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SYNTHETIC TRANSFORMATIONS OF HIGHER TERPENOIDS. XXVII.* SYNTHESIS OF 7-HYDROXYLABDANOIDS AND THEIR TRANSFORMATIONS

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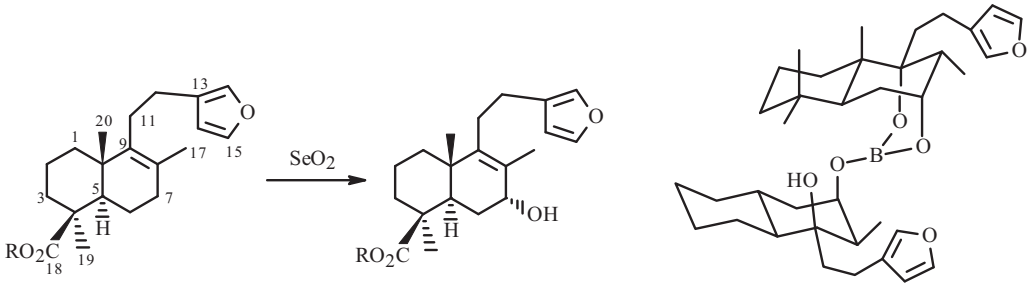
*Allylic oxidation of phlomisoic acid and its methyl ester by selenium dioxide occurred stereoselectively to form 7α-hydroxy derivatives of labdanoids, which were oxidized by active manganese dioxide to 7-ketofuranolabdanoids. Oxidation of the last by hydroxylamine hydrochloride in MeOH in the presence of NaOAc gave pure (*E*)-ketooximes. Beckmann rearrangement of 7-ketooximes of phlomisoic acid and its methyl ester occurred with formation of the corresponding octahydro-1*H*-benzoazepines.*

Keywords: phlomisoic acid, synthesis, 7*R*-hydroxy-15,16-epoxy-8(9),13(16),14-labdatrien-18-oic acid, 7-ketolabdanoids, oximes, 5-furan-3-ylethylbenzoazepines, XSA.

Furan-containing labdanoids functionalized in ring B were isolated from extracts of plants that exhibit sedative and uterotonic properties and are used in folk medicine for cardiovascular disorders [2]. 7-Keto- and 7-hydroxyfurolabdanoids showed antibacterial [3], antifeedant [4], and cytotoxic activity [5]. The isolation of 8,9-secofuranolabdanoids that exhibited cytotoxicity against human tumor cells was reported [6]. Promising inhibitors of N–O synthase were recently found among labdanoids modified in ring B [7]. Therefore, it seemed interesting to synthesize modified labdanoids. Currently known approaches are most often based on transformations of available natural metabolites [8, 9]. We proposed earlier methods for preparing the plant diterpenoid phlomisoic acid (**1**) and its ester **2** from lambertianic acid, an available metabolite of *Pinus sibirica* R. Major [10, 11]. Herein results from a study of the transformations of furanolabdanoids **1** and **2** in ring B are reported.

Allylic oxidation of **1** and **2** by SeO_2 in dioxane occurred stereoselectively to form 7α-hydroxy derivatives **3** and **4** (59 and 74% yields, respectively) (Scheme 1). This could be explained by attack of the reagent from the less hindered α-side. An analogous stereochemical result was obtained upon oxidation by this reagent of other labdanoids, in particular (+)-coronarin E [9].



1, 2 **3, 4** **5**

1, 3: R = H; **2, 4:** R = CH_3

Scheme 1

*For No. XXVI, see Ref. [1].

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TABLE 1. Parameters of H-Bonds for the Crystal Solvate of **3**

X–H…Y bond	H…X, Å	X...Y, Å	X-H...Y, °
O(1R)-H(1R)...O(4)	2.02	2.806 (2)	161
O(2)-H(2)...O(1R)	1.92	2.732 (2)	168
O(3)-H(3)...O(2)	1.86	2.662 (2)	164

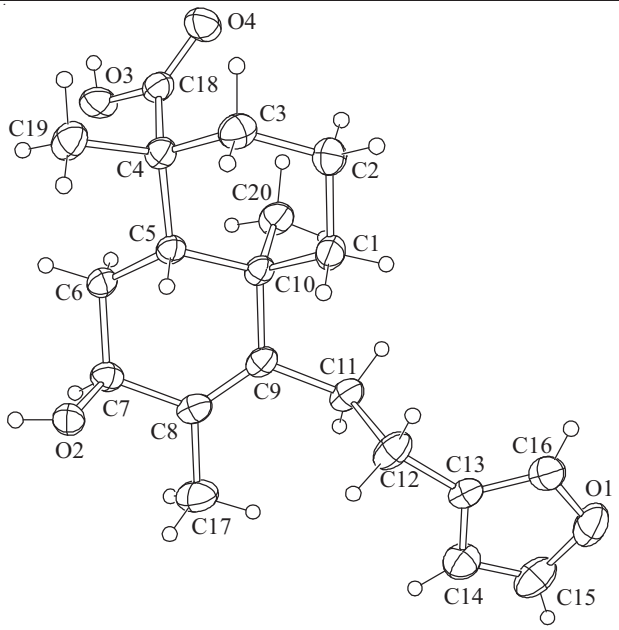


Fig. 1. Molecular structure of **3** from an XSA. The EtOH solvate molecule is not shown.

The structure of **3** was established by an x-ray crystal structure analysis (XSA) (Fig. 1). The unit cell contained one molecule of **3** and one EtOH molecule. The bond lengths and angles were similar within 3σ of the mean-statistical values [12]. The cyclohexane ring had the chair conformation; the cyclohexene moiety, a half-chair conformation. The furan ring was practically planar (mean-statistical deviation of atoms from the plane, 0.005 Å). Molecules of **3** in the crystal were linked through H-bonds with EtOH solvate molecules and to each other into infinite 3D-frameworks (Table 1). The presence of H...π interactions (distance from H to the furan-ring centroids H19B…Cg, 2.67 Å; H15…Cg, 2.92 Å) was also noteworthy. A structure with a similar framework and an analogous configuration of the substituents, hispanolane 1,7,7′-borate (**5**) [14], was found in the Cambridge Crystallographic Structure Database (CCSD) [13].

Oxidation of **3** and **4** by active manganese dioxide in CH_2Cl_2 gave the corresponding unsaturated ketones **6** and **7** (49 and 69% yields, respectively) (Scheme 2). We studied the possibility of transforming the labdanoid ketones into benzoazepine derivatives. Reaction of **6** or **7** with hydroxylamine hydrochloride in MeOH in the presence of NaOAc produced pure (*E*)-oximes **8** and **9** (89 and 98% yields, respectively). Treatment of ketooxime **8** with thionylchloride in anhydrous dioxane formed a mixture of isomeric lactams, derivatives of ocahydro-1*H*-benzo[*d*]azepine (**10**) and octahydro-1*H*-benzo[*c*]azepine (**11**) in 30 and 8% yields, respectively. Beckmann rearrangement of oxime **9** under the described conditions gave derivative **12** in 20% yield. The formation of **10** and **11** upon rearrangement of (*E*)-oxime **8** was obviously related to partial isomerization of **8** into the corresponding (*Z*)-oxime under the reaction conditions, which rearranged to form octahydro-1*H*-benzo[*c*]azepine **11**. The formation of **12** upon rearrangement of the (*E*)-oxime of methyl ester **9** indicated that it isomerized readily into the (*Z*)-oxime upon treatment with $SOCl_2$ in dioxane and rearranged subsequently. An attempt to perform the Beckmann rearrangement of the sulfonate of (*E*)-oxime **13** in acetic acid saturated with HCl was unsuccessful. Only starting **13** was isolated. An attempt to perform the reaction in trifluoroacetic acid afforded the corresponding (*E*)-oxime **9**.

The structure of **12** was established by an XSA. Two molecules of **12** and an EtOH solvate molecule were located in the independent unit part of the crystallographic cell. Figure 2 shows the molecular structure of **12**. The second molecule is highly disordered. The six-membered ring had the chair conformation with axial carboxymethyl and C-5a methyls. The conformation of seven-membered ring B in the disordered molecule was close to a boat with atoms N(22), C-29a, and C-21 deviating from the plane of the double bond by 0.910(7), 1.399(7), and 1.907(6) Å, respectively. A similar conformation of a seven-membered ring was noted in (4a*S*,6*S*,9a*S*)-6-methoxy-9-vinyl-1,2,3,4,4a,6,7,9a-octahydro-5*H*-benzo(7)annulen-5-one [15].

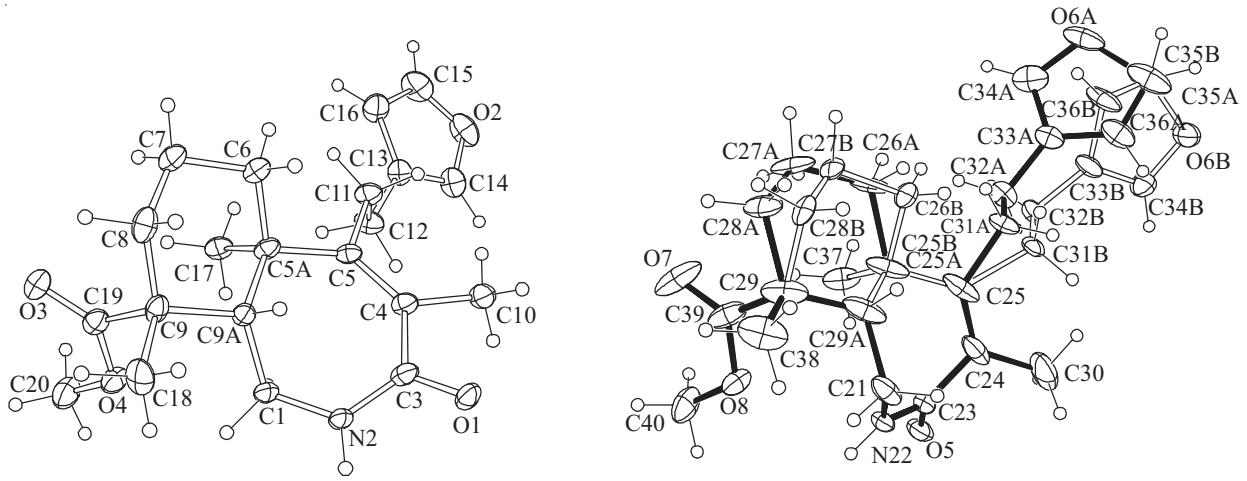
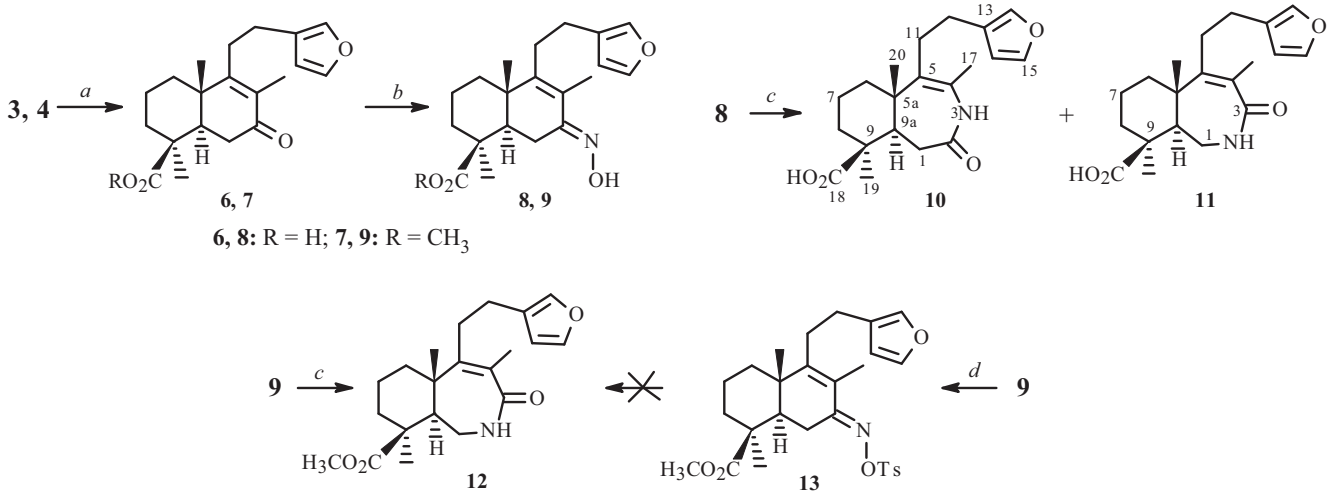


Fig. 2. General view of the crystallographically independent molecules of **12**. The EtOH solvate molecule is not shown.

The conformation of ring B in the ordered molecule of **12** was distorted, i.e., atom C-9a also lay in the plane of the double bond. The deviations of N(2) and C-1 from the plane of the double bond were 0.686(5) and 1.158(5) Å. The two independent molecules in the crystal formed pairs through two H-bonds N(2)–H…O(5) and N(22)–H…O(1) with parameters H…O 2.08 and 2.10, N…O 2.947(4) and 2.819(4) Å and N–H…O 169 and 138°. The EtOH solvate molecule was also bonded to these pairs through an H-bond O1…O1W 2.722(5) Å .



a. MnO_2; *b*. $NH_2OH{\cdot}HCl$, AcONa; *c*. $SOCl_2$; *d*. TsCl, Py, DMAP

Scheme 2

The compositions and structures of the prepared compounds were confirmed by elemental analysis and mass, IR, UV and NMR spectra. The axial orientation of the C-7 hydroxyl in **3** and **4** was confirmed by PMR spectra. Proton H-7 resonated as a doublet with spin–spin coupling constant 2.2–2.3 Hz with the H-6a proton. Oximes **8** and **9** were formed as pure geometric isomers. The C-6 protons in PMR spectra of **8** and **9** were shifted to weak field (δ 2.77 and 3.46 ppm for **8**) compared with the location of the corresponding protons in the spectra of ketones **6** and **7** (δ 2.74 and 2.96 ppm for **6**). A comparison of the chemical shifts in ^{13}C NMR spectra of resonances for C-6 and C-8 and the corresponding starting carbonyl compounds showed a significant strong-field shift for C-6 in **8** and **9** (Δδ = 14.3–15.3 ppm) (the change of shift for C-8 was about Δδ 5.7 ppm). These results confirmed that the oxime had the (*E*)-configuration [16].

PMR and ^{13}C NMR spectra of furan-substituted octahydro-1*H*-benzo[*d*]azepine **10** had characteristic differences that enabled the structure to be unambiguously determined. The magnetically non-equivalent C-1 protons were situated at stronger field than the corresponding protons in spectra of **11** and **12**. Atom C-1 in the ^{13}C NMR spectrum of **10** also had a characteristic strong-field shift (δ 28.82 ppm) compared with the locations of the C-1 resonances in **11** and **12** (δ 36.36 and 36.68 ppm). Atoms C-4, C-5a, C-9a, and C-17 experienced analogous strong-field shifts. The singlet for C-5 was shifted to weaker field δ 158.20 ppm than the corresponding C atom in isomers **11** and **12**.

Thus, methods for preparing 7-hydroxy- and 7-ketolabdanoids were developed based on the available labdanoid phlomisoic acid. The regioselectivity of the Beckmann rearrangement depended on the substituents in the bicyclic fragment of the corresponding 7-ketooxime.

EXPERIMENTAL

NMR spectra were taken from $CDCl_3$ solutions on Bruker AV-300 (operating frequency 300.13 for ^1H and 75.47 MHz for ^{13}C) and AV-600 (operating frequency 600.30 for ^1H and 150.96 MHz for ^{13}C) instruments. Resonances in NMR spectra were assigned using various types of H–H and C–H shift correlation spectroscopy (COSY, COXH, COLOC). Multiplicities of resonances in ^{13}C NMR spectra were determined by standard methods of recording spectra with J-modulation (JMOD). The atomic numbering of the diterpene framework given for the structures of **1**, **2** (for **3–9**), and **10** (for **10–12**) was used to describe the PMR and ^{13}C NMR spectra of the new diterpenoid derivatives.

Mass spectra were obtained in a DFS Thermo Scientific high-resolution mass spectrometer (ionizing electron energy 70 eV, vaporizer temperature 230–280°C). Specific rotation $[\alpha]_D^{20}$ was measured at room temperature (20–23°C) in $CHCl_3$ solution on a PoLAAr3005 polarimeter. IR spectra were recorded in KBr pellets on a Vector-22 instrument. UV absorption spectra were recorded in EtOH (*c* 10^{-4} M) on an HP 8453 UV–Vis spectrometer. The XSA was performed on a Kappa Apex II (Bruker) diffractometer with a two-coordinate CCD detector at room temperature (Mo Kα-radiation, graphite monochromator, ω–φ-scanning in the limit $2\theta = 54.4°$).

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using $CHCl_3$:EtOH (10:1) and petroleum ether:EtOAc (10:1). Spots were detected by spraying plates with aqueous H_2SO_4 (10%) with subsequent heating to 100°C or by illumination in UV light. Phlomisoic acid (**1**) was prepared from lambertianic acid according to the literature method [11]; the methyl ester of **1** (**2**), as before [10].

(1*S*,4a*S*,7*R*,8a*R*)-7-Hydroxy-1,4a,6-trimethyl-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylic Acid [7*R*-Hydroxy-15,16-epoxy-8(9),13(16),14-labdatrien-18-oic Acid] (3). A solution of **1** (1.00 g, 3.16 mmol) in dioxane under a stream of Ar was treated with SeO_2 (0.42 g, 3.79 mmol), stirred for 13 h, diluted with H_2O (50 mL), and extracted with $CHCl_3$ (3 × 50 mL). The organic layer was washed with H_2O (3 × 50 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was chromatographed over silica gel ($CHCl_3$ eluent). Crystallization from Et_2O afforded **3** (0.62 g, 59%) as a white solid, mp 103–105°C, $[\alpha]_D^{20}$ +94.4° (*c* 1.1). IR spectrum (ν, cm^{-1}): 3412, 2935, 2609, 1692, 1650, 1503, 1469, 1445, 1256, 1209, 1026, 874, 780, 600.

PMR spectrum (δ, ppm, J/Hz): 0.84 (3H, s, H_3-20), 1.06 (1H, dt, J = 13.3, 4.1, H-3), 1.24 (1H, m, H-1), 1.26 (3H, s, H_3-19), 1.52 (1H, dm, J = 13.0, 2.9, H-2), 1.73 (1H, dd, J = 11.7, 1.8, H-5), 1.75 (3H, s, H_3-17), 1.84, 1.87 (2H, m, H-1, 2), 1.91 (1H, m, H-6), 1.97 (1H, m, H-11), 2.16–2.77 (3H, m, H-3, 6, 11), 2.47 (2H, m, H-12), 3.47 (1H, m, OH), 3.50 (1H, d, J = 2.3, H-7), 3.72 (1H, m, OH), 6.27 (1H, dd, J = 1.8, 0.9, H-14), 7.21 (1H, dd, J = 1.4, 0.9, H-16), 7.33 (1H, dd, J = 1.8, 1.4, H-15).

^{13}C NMR spectrum (δ, ppm): 16.18 (q, C-20), 17.64 (q, C-17), 19.24 (t, C-2), 24.97 (t, C-12), 25.63 (t, C-6), 28.30 (q, C-19), 28.82 (t, C-11), 36.38 (t, C-3), 37.04 (t, C-1), 40.21 (s, C-10), 43.26 (s, C-4), 46.71 (d, C-5), 70.30 (d, C-7), 110.60 (d, C-14), 125.07 (s, C-13), 127.96 (s, C-8), 138.32 (d, C-16), 142.68 (d, C-15), 144.11 (s, C-9), 183.78 (s, C-18).

Mass spectrum (*m/z*, I_{rel}, %): 314 (14), 253 (14), 250 (33), 237 (24), 233 (48), 232 (23), 217 (16), 191 (21), 188 (12), 187 (79), 174 (17), 173 (100), 159 (32), 145 (39), 135 (27), 133 (31), 119 (49), 105 (36), 95 (44), 91 (44), 81 (80), 67 (27), 53 (32), 42 (27), 41 (40), 28 (30). $C_{20}H_{28}O_4$. [M] 332.1980.

(1*S*,4a*S*,7*R*,8a*R*)-Methyl-7-hydroxy-1,4a,6-trimethyl-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylate (4). A solution of **2** (1.00 g, 3.03 mmol) in dioxane under a stream of Ar was treated with SeO_2 (0.40 g, 3.63 mmol), stirred for 13 h, diluted with H_2O (50 mL), and extracted with $CHCl_3$ (3 × 50 mL). The organic layer was washed with H_2O (3 × 50 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was chromatographed over silica gel (petroleum ether:Et_2O eluent, 4:1) to afford **4** (0.76 g, 74%) as an oil, $[\alpha]_D^{20}$ +124.48° (*c* 2.1). IR spectrum (ν, cm^{-1}): 3391, 2948, 2873, 1724, 1651, 1501, 1466, 1443, 1380, 1234, 1198, 1161, 1143, 1054, 1026, 991, 874, 779, 756, 600.

PMR spectrum (δ, ppm, J/Hz): 0.71 (3H, s, H_3-20), 1.04 (1H, td, J = 13.5, 4.4, H-3), 1.20 (3H, s, H_3-19), 1.22 (1H, m, H-1), 1.53 (1H, dm, J = 13.9, H-2), 1.62 (1H, dd, J = 13.0, 2.2, H-5), 1.77 (3H, s, H_3-17), 1.82–1.91 (2H, m, H-1, 2), 1.95 (1H, dt, J = 14.4, 4.2, H-6), 2.05 (1H, td, J = 14.4, 2.0, H-6), 2.12 (1H, m, H-11), 2.22 (2H, m, H-3, 11), 2.43 (2H, m, H-12), 3.60 (3H, s, OCH_3), 3.93 (1H, d, J = 2.2, H-7), 6.26 (1H, dd, J = 1.6, 1.0, H-14), 7.20 (1H, dd, J = 1.0, 0.8, H-16), 7.32 (1H, dd, J = 1.6, 0.8, H-15).

^{13}C NMR spectrum (δ, ppm): 15.99 (q, C-20), 17.67 (q, C-17), 19.33 (t, C-2), 25.01 (t, C-12), 28.13 (q, C-19), 28.84 (t, C-11), 30.14 (t, C-6), 36.46 (t, C-3), 37.38 (t, C-1), 40.03 (s, C-10), 43.37 (s, C-4), 46.73 (d, C-5), 51.13 (q, OCH_3), 70.16 (d, C-7), 110.61 (d, C-14), 125.10 (s, C-13), 128.16 (s, C-8), 138.32 (d, C-16), 142.66 (d, C-15), 143.93 (s, C-9), 177.88 (s, C-18).

Mass spectrum (*m/z*, I_{rel}, %): 346 (6), 328 (18), 369 (18), 265 (21), 264 (100), 253 (17), 251 (47), 191 (96), 189 (19), 187 (31), 173 (45), 149 (17), 145 (17), 135 (72), 133 (19), 123 (27), 121 (19), 119 (21), 109 (25), 108 (18), 107 (23), 105 (26), 85 (19), 83 (29), 81 (79), 79 (22), 67 (26), 57 (18), 55 (24), 53 (30), 43 (22), 41 (32). $C_{21}H_{30}O_4$. [M] 346.2136.

(1*S*,4a*S*,8a*R*)-1,4a,6-Trimethyl-7-oxo-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylic Acid [7-Oxo-15,16-epoxy-8(9),13(16),14-labdatrien-18-oic Acid] (6). A solution of **3** (1.00 g, 3.01 mmol) in CH_2Cl_2 was stirred vigorously, treated with freshly prepared MnO_2 (6.54 g, 75.20 mmol), and stirred for 24 h at room temperature. The precipitate was filtered off and washed with CH_2Cl_2. The solvent was evaporated in vacuo. The solid was chromatographed over silica gel ($CHCl_3$ eluent). Ketone **6** (0.49 g, 49%) and starting **3** (0.50 g) eluted successively.

Compound 6: $[\alpha]_D^{20}$ +119.36° (*c* 2.52). UV spectrum (λ_{max}, nm, log ε): 248 (3.89). IR spectrum (ν, cm^{-1}): 3145, 2939, 2631, 1722, 1694, 1661, 1606, 1501, 1469, 1379, 1346, 1261, 1160, 1025, 874, 756, 600.

PMR spectrum (δ, ppm, J/Hz): 1.01 (3H, s, H_3-20), 1.08 (1H, dt, J = 13.6, 4.3, H-3), 1.24 (3H, s, H_3-19), 1.38 (1H, dt, J = 13.1, 3.6, H-1), 1.61 (1H, td, J = 14.1, 2.8, H-2), 1.79 (3H, s, H_3-17), 1.90 (1H, dd, J = 15.0, 3.2, H-5), 1.93 (1H, td, J = 14.1, 3.2, H-2), 1.99 (1H, dm, J = 12.6, H-1), 2.23 (1H, dm, J = 13.2, H-3), 2.38–2.45 (2H, m, H-11), 2.52 (2H, m, H-12), 2.74 (1H, dd, J = 17.6, 3.2, H-6), 2.96 (1H, dd, J = 17.6, 15.0, H-6), 6.28 (1H, d, J = 1.6, H-14), 7.24 (1H, d, J = 1.0, H-16), 7.34 (1H, dd, J = 1.0, 1.6, H-15).

^{13}C NMR spectrum (δ, ppm): 11.10 (q, C-20), 15.48 (q, C-17), 18.61 (t, C-2), 23.71 (t, C-12), 27.48 (q, C-19), 30.06 (t, C-11), 35.50 (t, C-3), 35.98 (t, C-6), 36.54 (t, C-1), 41.04 (s, C-10), 43.03 (s, C-4), 50.23 (d, C-5), 110.08 (d, C-14), 123.91 (s, C-13), 130.36 (s, C-8), 138.16 (d, C-16), 142.60 (d, C-15), 165.19 (s, C-9), 182.25 (s, C-18), 199.81 (s, C-7).

$C_{20}H_{26}O_4$. [M] 330.1823.

(1*S*,4a*S*,8a*R*)-Methyl 1,4a,6-trimethyl-7-oxo-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylate (7). A solution of **4** (1.00 g, 2.89 mmol) in CH_2Cl_2 was stirred vigorously, treated with active MnO_2 (6.54 g, 75.20 mmol), and stirred for 24 h. The solid was filtered off and washed with CH_2Cl_2. The solvent was evaporated in vacuo. The solid was chromatographed over silica gel (petroleum ether:Et_2O eluent, 4:1) to afford **7** (0.69 g, 69%), $[\alpha]_D^{20}$ +127.45° (*c* 1.96). UV spectrum (λ_{max}, nm, log ε): 203 (4.01), 246 (4.02). IR spectrum (ν, cm^{-1}): 3424, 2958, 2939, 2860, 1722, 1659, 1608, 1462, 1380, 1332, 1234, 1191, 1163, 1139, 1086, 1026, 870, 791.

PMR spectrum (δ, ppm, J/Hz): 0.83 (3H, s, H_3-20), 0.99t (1H, m, J_{gem} = 13.5, H-3), 1.09 (3H, s, H_3-19), 1.30 (1H, m, H-1), 1.53 (1H, dm, J = 14.4, H-2), 1.71 (3H, s, H_3-17), 1.80 (1H, dd, J = 15.0, 3.2, H-5), 1.81 (1H, m, H-2), 1.91 (1H, m, H-1), 2.16 (1H, m, H-3), 2.30–2.40 (2H, m, H-11), 2.43–2.45 (2H, m, H-12), 2.64 (1H, dd, J = 17.4, 3.2, H-6), 2.92 (1H, dd, J = 17.6, 15.0, H-6), 3.56 (3H, s, OCH_3), 6.21 (1H, d, J = 1.6, H-14), 7.22 (1H, d, J = 0.8, H-16), 7.30 (1H, dd, J = 1.6, 0.8, H-15).

^{13}C NMR spectrum (δ, ppm): 11.35 (q, C-20), 15.52 (q, C-17), 18.95 (t, C-2), 24.01 (t, C-12), 27.54 (q, C-19), 30.30 (t, C-11), 35.81 (t, C-3), 36.46 (t, C-6), 37.13 (t, C-1), 41.12 (s, C-10), 43.39 (s, C-4), 50.55 (d, C-5), 51.29 (q, OCH_3), 110.39 (d, C-14), 124.23 (s, C-13), 130.35 (s, C-8), 138.42 (d, C-16), 142.82 (d, C-15), 164.85 (s, C-9), 176.81 (s, C-18), 199.38 (s, C-7).

Mass spectrum (*m/z*, I_{rel}, %): 344 (13), 286 (39), 326 (15), 251 (10), 250 (18), 190 (12), 189 (75), 177 (15), 176 (51), 161 (11), 149 (10), 135 (25), 105 (11), 110 (10), 95 (11), 91 (13), 82 (15), 81 (100), 53 (14), 41 (13), 28 (17), 18 (38). $C_{21}H_{28}O_4$. [M] 344.1986.

(1*S*,4a*S*,8a*R*,*E*)-7-Hydroxyimino-1,4a,6-trimethyl-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylic Acid (8). A solution of **6** (1.00 g, 3.03 mmol) in MeOH (20 mL) was treated with hydroxylamine hydrochloride (0.38 g, 5.45 mmol) and NaOAc (1.37 g, 16.67 mmol), stirred for 5 h at room temperature, and left overnight. The solvent was evaporated. The solid was treated with H_2O (40 mL) and extracted with $CHCl_3$ (3 × 30 mL). The organic layer was washed with H_2O (3 × 30 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was chromatographed over silica gel ($CHCl_3$ eluent). Trituration of fractions containing the product in petroleum ether afforded **8** (0.93 g, 89%) as a white powder, mp 154–156°C, $[\alpha]_D^{20}$ +166.25° (*c* 2.08). UV spectrum (λ_{max}, nm, log ε): 243 (3.97). IR spectrum (ν, cm^{-1}): 3266, 2938, 2553, 1773, 1693, 1619, 1501, 1466, 1381, 1355, 1331, 1186, 1165, 1144, 1062, 1025, 978, 943, 909, 874, 811, 780, 751.

PMR spectrum (δ, ppm, J/Hz): 0.94 (3H, s, H_3-20), 1.07 (1H, m, H-3), 1.28 (3H, s, H_3-19), 1.32 (1H, m, H-1), 1.62 (1H, dd, J = 14.6, 2.8, H-5), 1.81 (1H, m, H-2), 1.84 (3H, s, H_3-17), 1.93 (1H, m, H-2), 2.00 (1H, m, H-1), 2.26 (1H, m, H-3), 2.34 (1H, m, H-1), 2.45–2.52 (4H, m, H-11, 12), 2.77 (1H, dd, J = 17.6, 14.6, H-6), 3.46 (1H, dd, J = 17.6, 2.8, H-6), 6.30 (1H, dd, J = 1.6, 0.8, H-14), 7.28 (1H, d, J = 0.8, H-16), 7.35 (1H, dd, J = 1.6, 0.8, H-15).

^{13}C NMR spectrum (δ, ppm): 13.32 (q, C-20), 16.68 (q, C-17), 19.33 (t, C-2), 21.68 (t, C-6), 25.17 (t, C-12), 28.21 (q, C-19), 29.66 (t, C-11), 36.31 (t, C-3), 37.48 (t, C-1), 40.27 (s, C-10), 43.66 (s, C-4), 49.67 (d, C-5), 110.55 (d, C-14), 124.12 (s, C-13), 124.57 (s, C-8), 138.45 (d, C-16), 142.82 (d, C-15), 153.54 (s, C-9), 158.17 (s, C-7), 182.84 (s, C-18).

Mass spectrum (*m*/*z*, I_{rel}, %): 345 (14), 328 (26), 315 (20), 314 (44), 264 (45), 251 (39), 250 (96), 248 (19), 234 (23), 233 (57), 232 (76), 188 (24), 187 (62), 186 (37), 175 (28), 174 (21), 173 (73), 171 (23), 159 (31), 145 (38), 133 (27), 131 (22), 119 (40), 107 (24), 105 (35), 96 (23), 95 (48), 93 (23), 91 (40), 81 (100), 79 (22), 77 (24), 67 (25), 55 (21), 53 (34). $C_{20}H_{27}O_4N$. [M] 345.1940.

(1*S*,4a*S*,8a*R*,*E*)-Methyl 7-Hydroxyimino-1,4a,6-trimethyl-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylate (9). A solution of **7** (1.00 g, 2.90 mmol) in MeOH (20 mL) was treated with hydroxylamine hydrochloride (0.24 g, 3.48 mmol) and NaOAc (1.31 g, 15.96 mmol), stirred for 5 h at room temperature, and left overnight. The solvent was evaporated. The solid was treated with H_2O (40 mL) and extracted with $CHCl_3$ (3 × 30 mL). The organic layer was washed with H_2O (3 × 30 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was chromatographed over silica gel (petroleum ether:Et_2O eluent, 4:1). Crystallization from petroleum ether afforded **9** (1.02 g, 98%) as a white powder, mp 131–133°C, $[\alpha]_D^{20}$ +134.50° (*c* 0.8). UV spectrum (λ_{max}, nm, log ε): 201 (4.1), 243 (4.25). IR spectrum (ν, cm^{-1}): 3248, 2943, 2854, 1724, 1626, 1502, 1462, 1439, 1379, 1356, 1236, 1196, 1143, 1026, 962, 904, 872, 779.

PMR spectrum (δ, ppm, J/Hz): 0.81 (3H, s, H_3-20), 1.04 (1H, dt, J = 13.5, 3.8, H-3), 1.25 (3H, s, H_3-19), 1.33 (1H, dt, J = 13.4, 3.5, H-1), 1.58 (2H, m, H-2, 5), 1.87 (3H, s, H_3-17), 1.92 (1H, m, H-2), 2.97 (1H, m, H-1), 2.23 (1H, m, H-3), 2.30 (1H, m, H-11), 2.41 (1H, m, H-11), 2.47–2.53 (2H, m, H-12), 2.69 (1H, dd, J = 17.7, 14.5, H-6), 3.43 (1H, dd, J = 17.7, 3.5, H-6), 3.65 (3H, s, OCH_3), 6.28 (1H, dd, J = 1.4, 0.9, H-14), 7.23 (1H, d, J = 0.9, H-16), 7.34 (1H, d, J = 1.4, 0.9, H-15).

^{13}C NMR spectrum (δ, ppm): 13.09 (q, C-20), 16.29 (q, C-17), 19.28 (t, C-2), 21.18 (t, C-6), 25.17 (t, C-12), 27.92 (q, C-19), 29.57 (t, C-11), 36.36 (t, C-3), 37.72 (t, C-1), 40.00 (s, C-10), 43.88 (s, C-4), 49.76 (d, C-5), 51.32 (q, OCH_3), 110.56 (d, C-14), 124.53* (s, C-13), 124.67* (s, C-8), 138.43 (d, C-16), 142.80 (d, C-15), 152.06 (s, C-9), 157.97 (s, C-7), 177.36 (s, C-18).

Mass spectrum (*m*/*z*, I_{rel}, %): 359 (7), 342 (19), 278 (26), 265 (36), 264 (100), 246 (35), 218 (43), 204 (18), 200 (14), 188 (10), 187 (11), 186 (52), 159 (12), 158 (11), 146 (13), 145 (11), 144 (14), 136 (11), 132 (10), 119 (10), 107 (14), 105 (16), 91 (21), 81 (73), 79 (14), 77 (14), 67 (11), 55 (13), 53 (38), 41 (22), 27 (11). $C_{21}H_{29}NO_4$. [M] 359.2087.

Beckmann Rearrangement of Oxime 8. A solution of **8** (0.50 g, 1.45 mmol) in anhydrous dioxane (20 mL) at 0°C was treated dropwise with freshly distilled $SOCl_2$ (2 mL), stirred for 10 min at 0°C and 1 h at room temperature, diluted with H_2O (30 mL), and extracted with $CHCl_3$ (3 × 40 mL). The organic layer was washed with H_2O (3 × 40 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was chromatographed over a column of silica gel ($CHCl_3$ eluent). Compounds **10** (0.15 g, 30%) and **11** (0.04 g, 8%) eluted successively. Crystallization of fraction 1 from petroleum ether isolated **(5a*S*,9*S*,9a*R*)-9-carboxy-4,5a,9-trimethyl-5-[2-(furan-3-yl)ethyl]-2-oxo-2,3,5a,6,7,8,9,9a-octahydro-1*H*-benzo[*d*]azepine (10)** as a white powder, mp 202–205°C. UV spectrum (λ_{max}, nm, log ε): 220 (3.91). IR spectrum (ν, cm^{-1}): 3433, 2959, 2938, 2858, 1693, 1614, 1468, 1443, 1221, 1165, 1146, 873, 819, 779, 721, 674.

PMR spectrum (δ, ppm, J/Hz): 0.81 (3H, s, H_3-19), 1.13 (1H, dt, J = 13.5, 4.1, H-8), 1.39 (3H, s, H_3-20), 1.48 (1H, dt, J = 13.5, 2.9, H-6), 1.63 (1H, m, H-7), 1.66 (1H, dd, J = 12.4, 3.2, H-9a), 1.99 (3H, s, H_3-17), 1.98 (1H, m, H-6), 2.17 (1H, td, J = 13.5, 2.7, H-7), 2.32 (1H, m, H-8), 2.42–2.54 (4H, m, H-11, 12), 3.18 (1H, dd, J = 16.8, 3.2, H-1), 3.53 (1H, dd, J = 16.8, 12.4, H-1), 6.27 (1H, d, J = 1.6, H-14), 7.23 (1H, d, J = 0.8, H-16), 7.34 (1H, dd, J = 1.6, 0.8, H-15).

^{13}C NMR spectrum (δ, ppm): 13.66 (q, C-17), 18.46 (q, C-20), 19.15 (t, C-7), 24.63 (t, C-12), 27.96 (q, C-19), 28.82 (t, C-1), 29.65 (t, C-11), 35.69 (t, C-6), 37.62 (t, C-8), 39.42 (s, C-5a), 44.93 (s, C-9), 46.85 (d, C-9a), 110.47 (d, C-14), 124.24* (s, C-13), 124.30* (s, C-4), 138.50 (d, C-16), 142.85 (d, C-15), 158.20 (s, C-5), 165.20 (s, C-2), 172.66 (s, C-18).

$C_{20}H_{27}NO_4$. [M] 345.1931.

(5a*S*,9*S*,9a*R*)-9-Carboxy-4,5a,9-trimethyl-5-[2-(furan-3-yl)ethyl]-3-oxo-2,3,5a,6,7,8,9,9a-octahydro-1*H*-benzo[*c*]azepine (11), oil. UV spectrum (λ_{max}, nm, log ε): 220 (3.90). IR spectrum (ν, cm^{-1}): 3432, 2954, 2938, 2861, 1724, 1649, 1468, 1458, 1227, 1169, 1149, 734, 673.

PMR spectrum (δ, ppm, J/Hz): 0.94 (1H, m, H-8), 1.24 (3H, s, H_3-19), 1.27 (3H, s, H_3-20), 1.37 (1H, m, H-6), 1.62–1.74 (2H, m, H-7, 9a), 1.91 (3H, s, H_3-17), 1.90–2.08 (2H, m, H-6, 7), 2.24 (1H, m, H-8), 2.40–2.55 (4H, m, H-11, 12), 3.48 (1H, m, H-1), 3.94 (1H, dd, J = 14.7, 4.6, H-1), 6.31 (1H, d, J = 1.5, H-14), 7.27 (1H, d, J = 0.8, H-16), 7.38 (1H, dd, J = 1.5, 0.8, H-15).

^{13}C NMR spectrum (δ, ppm): 15.57 (q, C-17), 19.81 (t, C-7), 21.93 (q, C-20), 25.28 (t, C-12), 30.17 (t, C-11), 30.22 (q, C-19), 36.36 (t, C-1), 39.16 (t, C-6), 40.39 (t, C-8), 42.32 (s, C-5a), 43.90 (s, C-9), 58.78 (d, C-9a), 110.74 (d, C-14), 124.43 (s, C-13), 127.87 (s, C-4), 138.71 (d, C-16), 143.05 (d, C-15), 152.17 (s, C-5), 177.87 (s, C-3), 182.28 (s, C-18).

$C_{20}H_{27}NO_4$. [M] 345.1937.

Beckmann Rearrangement of Oxime 9. A solution of **9** (0.50 g, 1.39 mmol) in anhydrous dioxane (20 mL) at 0°C was treated dropwise with freshly distilled $SOCl_2$ (2 mL), stirred for 9 h at room temperature, diluted with H_2O (30 mL), and extracted with $CHCl_3$ (3 × 40 mL). The organic layer was washed with H_2O (3 × 40 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was chromatographed over a column of silica gel (petroleum ether:Et_2O eluent) to afford **(5a*S*,9*S*,9a*R*)-9-methoxycarbonyl-4,5a,9-trimethyl-5-[2-(furan-3-yl)ethyl]-3-oxo-2,3,5a,6,7,8,9,9a-octahydro-1*H*-benzo[*c*]azepine (12)** as an oil (0.10 g, 20%). UV spectrum (λ_{max}, nm, log ε): 220 (3.86). IR spectrum (ν, cm^{-1}): 3421, 3290, 2890, 2945, 1755, 1724, 1649, 1468, 1382, 1363, 1232, 1203, 1153, 754.

PMR spectrum (δ, ppm, J/Hz): 0.95 (1H, dt, J = 13.5, 4.1, H-8), 1.08 (3H, s, H_3-19), 1.21 (3H, s, H_3-20), 1.53 (2H, m, H-6, 9a), 1.62 (1H, m, H-7), 1.72 (1H, m, H-6), 1.72 (1H, td, J = 13.2, 3.8, H-7), 1.94 (3H, s, H_3-17), 2.20 (1H, m, H-8), 2.35–2.48 (4H, m, H-11, 12), 3.46 (1H, dd, J = 12.7, 4.2, H-1), 3.64 (3H, s, OCH_3), 3.62 (1H, m, H-1), 6.26 (1H, d, J = 1.8, H-14), 6.47 (1H, br.s, NH), 7.21 (1H, d, J = 0.8, H-16), 7.32 (1H, dd, J = 1.8, 0.8, H-15).

^{13}C NMR spectrum (δ, ppm): 16.83 (q, C-17), 19.39 (t, C-7), 20.88 (q, C-20), 24.95 (t, C-12), 29.03 (q, C-19), 30.60 (t, C-11), 36.68 (t, C-1), 38.54 (t, C-6), 39.96 (t, C-8), 43.40 (s, C-5a), 44.17 (s, C-9), 51.72 (q, OCH_3), 58.18 (d, C-9a), 110.48 (d, C-14), 124.26 (s, C-13), 127.99 (s, C-4), 138.41 (d, C-16), 142.77 (d, C-15), 150.48 (s, C-5), 174.77 (s, C-3), 177.14 (s, C-18).

Mass spectrum (*m*/*z*, I_{rel}, %): 358 (36), 344 (32), 278 (33), 204 (23), 191 (100), 190 (89), 189 (34), 176 (35), 162 (28), 161 (24), 121 (20), 119 (21), 105 (31), 91 (35), 85 (30), 83 (49), 81 (84), 79 (23), 77 (21), 67 (20), 55 (21), 53 (32), 41(29). $C_{21}H_{22}NO_4$. [M] 358.2008.

(1*S*,4a*S*,8a*R*,*E*)-Methyl 1,4a,6-Trimethyl-5-[2-(furan-3-yl)ethyl]-7-[(tosyloxy)-imino]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylate (13). A solution of oxime **8** (1.00 g, 2.78 mmol) in Py (10 mL) was treated with tosyl chloride (2.65 g, 13.91 mmol) and 4-dimethylaminopyridine (0.01 g, 0.08 mmol), stirred for 8 h at room temperature, left overnight, treated with aqueous HCl (50 mL, 10%), and extracted with $CHCl_3$ (3 × 30 mL). The organic layer was washed with H_2O (3 × 30 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The residue afforded **13** (1.43 g, 100%) as an oil

PMR spectrum (δ, ppm, J/ Hz): 0.75 (3H, s, H_3-20), 1.00 (1H, dt, J = 13.4, 4.0, H-3), 1.21 (3H, s, H_3-19), 1.28 (1H, dt, J = 13.2, 4.0, H-1), 1.52 (1H, dd, J = 13.3, 3.2, H-5), 1.56 (1H, m, H-2), 1.76 (3H, s, H_3-17), 1.83 (1H, dt, J = 14.0, 3.5, H-2), 2.93 (1H, dt, J = 12.1, 3.1, H-1), 2.22 (1H, dt, J = 13.7, 3.1, H-3), 2.26–2.37 (2H, m, H-11), 2.41–2.48 (2H, m, H-12), 2.47 (3H, s, CH_3), 2.67 (1H, dd, J = 18.0, 14.5, H-6), 3.29 (1H, dd, J = 18.0, 3.8, H-6), 3.65 (3H, s, OCH_3), 6.26 (1H, dd, J = 1.6, 1.0, H-14), 7.22 (1H, d, J = 1.0, H-16), 7.32 (2H, d, J = 8.6, H-3′, 5′), 7.33 (1H, dd, J = 1.6, 0.8, H-15), 7.39 (2H, d, J = 8.6, H-2′, 6′).

^{13}C NMR spectrum (δ, ppm): 12.74 (q, C-20), 17.02 (q, C-17), 19.06 (t, C-2), 21.51 (q, CH_3), 22.54 (t, C-6), 24.69 (t, C-12), 27.66 (q, C-19), 29.79 (t, C-11), 36.86 (t, C-3), 37.35 (t, C-1), 40.08 (s, C-10), 43.57 (s, C-4), 49.08 (d, C-5), 51.38 (q, OCH_3), 110.51 (d, C-14), 123.32* (s, C-13), 124.36* (s, C-8), 128.88 (d, C-2′, 6′), 129.30 (d, C-3′, 5′), 138.43 (d, C-16), 141.36 (s, C-4′), 142.93 (d, C-15), 146.93 (s, C-1′), 157.63 (s, C-9), 164.30 (s, C-7), 176.73 (s, C-18).

$C_{28}H_{35}NO_6S$. [M] 513.2178.

X-ray Crystal Structure Analysis of 3. We used a crystal of the EtOH solvate (1:1 ratio) of size 0.20 × 0.030 × 0.40 mm. The crystals were orthorhombic, a = 7.7228(3), b = 14.8159(6), c = 18.7926(8) Å, V = 2150.3(2) $Å^3$, space group $P2_12_12_1$, Z = 4, $C_{20}H_{28}O_4 + C_2H_6O$, d_{calcd} = 1.169 g/cm^3, μ = 0.081 mm^{-1}. Intensities of 4755 independent reflections were measured. Absorption corrections were applied using the SADABS program [17], which used multiple measurements of the same reflections at different crystal orientations (transmission 0.59–0.74). The structure was solved by direct methods using the SHELXS-97 program [18]. Structure parameters were refined by anisotropic full-matrix least-squares methods using the SHELXL-97 program. Parameters of H atoms were calculated in each refinement cycle using coordinates of the corresponding non-hydrogen atoms. The final structure refinement was made over all F^2 to wR_2 = 0.1392, S = 1.06, 252 refined parameters

(R = 0.0490 for 3872 F > 4σ). A CIF file containing complete information on the structure was deposited in the CCDC, No. 729044, from where it can be obtained upon request at the internet site www.ccdc.cam.ac.uk/data_request/cif.

X-ray Crystal Structure Analysis of 12. The crystallographic data and parameters of the XSA for **12** are: $2(C_{21}H_{29}NO_4) + C_2H_6O$, MW 764.97, monoclinic system, space group $P2_1$, a = 10.6647(8), b = 11.3857(8), c = 17.6343(14) Å, β = 98.397(3)°, V = 2118.3(3) Å^3, Z = 2, d_{calcd} = 1.199 g/cm^3, μ = 0.083 mm^{-1}, scan range 2θ < 51.3°, 14,238 measured reflections, 6811 independent (R_{int} = 0.0409), 6053 reflections with $I \geq 2\sigma(I)$, 584 refined parameters, R_1 [$I \geq 2\sigma(I)$] = 0.0618, wR_2 = 0.1775 and GOF = 1.024 (over all reflections), absolute structure parameter (Flack) –0.1(14). The second crystallographically independent molecule was disordered. The six-membered ring was disordered in the ratio 0.63(3):0.37(3). The (furan-3-yl)ethyl substituent was disordered in the ratio 0.547(7):0.453(7). The EtOH solvate was also disordered. The occupancy ratio of the CH_2 groups was 0.82(2):0.18(2). The OH hydrogen atom of EtOH could not be located. A CIF file containing complete information on the structure was deposited in the CCDC, No. 832262, from where it can be obtained upon request at the internet site www.ccdc.cam.ac.uk/data_request/cif.

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REFERENCES

1. Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Bioorg. Khim.*, **38**, 127 (2012).
2. D. M. Boalino, S. McLean, W. F. Reynolds, and W. F. Tinto, *J. Nat. Prod.*, **67**, 714 (2004).
3. C. Gitoglu, M. Tanker, B. Sever, J. Englert, R. Anton, and L. Altanlar, *Planta Med.*, **64**, 484 (1998).
4. A. E. de Groot, B. J. M. Jansen, A. A. Verstegen-Haaksma, H. J. Swarts, R. V. A. Orru, G. A. Stork, and J. B. P. A. Wijnberg, *Pure Appl. Chem.*, **66**, 2053 (1994).
5. P. M. Giang, P. T. Son, K. Matsunami, and H. Otsuka, *Chem. Pharm. Bull.*, **53**, 938 (2005).
6. J. Kobayashi, M. Sekiguchi, H. Shigemori, and A. Ohsaki, *J. Nat. Prod.*, **63**, 375 (2000).
7. H. Matsuda, T. Morikawa, Y. Sakamoto, I. Toguchida, and M. Yoshikawa, *Bioorg. Med. Chem.*, **10**, 2527 (2002).
8. W. S. Cheung and H. N. C. Wong, *Tetrahedron*, **55**, 11001 (1999).
9. T. Miyake, K. Uda, M. Kinoshita, M. Fujii, and H. Akita, *Chem. Pharm. Bull.*, **56**, 398 (2008).
10. Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Zh. Org. Khim.*, **45**, 655 (2009).
11. M. E. Mironov, Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, I. Yu. Bagryanskaya, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 194 (2010).
12. Cambridge Crystallographic Data Centre: *Program MOGUL 1.0*.
13. I. J. Bruno, J. C. Cole, P. R. Edgington, M. Kessler, C. F. Macrae, P. McCabe, J. Pearson, and R. Taylor, *Acta Crystallogr. Sect. B: Struct. Sci.*, **58**, 389 (2002).
14. L. Rodriguez-Hahn, J. Cardenas, B. Esquivel, R. A. Toscano, and B. Rodriguez, *Tetrahedron Lett.*, **36**, 6391 (1995).
15. J. S. Clark, S. B. Wells, C. Wilson, S. P. East, and M. J. Drysdale, *Eur. J. Org. Chem.*, 323 (2006).
16. S. E. Denmark, M. S. Dappen, N. L. Sear, and R. T. Jacobs, *J. Am. Chem. Soc.*, **112**, 3466 (1990).
17. G. M. Sheldrick, SADABS, Version 2.01, Bruker AXS Inc., Madison, Wisconsin, USA, 2004.
18. G. M. Sheldrick, SHELXTL, Version 6.10, Bruker AXS Inc., Madison, Wisconsin, USA, 2004.