ (10 ml) was slowly added TiCl$_4$ (0.16 ml, 1.8 mmol) at −40 °C under nitrogen. The reaction mixture was stirred at −40 °C for 2 h. The resulting mixture was washed with saturated aqueous NaHCO$_3$ solution (30 ml) and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 30 ml). The combined organic layers were dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (20:1) to give a white solid of **6a** (0.17 g, 0.46 mmol, 57% yield); mp 88.9–90.4 °C; ν_{max} (KBr)/cm^{-1} 1693 (C=O); δ_H (400 MHz, CDCl$_3$) 0.71 (s, 3H), 1.39 (s, 3H), 1.49 (d, J 7.6 Hz, 3H), 1.50–1.71 (m, 4H), 1.55 (s, 3H), 1.76–1.82 (m, 2H), 1.89–2.00 (m, 1H), 2.13 (dd, J 4.8, 14.4 Hz, 1H), 2.41 (dq, J 7.2, 10.8 Hz, 1H), 2.95 (m, 1H), 3.11 (d, J 11.2 Hz, 1H), 3.18 (t, J 10.4 Hz, 1H), 7.24–7.34 (m, 3H), 7.40–7.43 (m, 2H); δ_C (100 MHz, CDCl$_3$) 20.4, 20.5, 25.7, 32.2, 32.3, 32.6, 43.2, 43.3, 46.6, 50.0, 52.3, 54.2, 59.3, 75.6, 127.2, 129.0, 132.2, 134.3, 212.3. C$_{21}$H$_{29}$ClOS requires C, 69.11; H, 8.01. Found: C, 69.33; H, 8.29%.

10-(1-Chloro-1-methylethyl)-3,7-dimethyl-4-phenylselenobi-cyclo[5.3.0]decan-2-one (6b). A white solid (59% yield); mp 74.6–78.0 °C; ν_{max} (KBr)/cm^{-1} 1699 (C=O); δ_H (400 MHz, CDCl$_3$) 0.68 (s, 3H), 1.37 (s, 3H), 1.47 (d, J 7.2 Hz, 1H), 1.48–1.81 (m, 6H), 1.54 (s, 3H), 1.91 (m, 1H), 2.26 (m, 1H), 2.44 (dq, J 7.2, 11.2 Hz, 1H), 2.94 (ddd, J 4.4, 7.2, 10.8 Hz, 1H), 3.10 (d, J 8.8 Hz, 1H), 3.24 (t, J 10.8 Hz, 1H), 7.27–7.33 (m, 3H), 7.55–7.58 (m, 2H); δ_C (100 MHz, CDCl$_3$) 20.5, 21.6, 25.7, 32.2, 32.3, 33.6, 43.3, 44.0, 46.4, 48.2, 50.0, 55.1, 59.2, 75.6, 127.9, 128.4, 129.1, 135.3, 212.5. C$_{21}$H$_{29}$ClOSe requires C, 61.24; H, 7.10. Found: C, 61.51; H, 7.31%.

11-Cyano-3,7,10,10-tetramethyl-4-phenylselenobicyclo[5.4.0]-undec-8-en-2-one (7b)

To a solution of **3b** (0.10 g, 0.20 mmol) in MeCN (2.0 ml) was added Pd(OAc)$_2$ (0.045 g, 0.20 mmol) at 50 °C under nitrogen. After stirring for 10 h, the solution was filtered through a Celite pad and the filtrate was washed with water (10 ml). The organic layer was dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (10:1) to give a colorless oil of **7b** (0.038 g, 0.095 mmol, 47% yield); ν_{max} (neat)/cm^{-1} 2243 (CN), 1707 (C=O); δ_H (400 MHz, CDCl$_3$) 0.74 (s, 3H), 1.18 (s, 3H), 1.20 (s, 3H), 1.48 (d, J 6.8 Hz, 3H), 1.55–1.77 (m, 3H), 2.30 (br dd, J 4.0, 11.2 Hz, 1H), 2.54 (dq, J 6.8, 11.2 Hz, 1H), 2.89 (d, J 12.0 Hz, 1H), 3.06 (dd, J 11.2, 11.2 Hz, 1H), 3.14 (d, J 12.0 Hz, 1H), 5.19 (d, J 9.6 Hz, 1H), 5.32 (d, J 9.6 Hz, 1H), 7.25–7.39 (m, 3H), 7.53–7.60 (m, 2H); δ_C (100 MHz, CDCl$_3$) 18.8, 20.9, 25.3, 29.1, 33.2, 34.1, 37.0, 37.3, 44.7, 47.3, 50.8, 54.9, 120.0, 127.9, 128.2, 129.2, 133.8, 135.6, 211.2. C$_{22}$H$_{27}$NOSe requires C, 65.99; H, 6.80; N, 3.50. Found: C, 65.89; H, 6.95; N, 3.34%.

10-Cyano-1-hydroxy-2,9,9-trimethyl-6-methylene-3-phenylthio-bicyclo[5.4.0]undecane (8a)

To a solution of **5a** (0.071 g, 0.20 mmol) in CHCl$_3$ (1 ml) was

added conc. HCl (one drop) at room temperature. After stirring for 1.5 h, the solution was washed with saturated aqueous NaHCO$_3$ solution (5 ml) and the aqueous layer was extracted with CHCl$_3$ (3 × 10 ml). The combined organic layers were dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (20 : 1) to give a white solid of **8a** (0.063 g, 0.17 mmol, 85%); mp 91.4–93.1 °C; ν_{max} (KBr)/cm^{-1} 3505 (OH), 2243 (CN); δ_H (400 MHz, CDCl$_3$) 1.05–1.11 (m, 6H), 1.15 (s, 3H), 1.25 (dd, J 3.2, 13.2 Hz, 1H), 1.79 (dd, J 4.0, 14.0 Hz, 1H), 1.88 (t, J 13.2 Hz, 2H), 1.96–2.11 (m, 2H), 2.11–2.23 (m, 1H), 2.23–2.33 (m, 1H), 2.42 (dd, J 3.2, 13.2 Hz, 1H), 2.60–2.71 (m, 1H), 2.87 (dd, J 4.0, 12.8 Hz, 1H), 3.30–3.45 (m, 2H), 4.88 (s, 1H), 5.09 (s, 1H), 7.22–7.36 (m, 3H), 7.38–7.45 (m, 2H); δ_C (100 MHz, CDCl$_3$) 16.9, 20.4, 30.0, 30.5, 32.4, 34.5, 35.0, 36.4, 41.0, 41.1, 46.6, 53.3, 74.3, 114.7, 121.6, 127.4, 129.1, 132.0, 135.5, 149.4. C$_{22}$H$_{29}$NOS requires C, 74.32; H, 8.22; N, 3.94. Found: C, 74.07; H, 8.38; N, 3.92%.

10-Cyano-1-hydroxy-2,9,9-trimethyl-6-methylene-3-phenyl-selenobicyclo[5.4.0]undecane (8b)

A white solid (82% yield); mp 117.4–118.8 °C; ν_{max} (KBr)/cm^{-1} 3457 (OH), 2236 (CN); δ_H (400 MHz, CDCl$_3$) 1.09 (s, 3H), 1.10 (d, J 8.0 Hz, 3H), 1.16 (s, 3H), 1.25 (dd, J 2.8, 13.2 Hz, 1H), 1.78–1.94 (m, 3H), 2.02–2.19 (m, 2H), 2.42 (dd, J 3.2, 13.2 Hz, 1H), 2.53–2.66 (m, 1H), 2.86 (dd, J 4.0, 12.0 Hz, 1H), 3.13 (br s, 1H), 3.39 (br t, J 7.2 Hz, 1H), 4.91 (s, 1H), 5.12 (s, 1H), 7.25–7.34 (m, 3H), 7.51–7.60 (m, 2H); δ_C (100 MHz, CDCl$_3$) 17.7, 20.4, 30.5, 30.5, 32.4, 35.0, 35.8, 36.1, 40.8, 41.0, 47.9, 49.4, 74.2, 115.2, 121.5, 127.8, 129.2, 131.1, 134.3, 149.1. C$_{22}$H$_{29}$NOSe requires C, 65.66; H, 7.26; N, 3.48. Found: C, 65.53; H, 7.33; N, 3.46%.

(1Z,8E)-5-Cyano-2,6,6,9-tetramethylcycloundeca-1,8-dien-3-one (9)

To a solution of **5b** (0.96 g, 2.4 mmol) in CH$_2$Cl$_2$ (20 ml) was added m-chloroperbenzoic acid (MCPBA) (0.56 g, 2.6 mmol) at 0 °C. The solution was stirred at room temperature for 0.5 h. The solution was washed with saturated aqueous Na$_2$S$_2$O$_3$ solution (30 ml) and saturated aqueous Na$_2$CO$_3$ solution (30 ml). The organic layer was dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (8 : 1) to give a white solid of **9** (0.50 g, 2.0 mmol, 85% yield); mp 79.4–81.1 °C; ν_{max} (KBr)/cm^{-1} 2246 (CN), 1694 (C=O), 1635 (C=C); δ_H (400 MHz, CDCl$_3$) 1.12 (s, 3H), 1.25 (s, 3H), 1.49 (s, 3H), 1.86 (br ddd, J 2.8, 10.0, 12.0 Hz, 1H), 1.91–2.10 (m, 6H), 2.13–2.26 (m, 1H), 2.32–2.47 (m, 1H), 2.57 (dd, J 4.4, 18.0 Hz, 1H), 2.68 (dd, J 4.4, 18.0 Hz, 1H), 3.13 (t, J 4.4 Hz, 1H), 4.89 (br dd, J 3.2, 9.2 Hz, 1H), 5.65 (br dt, J 1.2, 8.8 Hz, 1H); δ_C (100 MHz, CDCl$_3$) 17.1, 20.5, 24.4, 24.4, 28.5, 34.9, 35.6, 38.1, 38.5, 40.9, 120.3, 122.4, 134.0, 137.2, 138.1, 202.1. C$_{16}$H$_{23}$NO requires C, 78.32; H, 9.45; N, 5.71. Found: C, 78.11; H, 9.44; N, 5.55%.

(1Z)-5-Cyano-2,6,6,9-tetramethyl-8,9-epoxycycloundec-1-en-3-one (10/10′)

To a solution of **9** (0.75 g, 3.1 mmol) in AcOEt (30 ml) was added MCPBA (0.72 g, 3.4 mmol) at 0 °C and the resulting solution was stirred at room temperature for 2 h. It was washed with saturated aqueous Na$_2$S$_2$O$_3$ solution (30 ml) and saturated aqueous Na$_2$CO$_3$ solution (30 ml). The organic layer was separated and dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (4 : 1) to give a white solid of **10** (0.72 g, 2.8 mmol, 90%, **10** : **10′** = 84 : 16). Pure **10** was obtained by recrystallization from hexane–AcOEt

(10 : 1); mp 95.3–97.8 °C; ν_{max} (KBr)/cm^{-1} 2243 (CN), 1686 (C=O), 1623 (C=C); δ_H (400 MHz, CDCl$_3$) 1.15 (s, 3H), 1.27 (s, 3H), 1.28–1.34 (br m, 4H), 1.45–1.49 (m, 1H), 1.68–1.82 (m, 1H), 1.99 (s, 3H), 2.09–2.21 (m, 2H), 2.60 (dd, J 2.8, 6.0 Hz, 1H), 2.64–2.89 (m, 3H), 3.07 (dd, J 5.2, 6.8 Hz, 1H), 5.82 (t, J 8.0 Hz, 1H); δ_C (100 MHz, CDCl$_3$) 17.8, 20.7, 24.5, 26.2, 26.8, 36.2, 36.6, 36.9, 37.0, 41.2, 56.6, 60.5, 120.6, 136.5, 137.5, 203.2. C$_{16}$H$_{23}$NO$_2$ requires C, 73.53; H, 8.87; N, 5.36. Found: C, 73.32; H, 8.92; N, 5.26%.

Tricyclic ketone 11

To a solution of **10/10′** (0.13 g, 0.50 mmol, dr = 84 : 16) in THF (5.0 ml) was added lithium hexamethyldisilazanide (LHMDS, 1 M in THF, 0.60 ml, 0.60 mmol) at −78 °C and the mixture was stirred at −78 °C for 0.5 h under nitrogen. The solution was stirred at room temperature for 2 h. The solution was poured into saturated aqueous NH$_4$Cl solution (30 ml) and extracted with Et$_2$O (3 × 20 ml). The organic layer was dried over MgSO$_4$. The solvent was evaporated under vacuum and the residue was subjected to column chromatography on SiO$_2$ with hexane–AcOEt (6 : 1) to give two tricyclic compounds of **11** (0.05 g, 0.2 mmol, 40%) and **12** (0.02 g, 0.08 mmol, 15%). A white solid **11**; mp 121.4–122.8 °C; ν_{max} (KBr)/cm^{-1} 2240 (CN), 1694 (C=O); δ_H (400 MHz, CDCl$_3$) 1.18 (s, 3H), 1.20 (s, 3H), 1.22 (s, 3H), 1.24 (s, 3H), 1.28–1.35 (m, 1H), 1.64–1.76 (m, 2H), 1.88 (dt, J 8.4, 11.6 Hz, 1H), 2.07–2.20 (m, 2H), 2.41 (q, J 7.6 Hz, 1H), 2.63 (m, 1H), 3.07 (d, J 10.8 Hz, 1H), 3.19 (t, J 11.6 Hz, 1H), 4.35 (dd, J 4.0, 9.6 Hz, 1H); δ_C (100 MHz, CDCl$_3$) 16.3, 26.6, 28.9, 30.3, 31.4, 34.1, 38.4, 41.2, 43.6, 53.4, 54.4, 58.1, 80.6, 85.1, 119.6, 206.9. C$_{16}$H$_{23}$NO$_2$ requires C, 73.53; H, 8.87; N, 5.36. Found: C, 73.30; H, 8.96; N, 5.23%.

Tricyclic hemiketal 12. A white solid (15% yield); mp 146.8–148.0 °C; ν_{max} (KBr)/cm^{-1} 3356 (OH), 2234 (CN); δ_H (400 MHz, CDCl$_3$) 1.18 (s, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.43–1.83 (m, 4H), 1.87 (s, 3H), 1.89–1.96 (m, 1H), 2.41–2.49 (m, 1H), 2.56 (d, J 11.6 Hz, 1H), 2.90 (br s, 1H), 2.99–3.06 (m, 1H), 3.18 (t, J 11.6 Hz, 1H), 5.80 (dd, J 1.2, 8.0 Hz, 1H); δ_C (100 MHz, CDCl$_3$) 20.1, 23.2, 25.8, 27.3, 28.5, 36.7, 38.3, 42.8, 49.3, 53.8, 61.6, 81.9, 108.1, 120.4, 130.5, 137.6. C$_{16}$H$_{23}$NO$_2$ requires C, 73.53; H, 8.87; N, 5.36. Found: C, 73.53; H, 8.64; N, 5.25%.

X-Ray structure determinations †

Measurements were made on a Rigaku AFC-7R four-circle automated diffractometer with Mo-Kα radiation ($\lambda = 0.71069$ Å). Structures were solved by Patterson Methods (DIRDIF92 PATTY)[19] or direct methods (SIR92)[20] and expanded using Fourier techniques.

Crystal data for C$_{22}$H$_{30}$FNOS (**4a**), $M = 375.54$, monoclinic, space group $P2_1/a$ (no. 14), $a = 11.860(5)$, $b = 13.058(3)$, $c = 13.784(3)$ Å, $\beta = 98.57(2)°$, $V = 2110(1)$ Å^3, $Z = 4$, $D_c = 1.182$ g cm^{-3}, $F(000) = 808$, μ(Mo-Kα) = 1.72 cm^{-1}. At 296 K, 5302 reflections were measured, 5066 were unique ($R_{int} = 0.048$). The final residuals were $R = 0.047$ and $R_w = 0.062$. The maximum and minimum peaks in the final difference map were 0.44 and −0.37 e Å^{-3} respectively.

Crystal data for C$_{21}$H$_{29}$ClOS (**6a**), $M = 364.97$, triclinic, space group $P\bar{1}$ (no. 2), $a = 11.943(7)$, $b = 12.196(8)$, $c = 7.739(2)$ Å, $\alpha = 104.76(3)°$, $\beta = 99.19(3)°$, $\gamma = 69.53(4)°$, $V = 1018.1(9)$ Å^3, $Z = 2$, $D_c = 1.190$ g cm^{-3}, $F(000) = 392$, μ(Mo-Kα) = 2.95 cm^{-1}. At 296 K, 4901 reflections were measured, 4677 were unique ($R_{int} = 0.012$). The final residuals were $R = 0.061$ and $R_w = 0.064$. The maximum and minimum peaks in the final difference map were 0.24 and −0.35 e Å^{-3} respectively.

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