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SYNTHETIC TRANSFORMATIONS OF HIGHER TERPENOIDS. XXI.* PREPARATION OF PHLOMISOIC ACID AND ITS *N*-CONTAINING DERIVATIVES

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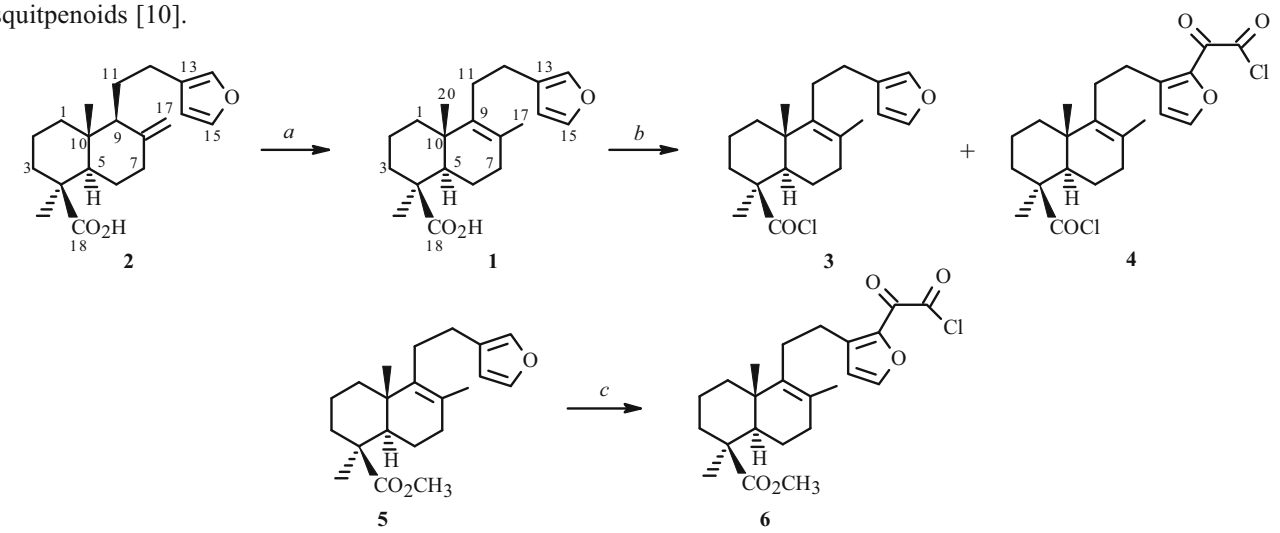
A method for preparing 15,16-epoxylabda-8(9),13(16),14-trien-18-oic (phlomisoic) acid was proposed. Its structure was confirmed by an XSA. N-*containing derivatives of phlomisoic acid that contained amines, hydrazides, and methyl esters of amino acids on the C-18 atom in addition to (2-oxo-2-aminoacetyl)-substituted derivatives of the C-16 methyl ester of phlomisoic acid were prepared.*

Keywords: phlomisoic acid, lambertianic acid, amides, XSA, synthesis.

15,16-Epoxylabda-8(9),13(16),14-trien-18-oic (phlomisoic) acid (**1**) is a product from enzymatic hydrolysis of plant glycosides found in medicinal plants of the family Lamiaceae, *Phlomis* spp. and *Eremostachys* spp. [2–4], and exhibiting a variety of biological activity [2, 3]. An examination of the structure of **1** suggested that it could be prepared from lambertianic acid (**2**), which is produced by Siberian pine *Pinus sibirica* R. Mayr. [5] and was used successfully by us earlier to synthesize pharmacologically valuable agents [6–9]. Herein we report the preparation of phlomisoic acid (**1**) and its amides and 16-acetylamido-substituted derivatives of phlomisoic acid methyl ester for subsequent studies of their pharmacological properties.

We found that **2** treated with *p*-toluenesulfonic acid in boiling benzene isomerized smoothly into **1** (86% yield) (Scheme 1). This regent was used successfully for isomerization of labdane diterpenoids in the total synthesis of drimane sesquitpenoids [10].



2 **1** **3** **4** **5** **6**

a. *p*-TsOH, C_6H_6, Δ; *b*. $(COCl)_2$, CH_2Cl_2, Et_3N, 0°C; *c*. $(COCl)_2$, CH_2Cl_2, Et_3N

Scheme 1

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

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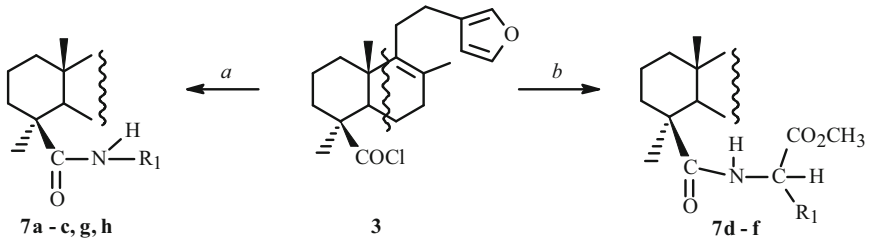
Amides of **1** were synthesized by reaction of phlomisoic acid chloride (**3**) with amines or methyl esters of amino acids. Acid chloride **3** was prepared by reaction of **1** with oxalylchloride under Ar at 0°C. If **1** was reacted with an excess of oxalylchloride (2 equiv.) under these conditions, the product from acylation of the furan ring, 16-(2-chloro-2-oxoacetyl)-15,16-epoxylabda-8(9),13(16),14-trien-18-oic acid chloride (**4**), also formed. The ease with which the acylation occurred was confirmed by studying the action of oxalylchloride on the methyl ester of **1** (**5**) [11] under the reported conditions. The main product from the reaction was methyl 16-(2-chloro-2-oxoacetyl)-15,16-epoxylabda-8(9),13(16),14-trienoate (**6**).

Condensation of **3** with amines (benzylamine, tyramine) and with the methyl esters of alanine, valine, methionine, 9-aminopelargonic acid, and 3-amino-3-phenylpropionic acid (used as the hydrochlorides) produced **7a-g**, which had secondary or tertiary amines on C-18 (Scheme 2). The amines were selected for either their intrinsic activity or structural features that enabled additional pharmacophores to be introduced into the diterpenoid molecule. The reaction was carried out at room temperature in anhydrous CH_2Cl_2 in the presence of triethylamine. The yields were 39–74%. Reaction of **3** with 2-hydrazinyl-2-oxo-*N*-phenylacetamide produced the corresponding hydrazide of phlomisoic acid **7h**. The yields of amides **7a-g** and hydrazide **7h** were calculated for starting **1**, i.e., were in fact total yields from two steps.

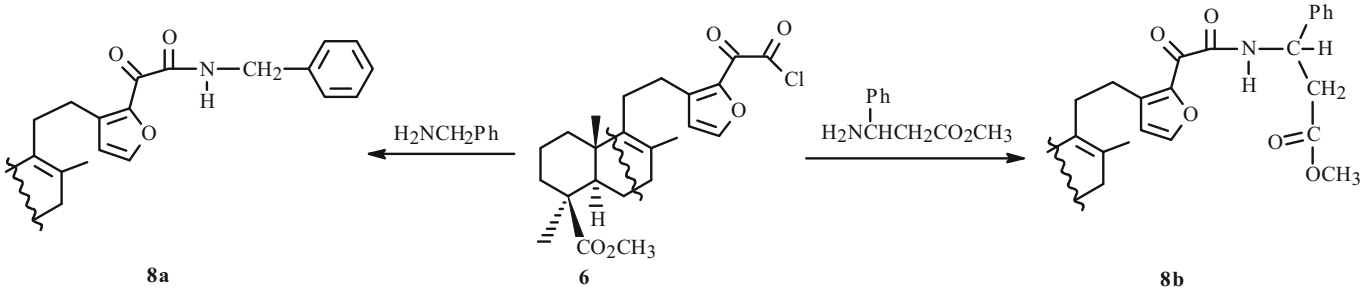


R_1 = CH_2Ph (**7a**); $(CH_2)_2$-C_6H_4-OH (**7b**); $(CH_2)_8CO_2Me$ (**7c**); R_1 = CH_3 (**7d**), $CH(CH_3)_2$ (**7e**) $(CH_2)_2SCH_3$ (**7f**); $CH(Ph)CH_2CO_2Me$ (**7g**); HNCOCONHPh (**7h**)

a. H_2N-R_1; *b*. $[H_3NCHR_1CO_2CH_3]^+Cl^-$

Scheme 2

We showed earlier that introducing aminomethyl and benzylaminomethyl substituents at the C-16 position of furanolabdanoids produced effective neurotropic agents and antioxidants [9, 12, 13]. We used the reaction of **6** with benzylamine or the methyl ester of 3-amino-3-phenylpropionic acid in order to introduce a 2-oxo-2-aminoacetyl substituent into the C-16 position of phlomisoic acid derivatives. Carrying out the condensation in CH_2Cl_2 in the presence of triethylamine produced the corresponding 16-(2-oxo-2-aminoacetyl)-derivatives of the methyl ester of phlomisoic acid **8a** and **b** in 64–67% yields (calculated for **5**) (Scheme 3).



Scheme 3

The structures of the synthesized compounds were elucidated by IR, PMR, and ^{13}C NMR spectroscopy in addition to high-resolution mass spectrometry. The structure of **1** was also confirmed by an x-ray structure analysis (XSA).

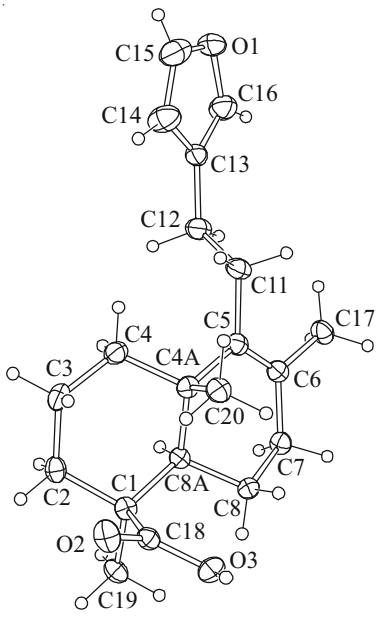


Fig. 1.

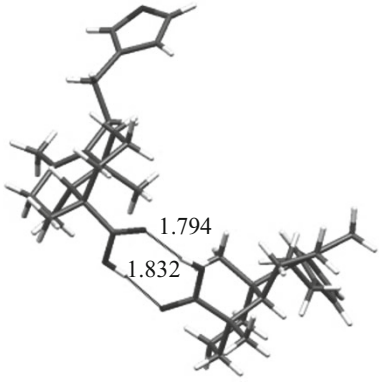


Fig. 2.

Fig.1. Molecular structure of one of the two independent molecules of phlomisoic acid (**1**) in the crystal.
Fig. 2. Molecular packing of phlomisoic acid in the crystal.

The asymmetric unit of **1** contained two molecules, the geometry and molecular structure of which agreed within 3σ. Figure 1 shows the molecular structure of one of them. The furan rings were planar with a mean-square deviation of the atoms from the plane of one molecule of 0.004; of the other, –0.003 Å. The cyclohexane rings had the chair conformation; the cyclohexene ring, a half-chair. The molecules in the crystal formed dimers through strong "forked" H-bonds (Fig. 2). The intermolecular distances O2...H and O2A...H are given in Fig. 2. The distances O2...O3A and O2A...O3 were 2.665(2) and 2.622(2) Å, angles O–H...O 171 and 168°, respectively.

The positions of H atoms in **1** were calculated geometrically and refined using a "rider" model (parameters of H atoms were calculated in each refinement cycle from coordinates of the corresponding C atoms). The final refinement of the structure over all F^2 gave $wR_2 = 0.1180$ and S = 0.97. A total of 415 parameters was refined (R = 0.0443 for 4717 F > 4σ). The Flack parameter for determining the absolute configuration of **1** was –0.88(1.06). However, despite the large uncertainty, refinement of the inverted structure gave a Flack parameter 1.87(1.06), which indirectly confirmed the absolute configuration of **1**.

Chemical shifts of H and C resonances of **1** in PMR and ^{13}C NMR spectra in $CDCl_3$ differed slightly from those reported [2] (spectra taken in C_5D_5N). However, we observed all couplings in two-dimensional spectra obtained in COLOC and NOESY modes that were previously reported [2].

The presence of amides in **7a-h** and **8a** and **b** was confirmed by absorption bands for C=O bonds in IR spectra at 1637–1680 cm^{-1} and broad bands for N–H stretching vibrations at 3238–3451 cm^{-1}. IR spectra of the synthesized acid chlorides **3**, **4**, and **6** had absorption bands at 1788–1805 cm^{-1} that corresponded to stretching vibrations of the COCl carbonyls.

Introducing a COCOCl substituent into the furan ring caused a weak-field shift of H-14 and H-15 in the PMR spectrum of **4** and **6** (for **6**, δ 6.60 and 7.63 ppm, respectively) compared with the position of the corresponding protons in **1** (δ 6.31 and 7.37 ppm, respectively). The ^{13}C NMR spectrum of **6** had two characteristic singlets at 165.01 and 169.60 ppm that corresponded to the oxo-acid chloride and a singlet at 143.80 ppm for C-16, which appeared in **5** as a doublet at 142.67 ppm [11].

Introducing primary amines and esters of amino acids into **1** and **5** produced a set of characteristic resonances in the PMR and ^{13}C NMR spectra that corresponded to the substituent. Resonances of certain protons in PMR spectra of amides **7e**, **f**, and **g** with amino acids were doubled, in particular, resonances for 17-CH_3, 19-CH_3, 20-CH_3, and OCH_3 and NCH groups were doubled. This was related to the use in the reaction of the corresponding amino-acid esters as a mixture of optical isomers (D and L).

Thus, we synthesized phlomisoic acid and prepared its derivatives that are of interest as pharmacologically valuable compounds.

TABLE 1. Chemical Shifts of C Atoms in ^{13}C NMR Spectra of **1**, **6**, **7a**–**h**, **8a**, and **8b** (δ, ppm)

C atom*	**1**	**6**	**7a**	**7b**	**7c**	**7d**
1	36.72 t	36.94 t	37.61 t	37.06 t	37.47 t	37.38 t
2	19.06 t	19.44 t	19.83 t	19.23 t	19.70 t	19.51 t
3	36.92 t	37.54 t	38.02 t	37.39 t	37.89 t	37.78 t
4	43.38 s	43.74 s	43.76 s	43.39 s	43.61 s	43.66 s
5	53.13 d	53.33 d	53.84 d	53.31 d	53.58 d	53.41 d
6	20.26 t	20.65 t	21.42 t	20.86 t	21.30 t	21.20 t
7	33.79 t	34.22 t	34.49 t	33.88 t	33.89 t	34.38 t
8	126.91 s	128.40 s	126.91 s	126.59 s	126.79 s	126.90 s
9	138.38 s	137.56 s	139.21 s	138.37 s	139.03 s	139.00 s
10	39.32 s	39.54 s	39.78 s	40.54 s	39.33 s	39.69 s
11	28.48 t	27.50 t	29.62 t	28.45 t	28.88 t	28.75 t
12	25.27 t	26.57 t	25.68 t	25.25 t	25.55 t	25.54 t
13	125.09 s	142.14 s	125.49 s	125.07 s	125.38 s	125.36 s
14	110.35 d	115.41 d	110.73 d	110.32 d	110.65 d	110.64 d
15	142.21 d	149.13 d	147.70 d	142.23 d	142.52 d	142.51 d
16	137.94 d	143.80 s	146.06 d	137.94 d	138.23 d	138.22 d
17	19.29 q	19.60 q	19.66 q	19.29 q	19.59 q	19.58 q
18	184.31 s	177.93 s	176.70 s	177.23 s	176.63 s	176.24 s
19	28.17 q	28.31 q	29.72 q	29.34 q	29.69 q	28.75 q
20	17.41 q	17.61 q	18.18 q	17.62 q	19.97 q	18.17 q

C atom*	**7e**	**7f**	**7g**	**7h**	**8a**	**8b**
1	39.21 t	37.19 t	37.83 t	36.75 t	36.91 t	36.95 t
2	21.35 t	19.44 t	19.53 t	19.22 t	19.48 t	20.69 t
3	39.45 t	37.73 t	37.94 t	36.97 t	37.57 t	37.60 t
4	45.83 s	43.66 s	43.82 s	43.33 s	43.74 s	43.77 s
5	53.09 d	53.32 d	53.49 d, 53.72 d	53.77 d	53.38 d	53.08 d
6	23.09 t	20.82 t	21.18 t	20.54 t	20.68 t	20.37 t
7	36.13 t	34.19 t	34.43 t	33.89 t	34.23 t	34.26 t
8	128.76 s	126.65 s	126.84 s	126.64 s	127.96 s	127.63 s
9	140.92 s	138.72 s	139.01 s	138.44 s	138.02 s	138.09 s
10	41.55 s	39.51 s	39.51 s	39.30 s	39.54 s	39.55 s
11	30.82 t	29.77 t	28.77 t	28.45 t	27.70 t	27.61 s
12	27.34 t	25.36 t	25.55 t	25.19 t	27.08 t	27.05 t
13	127.27 s	125.17 s	125.40 s	125.07 s	142.30 s	142.24 s
14	112.26 d	110.47 d	110.67 d	110.25 d	114.41 d	114.32
15	144.49 d	142.31 d	142.56 d	142.18 d	147.70 d	147.61 d
16	140.17 d	138.02 d	138.26 d	137.86 d	146.06 s	146.01 s
17	20.65 q	19.41 q	19.62 q	19.01 q	19.59 q	19.61 q
18	174.41 s	176.59 s	176.08 s	175.94 s	177.94 s	177.90 s
19	30.55 q	29.31 q	29.55 q, 29.69 q	28.69 q	28.32 q	28.31 q
20	19.30 q	17.95 q	17.98 q, 18.13 q	17.78 q	17.59 q	17.62 q

*Atom numbering of the diterpene skeleton given in the structure of **2** (Scheme 1) is used. *For **6**: 51.00 q (OCH_3), 165.01 s (COCOCl), 169.60 s (COCl); **7a**: 28.87 t ($NHCH_2$), 127.35 d (C-4′), 127.93 d (C-3′,5′), 128.63 d (C-2′,6′), 138.52 s (C-1′); **7b**: 34.02 t (CH_2Ar), 39.33 t ($NHCH_2$), 115.28 d (C-3′,5′), 129.21 d (C-2′,6′), 129.27 s (C-1′), 154.97 s (C-4′); **7c**: 24.73 t (C-4′,5′), 26.88 t (C-6′), 28.75 t (C-3′), 28.96 t (C-7′), 29.22 t (C-2′), 34.38 t (C-1′), 39.66 t (C-8′), 51.29 q (OCH_3), 174.12 s (CO_2CH_3); **7d**: 29.49 q ($SHCH_3$), 52.23 q (OCH_3), 53.62 d (NHCH), 173.86 s (CO_2CH_3); **7e**: 20.27 q ($CH(CH_3)_2$), 32.48 d ($CH(CH_3)_2$), 55.86 q (OCH_3), 59.77 d (NHCH), 180.12 s (CO_2CH_3); **7f**: 15.12 q (SCH_3), 28.58 t (CH_2SCH_3), 31.21 t ($CH_2CH_2SCH_3$), 51.12 d (NHCH), 52.09 q (OCH_3), 172.41 s (CO_2CH_3); **7g**: 37.44 t ($CH_2CO_2CH_3$), 49.29 d (SHPh), 51.70 q, 51.74 q (OCH_3), 126.07 d (C-4′), 126.99 s (C-1′), 127.34 d (C-4′,5′), 128.54 d (C-2′,6′), 171.91 s (CO_2CH_3); **7 h**: 119.75 d (C-4′), 124.91 d (C-3′,5′), 128.54 d (C-2′,6′), 135.94 s (C-1′), 156.33 s (CONHPh), 158.02 s (NHCO); CH_3 (on C-2″) – 14.48 q; **8a**: 50.97 q (OCH_3), 127.65 d (C-4′), 127.87 d (C-3′,5′), 128.63 d (C-2′,6′), 137.05 s (C-1′), 161.41 s (COCONH), 176.41 s (CONH); **8b**: 39.55 d (CH_2), 49.65 d (CH), 50.92, 51.73 (both q, OCH_3), 126.30 q (C-4′), 127.78 d (C-3′,5′), 127.93 s (C-8), 128.68 d (C-2′,5′), 139.57 s (C-1′), 160.83 s (CO_2CH_3), 170.85 s (CONH), 176.22 s (COCO).

EXPERIMENTAL

NMR spectra were taken on Bruker AV-300 [operating frequency 300.13 (^{1}H) and 75.47 MHz (^{13}C)] and Bruker DRX-500 [operating frequency 500.13 (^{1}H) and 125.76 MHz (^{13}C)] instruments. Multiplicity of resonances in ^{13}C NMR spectra were determined using standard methods for recording spectra in J-modulation (JMOD) and with off-resonance suppression of protons. Table 1 lists ^{13}C NMR spectra of **1**, **6**, **7a-h**, **8a**, and **8b**. Mass spectra were obtained in a DFS high-resolution mass spectrometer. Specific rotation was measured on a Polar 3005 polarimeter at room temperature (20–23°C). IR spectra were recorded in KBr on a Vector-22 instrument. UV absorption spectra were recorded on an HP 8453 UV Vis spectrometer in EtOH (*c* 10^{-4} M).

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using $CHCl_3$:EtOH (3:1) and petroleum ether:EtOAc (10:1). Spots were developed by spraying plates with aqueous H_2SO_4 (10%) with subsequent heating to 100°C or using UV illumination.

Lambertianic acid (**2**) was isolated by the literature method [14]. The synthesis of the methyl ester of phlomisoic acid (**5**) was reported by us earlier [11].

(1*S*,4a*S*,5*S*,8a*R*)-5-[2-(Furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carbonic Acid [15,16-Epoxylabda-8(9),13(16),14-trien-18-oic Acid, Phlomisoic Acid] (1). A solution of lambertianic acid (**2**, 8.88 g, 28.1 mmol) in benzene (30 mL) was treated with *p*-toluenesulfonic acid (0.24 g, 1.4 mmol) and refluxed for 8 h. Solvent was evaporated in vacuo. The solid was chromatographed over a column of silica gel ($CHCl_3$ eluent). Crystallization of product fractions from hexane afforded **1** (7.66 g, 86%), mp 119–122°C, $[\alpha]_D^{25}$ +181.5° (*c* 0.23, $CHCl_3$) {lit. [2] $[\alpha]_D^{14}$ +116.9° (*c* 0.31, CH_3OH)}. UV spectrum (EtOH, λ_{max}, nm, log ε): 203 (4.05).

PMR spectrum (δ, ppm, J/Hz): 0.91 (3H, s, 20-CH_3), 1.06 (1H, td, J = 13.9, 4.6, H-3), 1.24 (1H, t, J = 13.1, H-1), 1.30 (3H, s, 19-CH_3), 1.41 (1H, d, J = 11.9, H-5), 1.58 (2H, dm, J = 11.0, H-2), 1.66 (3H, s, 17-CH_3), 1.82 (1H, td, J = 12.3, 5.5, H-6), 1.93 (2H, dm, J = 13.3, H-6,1), 2.01 (1H, d, J = 5.7, H-7), 2.07–2.34 (4H, m, H-3,11,11,7), 2.47 (2H, t, J = 7.0, H-12), 6.31 (1H, dd, J = 1.7, 1.0, H-14), 7.25 (1H, dd, J = 1.3, 1.0, H-16), 7.37 (1H, dd, J = 1.3, 1.7, H-15).

Mass spectrum (*m*/*z*, I_{rel}, %): 317 (21), 316 (94), 301 (22), 235 (37), 234 (36), 221 (31), 189 (100), 188 (36), 133 (62), 119 (45), 105 (33), 91 (35), 82 (39), 81 (60), 56 (37), 43 (61). Found: $[M]^+$ 316.2040. $C_{20}H_{28}O_3$. Calcd: 316.2033.

Acid Chloride of (1*S*,4a*S*,8a*R*)-1,4a,6-Trimethyl-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylic Acid (Phlomisoic Acid Chloride) (3). Phlomisoic acid (**1**, 1.00 g, 3.2 mmol) in CH_2Cl_2 (10 mL) under Ar was cooled by ice, stirred vigorously, and treated dropwise with oxalylchloride (0.28 mL, 3.2 mmol) in CH_2Cl_2 (10 mL). The temperature was raised to ambient. Stirring was continued for 5 h. Solvent was evaporated in vacuo. The solid was treated with CH_2Cl_2 (10 mL) and again evaporated. This procedure was repeated four times. The solid afforded **3**, which was used immediately to synthesize the amides.

PMR spectrum (δ, ppm, J/Hz): 0.95 (3H, s, 20-CH_3), 1.10 (1H, d, J = 12.2, H-3), 1.22 (1H, td, J = 14.0, 3.4, H-1), 1.40 (3H, s, 19-CH_3), 1.52 (1H, m, H-5), 1.61 (2H, s, H-2), 1.67 (3H, s, 17-CH_3), 1.71–1.89 (2H, m, H-6), 1.91-2.37 (6H, m, H-1,3,7,7,11,11), 2.41–2.49 (2H, m, H-12), 6.31 (1H, s, H-14), 7.25 (1H, s, H-16), 7.37 (1H, s, H-15).

(1*S*,4a*S*,8a*R*)-Methyl 1,4a,6-trimethyl-5-{2-[2-(2-chloro-2-oxoacetyl)furan-3-yl]-ethyl}-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylate (6). Methyllabdatriene (**5**, 1.00 g, 3.0 mmol) in CH_2Cl_2 (15 mL) under Ar was cooled to 0°C and treated dropwise with oxalylchloride (0.53 mL, 6.0 mmol) in CH_2Cl_2 (6 mL). The temperature was raised to ambient. Stirring was continued for 5 h. Solvent was evaporated. The solid was treated with CH_2Cl_2 (10 mL) and again evaporated. This procedure was repeated another two times. The solid affored **6** as an oil. IR spectrum (ν, cm^{-1}): 1788, 1726, 1670, 1576, 1380, 1230, 1160, 1148, 1038, 982, 889, 782, 722, 682.

PMR spectrum (δ, ppm, J/Hz): 0.76 (3H, s, 20-CH_3), 1.00 (1H, td, J = 13.3, 4.4, H-3), 1.18 (1H, m, H-1), 1.19 (3H, s, 19-CH_3), 1.33 (1H, dd, J = 12.6, 2.5, H-5), 1.54 (2H, dm, J = 13.9, H-2), 1.65 (3H, s, 17-CH_3), 1.69–2.32 (8H, m, H-1,3,6,6,7,7,11,11), 2.88 (2H, t, J = 8.1, H-12), 3.61 (3H, s, OCH_3), 6.60 (1H, d, J = 1.5, H-14), 7.63 (1H, d, J = 1.5, H-15).

Mass spectrum (*m*/*z*, *I*rel, %): 420 (1), 405 (2), 357 (11), 235 (37), 330 (16), 316 (13), 301 (15), 189 (100), 175 (54), 133 (52), 121 (41), 119 (46), 105 (44), 91 (36), 81 (30), 55 (31). Found: $[M]^+$ 420.1707. $C_{23}H_{29}O_5Cl$. Calcd: 420.1698.

General Method for Preparing Amides of 8(9),13(16),14-labdatrien-18-oic Acid 7a-h. A solution of **3** (1.10 g, 3.2 mmol) in CH_2Cl_2 (15 mL) was treated in portions with amine (3.8 mmol) (hydrochlorides for methyl esters of amino acids) and then with triethylamine (2.11 mL, 15.2 mmol). The reaction mixture was left at room temperature with periodic stirring for 2 d. Solvent was evaporated in vacuo. The solid was treated with Et_2O. The resulting precipitate of triethylammonium

chloride was filtered off. The mother liquor was evaporated. The solid was purified by column chromatography over silica gel (20:1, $CHCl_3$:CH_3OH, 100:1) to afford amides **7a-h**.

(1*S*,4a*S*,8a*R*)-*N*-Benzyl-5-[2-(furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxamide (7a). Reaction of **3** (0.54 g, 1.6 mmol) with benzylamine in the presence of Et_3N afforded **7a** (0.41 g, 64%), $[\alpha]_D^{25}$ +105.6° (*c* 1.64, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3377, 1696, 1649, 1640, 1515, 1259, 1025, 874, 778, 724, 699.

PMR spectrum (δ, ppm, J/Hz): 0.85, 0.87 (3H, both s, 20-CH_3), 0.97 (1H, td, J = 13.9, 4.6, H-3), 1.09 (1H, td, J = 13.9, 4.6, H-1), 1.21, 1.25 (3H, both s, 19-CH_3), 1.37 (1H, dd, J = 12.5, 2.8, H-5), 1.53–1.56 (2H, m, H-2), 1.62 (3H, s, 17-CH_3), 1.71–2.27 (8H, m, H-1,3,6,6,7,7,11,11), 2.36–2.48 (2H, m, H-12), 4.34, 4.42 (2H, AB-X, J = 5.2, NHC$\underline{H}_2$), 5.80 (1H, s, NH), 6.27 (1H, s, H-14), 7.21–7.33 (7H, m, H-15,16 and 5H, Ph–H).

Mass spectrum (*m*/*z*, I_{rel}, %): 405.27 (17), 324 (36), 189 (46), 175 (22), 133 (31), 119 (30), 105 (21), 95 (30), 91 (100), 57 (52), 55 (38). Found: $[M]^+$ 405.2663, $C_{27}H_{35}NO_2$. Calcd: 405.2668.

(1*S*,4a*S*,8a*R*)-*N*-(4-Hydroxyphenethyl)-5-[2-(furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxamide (7b). Reaction of **3** (2.10 g, 6.3 mmol) with tyramine in the presence of Et_3N afforded **7b** (1.72 g, 63%) as an amorphous solid, mp 162–165°C, $[\alpha]_D^{25}$ +74.6° (*c* 1.17, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3255, 1660, 1638, 1594, 1560, 1515, 1365, 1231, 1105, 1024, 873, 830, 777.

PMR spectrum (δ, ppm, J/Hz): 0.81 (3H, s, 20-CH_3), 0.85–1.09 (2H, m, H-1,3), 1.13 (3H, s, 19-CH_3), 1.16–1.32 (1H, m, H-5), 1.50 (2H, dm, J = 13.8, H-2), 1.60 (3H, s, 17-CH_3), 1.64–2.27 (8H, m, H-1,3,6,6,7,7,11,11), 2.41 (2H, m, H-12), 2.71 (2H, t, J = 7.0, C$\underline{H}_2$Ar), 3.39–3.48 (2H, m, NHC$\underline{H}_2$), 5.68 (1H, br.s, NH), 6.26 (1H, s, H-14), 6.81 (2H, d, J = 8.5, H-2′,6′), 6.99 (2H, d, J = 8.5, H-3′,5′), 7.20 (1H, s, H-16), 7.32 (1H, s, H-15).

Mass spectrum (*m*/*z*, I_{rel}, %): 435.3 (6), 354 (22), 189 (100), 120 (83), 133 (71), 81 (62). Found: $[M]^+$ 435.2766. $C_{28}H_{37}NO_3$. Calcd: 435.2768.

(1*S*,4a*S*,8a*R*)-*N*-[(9-Methoxycarbonyl)nonyl]-5-[2-(furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxamide (7c). Reaction of **3** (1.10 g, 3.2 mmol) with the hydrochloride of 9-aminopelargonic acid methyl ester in the presence of Et_3N afforded **7c** (0.54 g, 35%), $[\alpha]_D^{25}$ +77.1° (*c* 0.74, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3391, 1738, 1644, 1520, 1249, 1196, 1170, 1063, 1025, 980, 873, 777, 755, 723.

PMR spectrum (δ, ppm, J/Hz): 0.85 (3H, s, 20-CH_3), 1.06 (1H, td, J = 13.6, 4.0, H-3), 1.15 (3H, s, 19-CH_3), 1.16–1.27 (9H, m, H-1,3′,3′,4′,4′,5′,5′,6′,6′), 1.32 (1H, dd, J = 12.6, 2.8, H-5), 1.48 (2H, m, H-7′), 1.57–1.62 (4H, m, H-2,2,2′,2′), 1.62 (3H, s, 19-CH_3), 1.70–1.91 (4H, m, H-1,7,6,6), 1.98–2.12 (2H, m, H-7,11), 2.23–2.29 (4H, m, H-3,11,1′,1′), 2.42 (2H, m, H-12), 3.18 (2H, m, H-8′), 3.64 (3H, s, OCH_3), 5.56 (1H, br.s, NH), 6.27 (1H, s, H-14), 7.21 (1H, s, H-16), 7.32 (1H, s, H-15).

Mass spectrum (*m*/*z*, I_{rel}, %): 485 (45), 404 (100), 81 (50), 55 (49). Found: $[M]^+$ 485.3508. $C_{30}H_{47}NO_4$. Calcd: 485.3499.

(1*S*,4a*S*,8a*R*)-*N*-(3-Methoxycarbonylpropan-2-yl)-5-[2-(furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxamide (7d). Reaction of **3** (1.10 g, 3.2 mmol) with the hydrochloride of D,L-alanine methyl ester in the presence of Et_3N afforded **7d** (0.73 g, 57%), $[\alpha]_D^{25}$ +145.9° (*c* 0.84, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3448, 3134, 1741, 1654, 1503, 1449, 1311, 1214, 1191, 1175, 1096, 1063, 1025, 980, 874, 825, 777, 755, 600.

PMR spectrum (δ, ppm, J/Hz): 0.83, 0.84 (3H, both s, 20-CH_3), 1.02–1.12 (1H, m, H-3), 1.18, 1.19 (3H, both s, 19-CH_3), 1.16-1.23 (2H, m, H-1,5), 1.36, 1.38 (3H, both d, J = 7.0, C$\underline{H}_3$), 1.56 (2H, dt, J_{gem} = 11.3, H-2), 1.62 (3H, s, 17-CH_3), 1.74–1.96 (4H, m, H-1,7,6,6), 2.01–2.14 (2H, m, H-7,11), 2.18–2.26 (2H, m, H-3,11), 2.40–2.44 (2H, m, H-12), 3.72 (3H, s, OCH_3), 4.56 (1H, qd, J = 7.3, 4.8, C$\underline{H}$), 6.17, 6.24 (1H, both d, J = 7.0, NH), 6.26 (1H, s, H-14), 7.20 (1H, s, H-16), 7.32 (1H, s, H-15).

Mass spectrum (*m*/*z*, I_{rel}, %): 477 (30), 271 (100), 189 (95), 201 (77), 107 (37). Found: $[M]^+$ 401.2550. $C_{24}H_{35}NO_4$. Calcd: 401.2561.

(1*S*,4a*S*,8a*R*)-*N*-(2-Methyl-4-methoxycarbonylbutan-3-yl)-5-[2-(furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxamide (7e). Reaction of **3** (1.10 g, 3.2 mmol) with the hydrochloride of D,L-valine methyl ester in the presence of Et_3N afforded **7e** (0.65 g, 47%), $[\alpha]_D^{25}$ +70.0° (*c* 0.67, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3451, 1739, 1669, 1502, 1466, 1371, 1306, 1265, 1206, 1154, 1063, 1025, 994, 874, 775 (NH).

PMR spectrum (δ, ppm, J/Hz): 0.82, 0.84 (3H, both s, 20-CH_3), 0.87, 0.90, 0.91, 0.92 [6H, all d, CH(C$\underline{H}_3$)$_2$], 0.90–1.18 (2H, m, H-3,1), 1.21, 1.23 (3H, both s, 19-CH_3), 1.38 (1H, m, H-5), 1.53–1.57 (2H, m, H-2), 1.62 (3H, s, 17-CH_3),

2.39–2.42 (9H, m, H-1,3,6,6,7,7,11,11), 2.45 [1H, m, C<u>H</u>$(CH_3)_2$], 2.39–2.45 (2H, m, H-12), 3.70, 3.71 (3H, both s, OCH_3), 4.51–4.56 (1H, m, NHC<u>H</u>), 6.03, 6.06 (1H, both d, NH), 6.27 (1H, s, H-14), 7.20 (1H, s, H-16), 7.32 (1H, s, H-15).

Mass spectrum (*m*/*z*, I_{rel}, %): 429 (14), 189 (100), 57 (58), 149 (48), 175 (41). Found: $[M]^+$ 429.2871. $C_{26}H_{39}NO_4$. Calcd: 429.2879.

(1*S*,4a*S*,8a*R*)-*N*-[(1-Methylthio)-4-methoxycarbonylbutan-2-yl]-5-[2-(furan-3-yl)-ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxamide (7f). Reaction of **3** (1.10 g, 3.2 mmol) with the hydrochloride of D, L-methionine methyl ester in the presence of Et_3N afforded **7f** (0.56 g, 39%), $[\alpha]_D^{25}$ +104.3° (*c* 0.49, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3442, 3387, 1741, 1660, 1504, 1344, 1300, 1261, 1225, 1175, 1100, 1063, 1024, 873, 800, 756, 667.

PMR spectrum (δ, ppm, J/Hz): 0.80 (3H, s, 20-CH_3), 0.85–0.92 (1H, m, H-3), 1.05 (1H, td, J = 13.7, 3.9, H-1), 1.18 (3H, s, 19-CH_3), 1.20–1.58 (3H, m, H-2,2,5), 1.59 (3H, s, 17-CH_3), 1.70–2.02 (8H, m, 6H, H-1,6,6,7,7,11 and 2H, C<u>H</u>$_2$SCH_3), 2.05 (3H, s, SCH_3), 2.06–2.25 (2H, m, H-3,11), 2.48 (2H, m, C<u>H</u>$_2$), 2.52 (2H, m, H-12), 3.71 (3H, s, OCH_3), 4.67 (1H, m, C<u>H</u>), 6.25 (1H, s, H-14), 6.30, 6.38 (1H, both d, NH), 7.18 (1H, s, H-16), 7.30 (1H, s, H-15). $C_{26}H_{39}NO_4S$.

(1*S*,4a*S*,8a*R*)-*N*-(3-Methoxy-1-phenylpropyl)-5-[2-(furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxamide (7g). Reaction of **3** (1.10 g, 3.2 mmol) with the hydrochloride of 3-amino-3-phenylpropionic acid methyl ester in the presence of Et_3N afforded **7g** (1.12 g, 74%), $[\alpha]_D^{25}$ +100.7° (*c* 0.91, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3435, 1731, 1658, 1628, 1600, 1504, 1438, 1369, 1281, 1211, 1165, 1064, 1025, 980, 874, 756, 720, 700, 666.

PMR spectrum (δ, ppm, J/Hz): 0.78, 0.81 (3H, both s, 20-CH_3), 1.02–1.17 (2H, m, H-3,1), 1.20, 1.22 (3H, both s, 19-CH_3), 1.35 (1H, m, H-5), 1.58 (2H, m, H-2), 1.62, 1.63 (3H, both s, 17-CH_3), 1.71–2.26 (8H, m, H-1,3,6,6,7,7,11,11), 2.42 (2H, m, H-12), 2.77, 2.94 (2H, both m, C<u>H</u>$_2$), 3.60, 3.62 (3H, both s, OCH_3), 5.42 (1H, m, C<u>H</u>), 6.27 (1H, s, H-14), 6.77, 6.82 (1H, both d, J = 8.3, NH), 7.20 (1H, s, H-16), 7.21–7.30 (5H, m, Ph–H), 7.36 (1H, s, H-15).

Mass spectrum (*m*/*z*, I_{rel}, %): 477 (30), 121 (100), 189 (73), 396 (55), 175 (41). Found: $[M]^+$ 477.2879. $C_{30}H_{39}NO_4$. Calcd: 477.2874.

(1*S*,4a*S*,8a*R*)-1,4a,6-Trimethyl-1-{2-[2-oxo-2-(phenylamino)acetyl]hydrazinocarbonyl}-5-[2-(furan-3-yl)ethyl]-1,2,3,4,4a,7,8,8a-octahydronaphthalene (7h). Reaction of **3** (1.10 g, 3.2 mmol) with 2-oxo-2-(phenylamino)acetohydrazide (0.74 g, 4.1 mmol) in the presence of Et_3N under the conditions for synthesizing amides **7a**-**g** afforded **7h** (0.36 g, 24%), mp 153°C (ether), $[\alpha]_D^{25}$ +39.6° (*c* 0.92, dioxane). IR spectrum (ν, cm^{-1}): 3437, 1702, 1672, 1658, 1625, 1602, 1535, 1500, 1320, 1225, 1103, 1053, 1021, 750, 691.

PMR spectrum (δ, ppm, J/Hz): 0.86 (3H, s, 20-CH_3), 1.08 (1H, dt, J_{gem} = 13.6, H-3), 1.21 (1H, m, H-1), 1.28 (3H, s, 19-CH_3), 1.42 (1H, dd, J = 12.6, 2.8, H-5), 1.62 (2H, m, H-2), 1.64 (3H, s, 17-CH_3), 1.71–1.95 (4H, m, H-1,7,6,6), 1.99–2.13 (2H, m, H-7,11), 2.16–2.28 (2H, m, H-3,11), 2.42 (2H, m, H-12), 6.27 (1H, s, H-14), 7.15 (1H, m, H-4′), 7.20 (1H, s, H-16), 7.33 (1H, s, H-15), 7.37 (2H, m, H-3′,5′), 7.58–7.66 (2H, m, H-2′,6′), 8.25 (1H, t, J = 7, CON<u>H</u>Ph), 9.10 (1H, br.s, N<u>H</u>NH), 9.29 (1H, br.s, NHN<u>H</u>).

Mass spectrum (*m*/*z*, I_{rel}, %): 477 (30), 271 (100), 201 (77), 189 (95), 107 (37). Found: $[M]^+$ 477.2619. $C_{28}H_{35}N_3O_4$. Calcd: 477.2622.

(1*S*,4a*S*,8a*R*)-Methyl-5-{2-[2-(2-oxo-2-benzylaminoacetyl)furan-3-yl]ethyl}-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylate (8a). Compound **5** (1.00 g, 3.0 mmol) in CH_2Cl_2 (8 mL) was treated with benzylamine (0.68 mL, 6.0 mmol) and Et_3N (0.62 mL, 4.5 mmol) and stirred at room temperature for 1 d. Solvent was evaporated in vacuo. The solid was treated with Et_2O. The resulting precipitate was filtered off. The mother liquor was evaporated. The solid was chromatographed over silica gel ($CHCl_3$ eluent) to afford **8a** as an oil (0.93 g, 67%), $[\alpha]_D^{25}$ +69.9° (*c* 0.87, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3350, 1723, 1680, 1618, 1572, 1526, 1497, 1230, 1160, 1140, 1130, 1113, 1065, 1037, 982, 881, 780, 754, 700. UV spectrum (EtOH, λ_{max}, nm, log ε): 241 (3.62), 290 (3.97).

PMR spectrum (δ, ppm, J/Hz): 0.76 (3H, s, 20-CH_3), 0.99 (1H, td, J = 9.4, 4.0, H-3), 1.18 (3H, s, 19-CH_3), 1.23 (1H, m, H-1), 1.32 (1H, d, J = 11.7, H-5), 1.52 (2H, dm, J = 14.1, H-2), 1.65 (3H, s, 17-CH_3), 1.69–2.29 (8H, m, H-1,3,6,6,7,7,11,11), 2.87 (2H, t, J = 8.9, H-12), 3.60 (3H, s, OCH_3), 4.53 (2H, d, J = 6.9, C<u>H</u>$_2$Ph), 6.51 (1H, d, J = 1.6, H-14), 7.24–7.31 (5H, m, Ph), 7.60 (1H, d, J = 1.6, H-15).

Mass spectrum (*m*/*z*, I_{rel}, %): 491 (4), 243 (100), 91 (33), 152 (19), 244 (18). Found: $[M]^+$ 491.2655. $C_{30}H_{37}NO_5$. Calcd: 491.2666.

(1*S*,4a*S*,8a*R*)-Methyl-5-{2-[2-(2-oxo-2-benzylaminoacetyl)furan-3-yl]ethyl}-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-carboxylate (8b). Compound **5** (1.00 g, 3.0 mmol) in CH_2Cl_2 (8 mL) was treated with 3-amino-3-phenylpropionic acid (0.97 g, 4.5 mmol) and Et_3N (0.83 mL, 6 mmol) and stirred at room temperature for 1 d. Solvent was evaporated in vacuo. The solid was treated with Et_2O. The resulting precipitate was filtered off. The mother liquor was evaporated. The solid was chromatographed over silica gel ($CHCl_3$ eluent) to afford **8b** as an oil (1.08 g, 64%), $[\alpha]_D^{25}$ +49.6° (*c* 1.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3380, 1720, 1675, 1620, 1575, 1530, 1498, 1240, 1165, 1140, 1135, 1110, 1048, 1013, 982, 880, 780, 755, 702. UV spectrum (EtOH, λ_{max}, nm, log ε): 242 (3.89), 290 (4.05).

PMR spectrum (δ, ppm, J/Hz): 0.76 (3H, s, 20-CH_3), 1.00 (1H, td, J = 12.0, 4.0, H-3), 1.18 (3H, s, 19-CH_3), 1.24 (1H, m, H-1), 1.32 (1H, d, J = 12.0, H-5), 1.52 (2H, dm, J = 16.0, H-2), 1.64 (3H, s, 17-CH_3), 1.70 (1H, dd, J = 12.0, 6.0, H-6), 1.82 (1H, dm, J = 12.0, H-6), 1.92 (1H, m, H-7), 1.95 (1H, m, H-1), 2.00 (1H, m, H-7), 2.10 (1H, m, H-11), 2.19 (1H, dm, J = 12.0, H-3), 2.24 (1H, m, H-11), 2.87 (2H, dd, J = 12.0, 6.0, H-12), 2.92 (1H, d, J = 6.0, CH_2), 3.02 (1H, dd, J = 18.0, 6.0, CH_2), 3.60 (3H, s, OCH_3), 5.50 (1H, dd, J = 12.0, 6.0, CH), 6.53 (1H, d, J = 1.5, H-14), 7.29–7.35 (5H, m, Ph), 7.60 (1H, d, J = 1.7, H-15), 7.80 (1H, d, J = 6.0, NH). $C_{33}H_{41}NO_7$.

XSA of 1. The XSA of **1** was performed on a Kappa Apex II diffractometer (Bruker) with a two-coordinate CCD detector using ω–φ scanning at –100°C. A total of 16,568 reflections was measured in the range $2\theta < 51°$. Of these, 6,308 were independent (R_{int} = 0.067). A colorless crystal (0.10 × 0.10 × 0.40 mm) was selected. The crystals were pseudo-orthorhombic because averaging equivalent reflections for the orthorhombic system gave R_{int} = 36.6% (for 14,628 reflections); for monoclinic, R_{int} = 7.1% (for 13,009 reflections). The unit-cell constants were a = 10.6941(4), b = 10.2198(8), c = 16.221(2) Å, β = 90.00(1)°, V = 1772.8(3) $Å^3$, space group $P2_1$, Z = 4, d_{calc} = 1.186 g/cm^3. Absorption corrections were applied using the SADABS program [15], which used multiple measurements of the same reflections at different crystal orientations (transmission 0.62–0.75). The structure model was found by direct methods and refined with anisotropic thermal factors for nonhydrogen atoms using the program set SHELXL [16]. The Cif file containing complete information on the structure was deposited in the CCDC (CCDC 748547), from where it can be obtained free upon request to the following internet site: www.ccdc.cam.ac.uk/data_request/cif.

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