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SYNTHESIS OF CARYOPHYLLANE OXIMES AND HYDRAZONE AND THEIR *O*- AND *N*-ACYLATED DERIVATIVES

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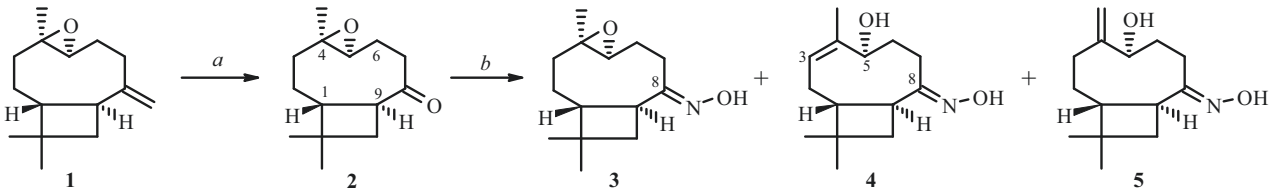
Kobusone oxime and hydrazone were synthesized for the first time in yields of 78 and 71%, respectively, via condensation of the sesquiterpene ketone kobusone, which was prepared by oxidation of caryophyllene oxide, with hydroxylamine and hydrazine. Acylation of the caryophyllane oxime and hydrazone produced series of O- *and* N*-derivatives in preparative yields up to 90%. The molecular structures of the acyloximes and acetylhydrazone were established by X-ray crystal structure analyses.*

Keywords: caryophyllene oxide, kobusone, oximes, hydrazone, acyloximes.

Oximes and hydrazones are widely used in organic chemistry as synthons to prepare various classes of compounds [1–8] and in medicinal chemistry as biologically active compounds. For example, several oximes exhibit antifungal [9] and anticancer properties [10, 11]. *O*-Alkylated oximes with antifungal, antimicrobial, and anticonvulsant activity are also promising for research and practical application [10]. Oxime esters of natural compounds, e.g., verbenone, were active against phytopathogenic fungi *Fusarium oxysporum f.* sp. *cucumerinum*, *Cercospora arachidicola*, *Physalospora piricola*, *Alternaria solani*, *Gibberella zeae*, *Rhizoctonia solani*, *Bipolaris maydis*, and *Colleterichum orbicalare* [12]. Carvone oxime ethers could be used in perfumery as fragrances [13].

Herein, syntheses of oximes and the hydrazone of the sesquiterpene caryophyllene oxide and their esters are reported.

The classical method for preparing oximes is condensation of carbonyl compounds with hydroxylamine. For this, caryophyllene oxide (**1**) was oxidized by $KMnO_4$ in Me_2CO to the sesquiterpene ketone kobusone (**2**). Oximation of **2** with a ketone–NH_2OH·HCl mole ratio of 1:1.2 formed **3**–**5** (Scheme 1).



a. $KMnO_4$, Me_2CO; *b*. NH_2OH·HCl, reflux

Scheme 1

The main reaction product was oxime **3**. The resonance for quaternary C-8 was shifted in its ^{13}C NMR spectrum to stronger field (162.3 ppm) as compared to starting epoxyketone **2** (214.0 ppm). The OH proton was recorded in the PMR spectrum as a singlet at 9.00 ppm.

A chromatographically inseparable mixture of oximes **4** and **5** was formed in addition to **3** during the reaction. The epoxide ring was transformed in **4** and **5** into an OH group and a double bond in the cyclononane moiety. The ^{13}C NMR spectrum (Jmod) of the mixture of **4** and **5** showed resonances for C-5 bound to the OH group in the range 70–71 ppm.

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TABLE 1. Optimization of Conditions for Oximation of Kobusone (**2**)

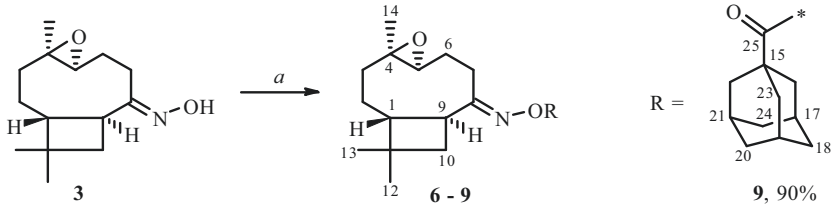
Synthesis conditions	Product yields	Synthesis conditions	Product yields
5 mol% NaOAc, H_2O, MeOH, 60°C, 12 h	**4** + **5** – 47%	EtOH, 5 mol% NaOAc, Na_2SO_4, reflux	**4** + **5** – 74%
C_6H_6, reflux	–	EtOH, Na_2SO_4, reflux	**3** – 74%, **4** + **5** – 25%
C_6H_6, 3 drops Py, reflux	–	MeOH, KOH, Na_2SO_4, reflux	**3** – 84%
C_6H_6, 5 mol% NaOAc, reflux	–		

The ^{13}C NMR spectrum (Jmod) of oxime **4** had C-3 and C-4 resonances of the endocyclic double bond at δ 125 and 137 ppm, respectively. The C-4 and C-14 resonances of the exocyclic C=C bond in **5** were observed at δ 148 and 113 ppm, respectively. C-5 resonated at δ 70.2 ppm. In general, these were characteristic of the α-betulenol structure. The PMR spectrum of **5** exhibited the resonance of the C-14 terminal methylene as a doublet at 5.30 ppm.

The reaction conditions were varied to increase the selectivity for and yield of **3** (Table 1).

The condensation of kobusone (**2**) with $NH_2OH·HCl$ was not promoted by using benzene as the solvent. A mixture of **4** and **5** was formed in overall yield 47% with significant polymerization of the reaction mixture if the condensation was performed in MeOH with added (5 mol%) NaOAc. Replacing the solvent by EtOH increased the yield of hydroxyoximes **4** and **5** to 74%. The formation of **4** and **5** decreased substantially for oximation in EtOH without a catalyst so that the major condensation product became **3** in 74% yield. Condensation of ketone **2** in MeOH with preliminary treatment of $NH_2OH·HCl$ with KOH produced **3** in preparative yield 84%, **4** and **5** practically not formed in this instance.

Esters **6**–**9** were synthesized via *O*-acylation of epoxyoxime **3** (Scheme 2).



R = Ac (**6**) 87%; Bz (**7**) 84%; *p*-NO_2Bz (**8**) 70%

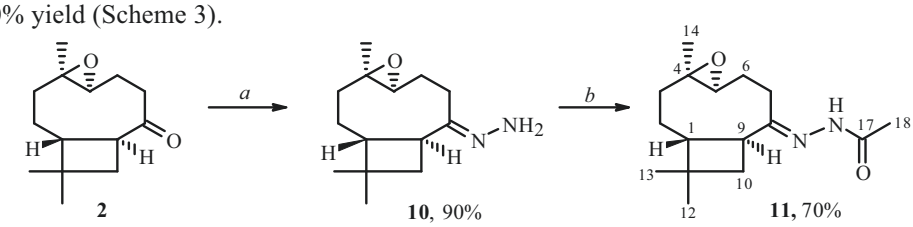
a. RCl, DCM, Et_3N

Scheme 2

The conditions for preparing the acyloximes were optimized using acetylation of kobusone oxime **3** as a model. Acetylation of **3** in benzene or CH_2Cl_2 at 0°C gave **6** in 43% yield in both cases. Use of anhydrous CH_2Cl_2 at 0°C under an Ar atmosphere produced **6** in 87% yield. Esters **7**–**9** were synthesized under these conditions because this version gave the maximum acylation yield.

The molecular structures of crystalline acyloximes **6**–**8** and the *E*-configuration of the substituents on the C=N bond were unambiguously proven by X-ray crystal structure analyses (XSAs) (Fig. 1).

Condensation of kobusone (**2**) with hydrazine hydrate produced hydrazone **10** (90% yield), *N*-acetylation of which synthesized **11** in 70% yield (Scheme 3).



a. $NH_2NH_2·H_2O$, PhH, reflux; *b*. AcCl, Et_3N, PhH

Scheme 3

The PMR spectrum of **10** gave the NH_2 resonance as a broad singlet at 5.03 ppm. The ^{13}C NMR spectrum showed the C=N resonance at 154.1 ppm. The ^{13}C NMR spectrum of acetylhydrazone **11** exhibited the C-8 C=N resonance at 155.3 ppm. The PMR spectrum contained an NH resonance as a singlet at 8.78 ppm.

The molecular structure of **11** was proven by an XSA. A distinguishing feature of the crystal of this compound was the presence of intermolecular H-bonds between NH groups and acyl O atoms that joined molecules into spiral structures. In general, the configuration of **11** (Fig. 1) was analogous to those described above for oxime esters **6**–**9**.

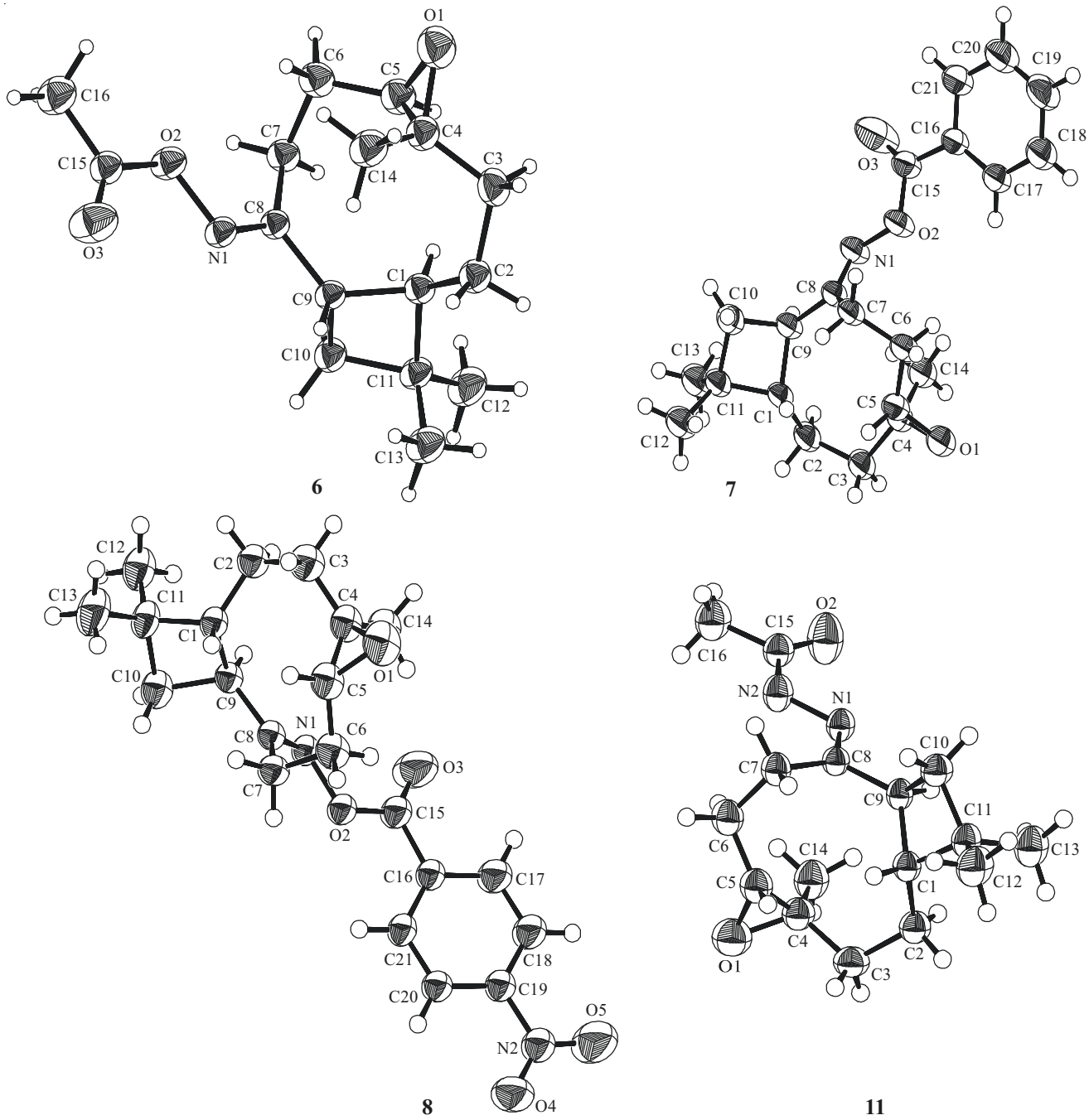


Fig. 1. X-ray molecular structures of acyloximes **6**–**8** and acetylhydrazone **11**.

Thus, kobusone oxime **3** and hydrazone **10** and their acylated derivatives **6**–**9** and **11** were synthesized for the first time. The synthesized compounds could be promising for use in organic synthesis as intermediates.

EXPERIMENTAL

IR spectra were recorded from thin layers or KBr pellets on a Shimadzu IR Prestige 21 FT-IR spectrometer. PMR and ^{13}C NMR spectra were taken in $CDCl_3$ with residual solvent resonances as internal standards on a Bruker Avance-300 spectrometer (300.17 MHz for ^{1}H and 75.48 MHz for ^{13}C). ^{13}C NMR spectra were recorded in J-modulation mode. Resonances of ^{1}H and ^{13}C were fully assigned using 2D homo- (^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY) and heteronuclear experiments (^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC). Mass spectra were recorded on a Thermo Finnigan LCQ Fleet instrument equipped with an

MS detector. Masses were scanned in the *m/z* range 50–2000 (ESI, 10 eV). Melting points were determined on a Gallenkamp MPD350BM3.5 apparatus (Sanyo) and were uncorrected. Optical rotation angles were measured on a PolAAr 3001 automated digital polarimeter (Optical Activity, England).

The XSAs were performed on an Xcalibur 3 automated four-circle diffractometer with a CCD detector using the standard procedure [Mo Kα-radiation, graphite monochromator, ω-scanning in 1° steps, 295(2) K]. Absorption corrections were made empirically. Anomalous scattering was neglected. The structures were solved and refined using the SHELXL software [14]. The structures were solved by direct methods using the SHELXS program and refined by anisotropic full-matrix least-squares methods over F^2 for all nonhydrogen atoms. H atoms in C–H bonds were placed in the calculated positions and refined using a rider model with dependent thermal parameters. N–H hydrogen atoms were isotropically refined independently.

Data from the XSAs were deposited in the Cambridge Structural Database and can be obtained free upon request to www.ccdc.cam.ac.uk/data_request/cif.

TLC used Sorbfil plates with detection by vanillin and phosphomolybdic acid. Column chromatography used Alfa Aesar silica gel (0.06–0.2 mm). The sesquiterpene derivatives were synthesized using commercial (–)-caryophyllene oxide (95%), $[\alpha]_D^{26}$ –70.0° (*c* 1.0, EtOH) (Sigma-Aldrich). Adamantane-1-carboxylic acid (AdCOOH, 99%) was purchased (Alfa Aesar).

Adamantane-1-carboxylic acid chloride was prepared as before [15].

(1*R*,4*R*,6*R*,10*S*)-4,12,12-Trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodcan-9-one (2). Caryophyllene oxide (**1**, 3 g, 14 mmol) in a mixture of Me_2CO (36 mL) and H_2O (2.5 mL) was chilled in ice, stirred, and treated in portions with powdered $KMnO_4$ (7.5 g, 47 mmol). The course of the reaction was monitored by TLC ($CHCl_3$ eluent). When the reaction was finished, the precipitate was filtered off. The filtrate was evaporated *in vacuo*. The product was chromatographed ($CHCl_3$ eluent). Yield 40–45%. Colorless oil. IR spectrum (KBr, ν, cm^{-1}): 1695 (C=O). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 223.08 (100) $[M + H]^+$. MM 222.3232, $C_{14}H_{22}O_2$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87–0.99 (1H, m, H-3a), 1.02 (6H, s, CH_3-12, 13), 1.30 (3H, s, CH_3-14), 1.35–1.75 (5H, m, H-2a, 2b, 6a, 6b, 10a), 1.93 (1H, t, J = 9.7, H-9), 2.20–2.21 (1H, m, H-10b), 2.30–2.46 (1H, m, H-6b), 2.47–2.59 (1H, m, H-7b), 2.68 (1H, dd, J = 9.8, 4.8, H-5), 3.05 (1H, q, J = 8.8, H-1). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 52.58 (CH, C-1), 24.75 (CH_2, C-2), 39.00 (CH_2, C-3), 58.91 (C, C-4), 61.62 (CH, C-5), 26.46 (CH_2, C-6), 37.67 (CH_2, C-7), 214.08 (C, C-8), 51.33 (CH, C-9), 35.28 (CH_2, C-10), 34.47 (C, C-11), 22.18 (CH_3, C-12, 13), 29.30 (CH_3, C-13, 12), 16.18 (CH_3, C-14).

(1*R*,4*R*,6*R*,10*S*,*E*)-4,12,12-Trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-one Oxime (3). A solution of $NH_2OH{\cdot}HCl$ (10.80 mmol) in MeOH (20 mL) was treated with KOH (10.80 mmol) and stirred for 10 min. The precipitate was filtered off (the filtration step could be omitted if the reaction was performed with smaller quantities). The filtrate was treated with kobusone (**2**, 9.00 mmol) in MeOH (15 mL) and a small amount of anhydrous Na_2SO_4 as a dehydrating agent. The mixture was refluxed until the reaction was finished (TLC monitoring, petroleum ether–EtOAc eluent, 2:1). The solvent was evaporated. The solid was extracted with EtOAc. The extract was washed with NaCl solution, dried over Na_2SO_4, and evaporated *in vacuo*. The solid was chromatographed over silica gel with elution by petroleum ether–EtOAc (2:1). Yield 84%. Colorless oil, $[\alpha]_D^{26}$ –6.3° (*c* 0.5, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3305 (OH), 1460 (C=N). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 238.19 (100) $[M + H]^+$. MM 237.3379, $C_{14}H_{23}NO_2$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.93–1.02 (1H, m, H-3a), 1.02, 1.03 (3H each, s, CH_3-12, 13), 1.15 (3H, s, CH_3-14), 1.34–1.53 (1H, m, H-7a), 1.55–1.80 (4H, m, H-6a, 7b, 10a, 10b), 1.95 (1H, t, J = 10, H-1), 2.09 (1H, d, J = 12.6, H-3b), 2.25–2.49 (2H, m, H-2a, 6b), 2.55–2.68 (1H, m, H-2b), 2.74–2.51 (2H, m, H-5, 9), 8.97 (1H, br.s, OH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 49.49 (CH, C-1), 23.06 (CH_2, C-2), 38.46 (CH_2, C-3), 59.76 (C, C-4), 64.23 (CH, C-5), 23.71 (CH_2, C-6), 26.56 (CH_2, C-7), 162.30 (C, C-8), 45.90 (CH, C-9), 37.68 (CH_2, C-10), 35.23 (C, C-11), 21.19 (CH_3, C-12, 13), 29.77 (CH_3, C-13, 12), 16.04 (CH_3, C-14).

General Method for Acylation of Kobusone Oxime 3. A solution of oxime **3** (0.42 mmol) in dry CH_2Cl_2 (3 mL) was treated dropwise in the cold under a stream of Ar with the acyl chloride (0.42 mmol) and Et_3N (2 drops) and stirred (TLC monitoring, petroleum ether–EtOAc eluent, 2:1). When the reaction was finished, the mixture was diluted with CH_2Cl_2 (10–15 mL), washed with NaCl solution, dried over Na_2SO_4, and evaporated. The solid was chromatographed over silica gel with elution by petroleum ether-–Et_2O (1:1).

(1*R*,4*R*,6*R*,10*S*,*E*)-4,12,12-Trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-one *O*-Acetyloxime (6). Yield 87%, white powder, mp 166°C, $[\alpha]_D^{25}$ +43.7° (*c* 0.3, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1751 (C(O)O-), 1458 (C=N). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 302.58 (100) $[M + Na]^+$. MM 279.3746, $C_{16}H_{25}NO_3$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.98–1.00 (1H, m, H-3a), 1.02, 1.03 (3H each, s, CH_3-12, 13), 1.12 (3H, s, CH_3-14), 1.36–1.84 (5H, m, H-6a, 7a, 7b,

10a, 10b), 1.98–2.12 (2H, m, H-3b, 9), 2.15 (3H, s, CH_3-16), 2.25–2.47 (2H, m, H-2a, 6b), 2.74 (1H, ddd, J = 12.5, 6.3, 3.5, H-2b), 2.87 (1H, dd, J = 11.2, 3.8, H-5), 3.11 (1H, q, J = 10.15, H-1). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 48.29 (CH, C-1), 23.72 (CH_2, C-2), 38.05 (CH_2, C-3), 69.60 (C, C-4), 63.79 (CH, C-5), 24.72 (CH_2, C-6), 26.21 (CH_2, C-7), 169.67 (C, C-8), 45.46 (CH, C-9), 37.68 (CH_2, C-10), 36.01 (C, C-11), 20.86 (CH_3, C-12, 13), 29.70 (CH_3, C-13, 12), 16.15 (CH_3, C-14), 168.34 (C, C-15), 19.59 (CH_3, C-16). A colorless prismatic crystal of the orthorhombic system had size 0.46 × 0.37 × 0.25 mm, space group $P2_12_12_1$, a = 7.6753(10), b = 11.4677(13), c = 17.900(3) Å, $\alpha = \beta = \gamma = 90°$, V = 1575.5(4) Å^3, Z = 4, μ(Mo Kα) = 0.080 mm^{-1}. A dataset of 6448 reflections was collected at scattering angles 3.73° < θ < 30.93°, of which 3859 were independent (R_{int} = 0.0457), including 1830 reflections with $I > 2\sigma(I)$. The final refinement parameters were R_1 = 0.1512, wR_2 = 0.1972 (all data), R_1 = 0.0642, wR_2 = 0.1330 [$I > 2\sigma(I)$] with GooF = 1.007. $\Delta\rho_e$ = 0.203/–0.187 e Å^{-3}; Flack parameter = 2(2). CCDC 1991154.

(1*R*,4*R*,6*R*,10*S*,*E*)-4,12,12-Trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-one *O*-Benzoyloxime (7). Yield 84%, White powder, mp 132°C, $[\alpha]_D^{25}$ +102.3° (*c* 0.21, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1741 (C(O)O-), 1454 (C=N). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 364.69 (100) [M + Na]$^+$. MM 341.4439, $C_{21}H_{27}NO_3$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95–1.08 (1H, m, H-3a), 1.07, 1.08 (3H each, s, CH_3-12, 13), 1.18 (3H, s, CH_3-14), 1.37–1.94 (5H, m, H-6a, 7a, 7b, 10a, 10b), 2.01–2.18 (2H, m, H-1, 6b), 2.35–2.60 (2H, m, H-2a, 3b), 2.84–3.01 (2H, m, H-2b, 5), 3.17–3.33 (1H, m, H-9), 7.42 (2H, t, J = 7.6, H-18, 20), 7.53–7.69 (1H, m, H-19), 7.95–8.09 (2H, m, H-17, 21). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 48.26 (CH, C-1), 23.91 (CH_2, C-2), 38.08 (CH_2, C-3), 59.79 (C, C-4), 63.92 (CH, C-5), 24.98 (CH_2, C-6), 26.27 (CH_2, C-7), 170.71 (C, C-8), 45.59 (CH, C-9), 37.84 (CH_2, C-10), 36.23 (C, C-11), 20.91 (CH_3, C-12, 13), 29.77 (CH_3, C-13, 12), 16.26 (CH_3, C-14), 163.64 (C, C-15), 129.06 (C, C-16), 129.49 (2CH, C-17, 21), 128.60 (2CH, C-18, 20), 133.33 (CH, C-19). A colorless prismatic crystal of the monoclinic system had size 0.44 × 0.37 × 0.28 mm, space group $P2_1$, a = 9.5078(8), b = 10.3720(9), c = 10.0501(8) Å, $\alpha = \gamma = 90°$, β = 103.621(8)°, V = 963.21(14) Å^3, Z = 2, μ(Mo Kα) = 0.078 mm^{-1}. A dataset of 7034 reflections was collected at scattering angles 3.90° < θ < 30.87°, of which 2731 were independent (R_{int} = 0.0353), including 1759 reflections with $I > 2\sigma(I)$. The final refinement parameters were R_1 = 0.0908, wR_2 = 0.1864 (all data), R_1 = 0.0526, wR_2 = 0.1404 [$I > 2\sigma(I)$] with GooF = 1.003. $\Delta\rho_e$ = 0.129/–0.209 e Å^{-3}, Flack parameter = 0. CCDC 1991153.

(1*R*,4*R*,6*R*,10*S*,*E*)-4,12,12-Trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-one *O*-(4-Nitrobenzoyl)oxime (8). Yield 70%. White powder, mp 144°C (dec.), $[\alpha]_D^{25}$ +97.7° (*c* 0.13, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1739 (C(O)O-), 1523 ($PhNO_2$), 1456 (C=N). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 409.68 (100) [M + Na]$^+$. MM 387.4494, $C_{21}H_{27}N_2O_5$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.96–1.05 (1H, m, H-3a), 1.08, 1.09 (3H each, s, CH_3-12, 13), 1.18 (3H, s, CH_3-14), 1.42–1.60 (1H, m, H-7a), 1.61–1.80 (2H, m, H-6a, 7b), 1.80–1.94 (2H, m, H-10), 2.06–2.19 (2H, m, H-1, 3b), 2.47 (1H, ddd, J = 12.8, 6.5, 3.4, H-6b), 2.51–2.64 (1H, m, H-2a), 2.83–3.02 (2H, m, H-2b, 5), 3.18–3.31 (1H, m, H-9), 8.21 (2H, d, J = 9.1, H-17, 21), 8.33 (2H, d, J = 9.1, H-18, 20). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 48.35 (CH, C-1), 24.04 (CH_2, C-2), 37.99 (CH_2, C-3), 59.71 (C, C-4), 63.65 (CH, C-5), 25.02 (CH_2, C-6), 26.22 (CH_2, C-7), 171.91 (C, C-8), 45.50 (CH, C-9), 37.84 (CH_2, C-10), 36.29 (C, C-11), 20.91 (CH_3, C-12, 13), 29.77 (CH_3, C-13, 12), 16.26 (CH_3, C-14), 161.85 (C, C-15), 134.50 (C, C-16), 130.57 (2 CH, C-17, 21), 123.79 (2 CH, C-18, 20), 150.72 (C, C-19). A colorless prismatic crystal of the orthorhombic system had size 0.49 × 0.36 × 0.24 mm, space group $P2_12_12_1$, a = 7.4143(5), b = 11.6984(9), c = 23.653(2) Å, $\alpha = \beta = \gamma = 90°$, V = 2051.5(3) Å^3, Z = 4, μ(Mo Kα) = 0.090 mm^{-1}. A dataset of 13,958 reflections was collected at scattering angles 3.59° < θ < 30.94°, of which 3324 were independent (R_{int} = 0.0486), including 1927 reflections with $I > 2\sigma(I)$. The final refinement parameters were R_1 = 0.1053, wR_2 = 0.1904 (all data), R_1 = 0.0536, wR_2 = 0.1425 [$I > 2\sigma(I)$] with GooF = 1.003. $\Delta\rho_e$ = 0.193/–0.172 eÅ^{-3}, Flack parameter = 0. CCDC 1991152.

(1*R*,4*R*,6*R*,10*S*,*E*)-4,12,12-Trimethyl-5-oxatriyclo[8.2.0.0^{4,6}]dodecan-9-one *O*-[(3*S*,5*S*,7*S*)-Adamantyl-1-carbonyl]oxime (9). Yield 90%. White powder, mp 207–208°C (dec.), $[\alpha]_D^{25}$ +55.2° (*c* 0.31, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1761 (C(O)O-), 1454 (C=N). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 438.82 (63) [M + Na]$^+$. MM 415.6086, $C_{26}H_{41}NO_3$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.91–1.01 (1H, m, H-3a), 1.04 (6H, s, CH_3-12, 13), 1.13 (3H, s, CH_3-14), 1.37–1.55 (1H, m, H-6a), 1.56–1.86 (10H, m, 2H-7, 10, 18, 20, 24), 1.96 (6H, br.s, 2H-16, 22, 23), 1.98–2.15 (5H, m, H-1, 3b, 17, 19, 21), 2.29–2.48 (2H, m, H-2a, 6b), 2.68–2.70 (1H, m, H-2b), 2.91 (1H, dd, J = 11.0, 3.7, H-5), 3.09–3.23 (1H, m, H-9). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 48.23 (CH, C-1), 23.72 (CH_2, C-2), 37.71 (CH_2, C-3), 59.82 (C, C-4), 63.93 (CH, C-5), 24.85 (CH_2, C-6), 26.22 (CH_2, C-7), 169.97 (C, C-8), 45.58 (CH, C-9), 38.08 (CH_2, C-10), 36.13 (C, C-11), 20.86 (CH_3, C-12, 13), 29.71 (CH_3, C-13, 12), 16.22 (CH_3, C-14), 40.74 (C, C-15), 38.91 (3 CH_2, C-16, 22, 23), 27.85 (3 CH, C-17, 19, 21), 36.29 (3 CH_2, C-18, 20, 24), 173.98 (C, C-25).

(*E*)-{(1*R*,4*R*,6*R*,10*S*)-4,12,12-Trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-ylidene}hydrazine (10). A solution of kobusone (**2**, 0.68 mmol) in anhydrous benzene (5 mL) was treated with $NH_2NH_2 \cdot H_2O$ (0.68 mmol) and a small amount of

anhydrous Na_2SO_4 as a dehydrating agent. The mixture was refluxed until the reaction was finished (TLC monitoring, $CHCl_3$–*i*-PrOH eluent, 50:1), diluted with benzene (15 mL), washed with NaCl solution, dried over Na_2SO_4, and evaporated. The product was purified by column chromatography over silica gel with elution by $CHCl_3$–*i*-PrOH (50:1). Yield 90%. White powder, mp 106–107°C, $[\alpha]_D^{25}$ –43.5° (*c* 0.30, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3222, 3292 (NH_2), 1635, 1456 (C=N). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 237.20 (100) $[M + H]^+$. MM 236.3531, $C_{14}H_{24}N_2O$. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90–1.05 (1H, m, H-3a), 1.00, 1.01 (3H each, s, CH_3-12, 13), 1.22 (3H, s, CH_3-14), 1.36–1.59 (2H, m, H-2a, 7a), 1.59–1.94 (4H, m, H-1, 7b, 10a, 10b), 2.10 (1H, dt, J = 12.9, 3.5, H-7b), 2.21–2.39 (2H, m, H-2b, 6a), 2.42–2.60 (1H, m, H-6b), 2.66–2.88 (2H, m, H-5, 9), 5.03 (2H, s, NH_2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 50.38 (CH, C-1), 21.87 (CH_2, C-2), 38.69 (CH_2, C-3), 59.79 (C, C-4), 63.71 (CH, C-5), 22.88 (CH_2, C-6), 26.99 (CH_2, C-7), 154.06 (C, C-8), 48.92 (CH, C-9), 37.68 (CH_2, C-10), 34.52 (C, C-11), 21.45 (CH_3, C-12, 13), 29.70 (CH_3, C-13, 12), 15.94 (CH_3, C-14).

***N′*-{(1*R*,4*R*,6*R*,10*S*,*E*)-4,12,12-Trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-ylidene}acetohydrazide (11).** A solution of hydrazone **10** (100 mg, 0.42 mmol) in anhydrous benzene (5 mL) and Et_3N (2 drops) was treated dropwise with AcCl (0.42 mmol) and stirred at room temperature. When the reaction was finished, the mixture was diluted with benzene (15 mL), washed with NaCl solution and H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The solid was chromatographed with elution by $CHCl_3$–*i*-PrOH (50:2). Yield 70%, White powder, mp 155°C, $[\alpha]_D^{25}$ –41.1° (*c* 0.10, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3190 (NH), 1674 (C=O), 1456 (C=N). Mass spectrum (ESI, 10 eV), *m/z* (I_{rel}, %): 279.51 (100) $[M + H]^+$. MM 278.3898, $C_{16}H_{26}N_2O_2$. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.90–1.00 (1H, m, H-3a), 1.03, 1.04 (3H each, s, CH_3-12, 13), 1.19 (3H, s, CH_3-14), 1.33–1.58 (2H, m, H-2a, 7a), 1.61–1.80 (2H, m, H-7b, 10a), 1.81–1.97 (2H, m, H-1, 6b), 2.04–2.18 (1H, m, H-3b), 2.27 (3H, s, CH_3-18), 2.23–2.40 (2H, m, H-2b, 6a), 2.52–2.88 (1H, m, H-6b), 2.69–2.85 (2H, m, H-5, 9), 8.78 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 51.06 (CH, C-1), 22.91 (CH_2, C-2), 38.71 (CH_2, C-3), 59.42 (C, C-4), 62.69 (CH, C-5), 24.44 (CH_2, C-6), 26.69 (CH_2, C-7), 155.32 (C, C-8), 48.74 (CH, C-9), 37.78 (CH_2, C-10), 34.36 (C, C-11), 21.70 (CH_3, C-12, 13), 29.84 (CH_3, C-13, 12), 15.93 (CH_3, C-14), 173.61 (C, C-17), 20.45 (CH_3, C-18). A colorless prismatic crystal of the monoclinic system had size 0.48 × 0.41 × 0.37 mm, space group *C*2, *a* = 17.8793(19), *b* = 7.1832(6), *c* = 13.5585(11) Å, $\alpha = \gamma = 90°$, $\beta = 109.651(10)°$, *V* = 1639.9(3) $Å^3$, *Z* = 4, μ(Mo Kα) = 0.074 mm^{-1}. A dataset of 6159 reflections was collected at angles $3.65° < \theta < 30.91°$, of which 2456 were independent (R_{int} = 0.0334), including 1683 with $I > 2\sigma(I)$. The final refinement parameters were R_1 = 0.0774, wR_2 = 1487 (all data), R_1 = 0.0466, wR_2 = 0.1166 [$I > 2\sigma(I)$] with GooF = 1.003. $\Delta\rho_e$ = 0.119/–0.155 e$Å^{-3}$, Flack parameter = 0. CCDC 1991151.

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