

Vilsmeier—Haack reaction of methyl lambertianate and non-sensitized photocyclization of the resulting product

D. A. Klok,^a M. M. Shakirov,^b V. V. Grishko,^b and V. A. Raldugin^{b*}

^aNovosibirsk State University,
2 ul. Pirogova, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383 2) 355 235

^bNovosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences,
9 prosp. Akad. Lavrent'eva, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383 2) 354 752. E-mail: root@orchem.nsk.su.

Vilsmeier—Haack formylation of methyl lambertianate results in its 16-formyl derivative as the predominant product, which readily enters the intramolecular reaction of photochemical [2+2]-cycloaddition in the absence of a sensitizer.

Key words: diterpenoids; alkylfurans; formylation; intramolecular photocyclization.

Lambertianic acid and its methyl ester (**1**) are well known diterpenoids, which are present in galipot and the extractive compounds from some arboreal plants of the *Pinus* L. genus.^{1–3} In spite of the availability of these substances,⁴ there are only a few investigations of their chemistry.

It has been recently found that the irradiation of a solution of **1** in hexane or benzene with the light of the mercury vapor lamp leads to reversible intramolecular [2+2]-photocycloaddition resulting in pentacyclic oxide (**2**) (with conversion of 0.4 % in hexane and 10 % in benzene).⁵

Using acetone as a sensitizer increases the yield of oxide **2** to 13 %, but results in a large amount of the products of acetone photoaddition to the furan ring of the molecule of ester **1**.⁶

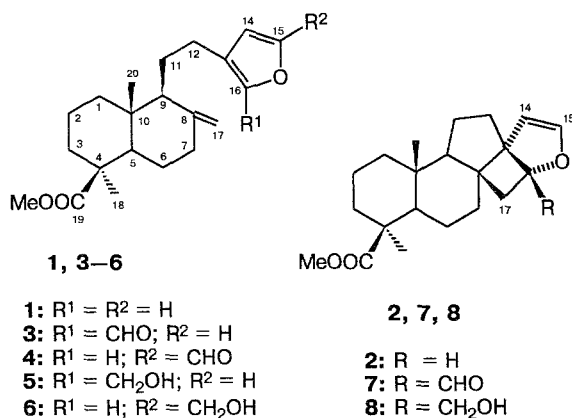
In addition involving the furan ring and the non-conjugate double bond, we suggested introduction of an additional chromophore to the furan moiety of the ester as the "inner sensitizer." We chose the formyl group for this purpose as the simplest one and also adopted the Vilsmeier—Haack reaction⁷ for its introduction. This reaction is well known for 3-methylfuran,⁸ but can also take place at the methylene group.⁹

Ester **1** was found to react smoothly with DMF and POCl₃ only at its furan fragment resulting in the oily mixture of two formyl derivatives **3** and **4** (in a 10:1 ratio according to ¹H NMR data) hardly separable by chromatography. The yield of this mixture after the chromatographic partition of the unreacted ester **1** (10.4 %) was 77 %. Methyl 16-formyllambertianate (**3**), the predominant isomer, was easily crystallized from the solution of a mixture in hexane.

The position of the formyl group in the molecule of **3** has been elucidated from ¹H NMR spectrum, as the signals of the furan protons appeared as two doublets at δ 6.37 (C(14)H) and 7.49 (C(15)H) with *J*_{AB} = 1.7 Hz. ¹³C NMR data for compounds **1** and **3** are shown in Table 1.

The mother liquor after the crystallization of ester **3** contained the mixture of esters **3** and **4** in a 12:10 ratio (GLC and ¹H NMR data). The signals of C(14)H and C(16)H protons in the spectrum of isomer **4** are observed as singlets at 7.03 and 7.36 ppm. Treating the mixture of **3** and **4** with NaBH₄ in EtOH yielded a mixture of easily separable methyl 16- and 15-hydroxymethylambertianates (**5** and **6**).

Thus, Vilsmeier—Haack reaction is promising for obtaining the derivatives of natural ester **1** functionalized at the furan ring.



To further study the possibilities of the first found process of intramolecular photochemical [2+2]-cyclo-

Table 1. ^{13}C NMR spectra of compounds **1**, **3**, and **5** (CDCl_3 , tetramethylsilane, δ)

Atom or group	1	3	5
C(1)	38.88 t	38.81 t	38.95 t
C(2)	19.75 t	19.65 t	19.84 t
C(3)	38.00 t	37.88 t	38.08 t
C(4)	39.95 s	39.96 s	40.04 s
C(5)	56.05 d	55.96 d	56.16 d
C(6)	26.05 t	25.98 t	26.18 t
C(7)	38.52 t	38.38 t	38.60 t
C(8)	147.66 s	147.27 s	147.85 s
C(9)	55.04 d	54.94 d	55.16 d
C(10)	44.05 s	44.00 s	44.21 s
C(11)	23.37 t	23.19 t	23.01 t
C(12)	24.05 t	24.03 t	24.46 t
C(13)	125.16 s	138.56 s	122.63 s
C(14)	110.70 d	113.78 d	111.42 d
C(15)	138.50 d	147.10 d	141.66 d
C(16)	142.44 d	149.36 s	149.32 s
C(17)	106.17 t	106.37 t	106.39 t
C(18)	28.55 q	28.48 q	28.65 q
C(19)	177.35 s	177.21 s	177.54 s
C(20)	12.40 q	12.36 q	12.54 q
OCH ₃	50.80 q	50.79 q	50.95 q
CH ₂ OH	—	—	54.76 t
CHO	—	177.16 d	—

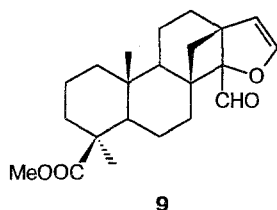
Table 2. ^{13}C NMR spectra of compounds **2**, **7**, and **8**

Atom or group	2*	7**	8
C(1)	39.83 t	40.41 t	39.84 t
C(2)	18.61 t	19.20 t	18.65 t
C(3)	38.34 t	39.00 t	38.36 t
C(4)	43.48 s	43.93 s	43.54 s
C(5)	56.95 d	57.50 d	56.91 d
C(6)	20.37 t	20.87 t	20.40 t
C(7)	37.02 t	36.71 t	37.18 t
C(8)	52.56 s	50.61 s	49.89 s
C(9)	60.01 d	60.48 d	59.67 d
C(10)	37.95 s	38.60 s	37.94 s
C(11)	23.21 t	23.46 t	23.77 t
C(12)	32.95 t	30.03 t	28.42 t
C(13)	60.51 s	60.48 s	59.92 s
C(14)	103.16 d	105.03 d	105.15 d
C(15)	148.87 d	149.38 d	147.90 d
C(16)	82.82 d	96.60 s	88.20 s
C(17)	36.62 t	35.03 t	36.54 t
C(18)	28.70 q	29.33 q	28.75 q
C(19)	177.54 s	177.00 s	177.68 s
C(20)	13.44 q	13.97 q	13.37 q
C(21)	—	200.93 s	63.29 t
OCH ₃	50.90 q	51.32 q	50.99 q

* See Ref. 5. ** Solution in a CCl_4 — CDCl_3 (4:1) mixture.

The irradiation of aldehyde **3** in a hexane— Et_2O (1:1) mixture with the light of a high-pressure mercury vapor lamp resulted in the formation of the less polar product (TLC data). Its amount becomes much the same as that of the starting compound after 2 h. The product was isolated by chromatography. Its structure as compound **7** was elucidated on the basis of ^{13}C (Table 2) and ^1H NMR data and by conversion in the corresponding alcohol **8**. The signals in the ^{13}C and ^1H NMR spectra were assigned using two-dimensional ^1H — ^1H and ^{13}C — ^1H (COSY) NMR spectroscopy and by comparing with NMR data for oxide **2**⁵ (quaternary carbon signals).

We could not rule out that the aldehyde group in furan ring of **3** would change the direction of [2+2]-cycloaddition to result in hypothetical isomer **9**. However, the structure **9** is excluded on the basis of ^{13}C (see Table 2) and ^1H NMR data. Thus, the signals of C(7)— α -H and C(7)— β -H protons hold their positions when going from the spectrum of compound **2**⁵ to the spectra of **7** and **8**. The signal of C(17)— β -H proton is shifted from 2.50 ppm in the spectrum of **2** to 2.87 ppm and 2.22 ppm in the spectra of **7** and **8**, respectively. The position of the signal of C(17)— α -H proton varies moderately (by ± 0.2 ppm).



The formation of aldehyde **7** appears to be irreversible, as the irradiation of **7** under the same conditions does not give the starting compound **3**, but results in the progressive conversion of **7** into a mixture of nonidentified highly polar compounds (probably due to intermolecular reactions).

Alcohol **5** behaves similarly to ester **1** as regards its photochemistry. Its irradiation in the hexane— Et_2O mixture gives traces of alcohol **8** (TLC data), while irradiation in the acetone solution results in irreversible formation of alcohol **8** (10 %) and unidentified products.

Thus, the introduction of the formyl group in the C(16)-position of the molecule of ester **1** allows us to increase the efficiency of the intramolecular photochemical [2+2]-cycloaddition involving the furan ring and the exo-methylene double bond. In this case, the process is sufficiently efficient without sensitization with acetone.

Experimental

Melting points were determined on a Kofler block. IR spectra were recorded on a UR-20 instrument in CCl_4 . UV spectra were taken on a Specord UV-VIS spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AM-400 spectrometers. Two-dimensional ^1H — ^1H and ^{13}C — ^1H (COSY) NMR spectra were recorded using standard Bruker programs. Mass spectra (EI, 70 eV) were taken on a Finnigan MAT 8200 instrument. The optical rotations were obtained on Zeiss (at Na D-line) and Polamat

A (at 580 nm) polarimeters in CHCl_3 . GLC was performed on a Chrom-5 instrument (N_2 as carrier gas, column 2500 \times 3 mm, 5 % SE-30 on Chromaton N, 240 °C). Column chromatography was carried out on silica gel (Akunk, Yerevan) at a compound-sorbent ratio of ~1:20 and with elution with hexane- Et_2O (0–50 %).

Methyl 16-formyllambertianate (3). POCl_3 (0.3 mL) was added dropwise to a solution of ester **1** (1.15 g, 3.48 mmol) in DMF (10 mL) at 20 °C with stirring. The reaction mixture was kept at –20 °C for 48 h and poured into ice water (50 mL). After addition of a saturated aqueous solution of NaOAc (10 mL), the resulting mixture was extracted with Et_2O . The extract was washed with 5 % aqueous NaHCO_3 and dried with Na_2SO_4 . The solvent was removed, and the residue was chromatographed to give unreacted ester **1** (0.12 g) and an oil (0.96 g), which was crystallized from hexane- Et_2O to yield aldehyde **3** (0.77 g, 61.5 %) as colorless crystals with m.p. 79–80 °C (hexane- Et_2O) and $[\alpha]_{\text{D}}^{20} +33.7^\circ$ (c 3.86). UV (EtOH, λ_{max} /nm): 282 (ϵ 10600). IR, ν/cm^{-1} : 1725 (COOMe); 1645, 3080 ($\text{CH}_2=\text{C}$); 1685, 2725 (CHO). ^1H NMR (CDCl_3), δ : 0.42 (s, 3 H, C(20) H_3); 1.08 (s, 3 H, C(18) H_3); 2.60 (dt, 1 H, $^2J = 14.4$ Hz and $^3J = 8.0$ Hz, C(12)- α -H); 2.80 (ddd, 1 H, $^2J = 14.4$ Hz, $^3J = 9.0$ and 4.5 Hz, C(12)- β -H); 3.58 (s, 3 H, OMe); 4.53 and 4.84 (narrow m, 1 H, $\text{H}_2\text{C}=\text{C}$); 6.37 (d, 1 H, $^3J = 1.7$ Hz, C(14)H); 7.49 (d, 1 H, $^3J = 1.7$ Hz, C(15)H); 9.60 (s, 1 H, HCO). For ^{13}C NMR data see Table 1. MS, m/z : 358.2141 $[\text{M}]^+$. Calculated for $\text{C}_{22}\text{H}_{30}\text{O}_4$: 358.2144.

Methyl 16-hydroxymethylambertianate (5). NaBH_4 (0.2 g) was added to a solution of aldehyde **3** (0.12 g, 0.33 mmol) in EtOH (5 mL) with stirring. The reaction mixture was kept for 20 min, diluted with water, and extracted with Et_2O . The extract was washed with water (50 mL) and dried with Na_2SO_4 . The solvent was removed to give oily ester **5** (0.1 g, 83 %), $[\alpha]_{\text{D}}^{20} +36.2^\circ$ (c 4.9). IR, ν/cm^{-1} : 1725 (COOMe); 3625 (OH). ^1H NMR (CDCl_3), δ : 0.47 (s, 3 H, C(20) H_3); 1.14 (s, 3 H, C(18) H_3); 3.58 (s, 3 H, OMe); 4.49 (s, 2 H, $\text{H}_2\text{C}-\text{O}$); 4.58 and 4.90 (narrow m, 1 H, $\text{H}_2\text{C}=\text{C}$); 6.22 (d, 1 H, $^3J = 1.7$ Hz, C(14)H); 7.30 (d, 1 H, $^3J = 1.7$ Hz, C(15)H). For ^{13}C NMR data see Table 1.

Methyl 15-hydroxymethylambertianate (6). The mother liquor after the crystallization of aldehyde **3** was evaporated to dryness. The residue (0.18 g) was dissolved in EtOH (5 mL) and treated with NaBH_4 (0.2 g) as described above for obtaining ester **5**. The resulting product was chromatographed to give ester **5** (0.07 g) and ester **6** (0.07 g) as an oil with $[\alpha]_{\text{D}}^{20} +57.2^\circ$ (c 11.8). IR, ν/cm^{-1} : 880, 1640, 3080 ($\text{CH}_2=\text{C}$); 1725 (C=O); 3625 (OH). ^1H NMR (CDCl_3), δ : 0.48 (s, 3 H, C(20) H_3); 1.15 (s, 3 H, C(18) H_3); 3.58 (s, 3 H, OMe); 4.53 (br.s, 3 H, $\text{H}_2\text{C}-\text{O}$ and C(17)- α -H); 4.86 (br.s, 1 H, C(17)- β -H); 6.14 (s, 1 H, C(14)H); 7.12 (s, 1 H, C(16)H).

(1R,2R,6S,7R,10S,12R,16S)-6-Carboxymethyl-12-formyl-2,6-dimethyl-13-oxapentacyclo[8.8.0.0^{2,7}.0^{10,16}.0^{12,16}]octadec-14-ene (7). A solution of aldehyde **3** (0.280 g, 0.78 mmol) in a hexane- Et_2O (1:1) mixture (20 mL) was irradiated in a quartz cuvette by a DRSh-1000 high-pressure mercury vapor lamp on cooling with a ventilator (the solution temperature being 40 °C) for 2 h. Then the solution was evaporated, and the residue was chromatographed to give compound **7** (0.097 g, 22.5 %), the starting compound **3** (0.090 g), and a complex mixture of highly polar products (0.080 g), sequentially. For compound **7**: m.p. 144–145 °C (hexane), $[\alpha]_{\text{D}}^{20} +94.4^\circ$ (c 1.11). IR, ν/cm^{-1} : 1120, 1145, 1230 (C–O); 1725 (C=O); 2715 (CHO). ^1H NMR (CDCl_3 - CCl_4 (1:4)), δ : 0.67 (s, 3 H, C(20) H_3); 1.08 (dddd, 1 H, $^2J = ^3J_{7\alpha,6\beta} = 13$ Hz, $^3J_{7\alpha,6\alpha} = 4$ Hz, and $^4J_{7\alpha,17\beta} = 1.3$ Hz, C(7)- α -H); 1.13 (s,

3 H, C(18) H_3); 1.75 (d, 1 H, $^3J = 14$ Hz, C(17)- α -H); 1.90 (ddd, 1 H, $^2J = 13$ Hz and $^3J_{7\alpha,6\alpha} = ^3J_{7\alpha,6\beta} = 4$ Hz, C(7)- β -H); 2.14 (m, 1 H, C(3)- β -H); 2.87 (dd, 1 H, $^2J = 14$ Hz and $^4J_{17\beta,7\alpha} = 1.3$ Hz, C(17)- β -H); 3.58 (s, 3 H, OMe); 4.63 (d, 1 H, $^3J = 2.6$ Hz, C(14)H); 6.57 (d, 1 H, $^3J = 2.6$ Hz, C(15)H); 9.47 (s, 1 H, HCO). For ^{13}C NMR data see Table 2. MS, m/z : 358.2163 $[\text{M}]^+$. Calculated for $\text{C}_{22}\text{H}_{30}\text{O}_4$: 358.2144.

(1R,2R,6S,7R,10S,12R,16S)-6-Carboxymethyl-12-hydroxymethyl-2,6-dimethyl-13-octapentacyclo[8.8.0.0^{2,7}.0^{10,16}.0^{12,16}]octadec-14-ene (8). A. NaBH_4 (0.1 g) was added to a solution of compound **7** (0.20 g, 0.55 mmol) in THF (5 mL) at 20 °C. The mixture was stirred and kept for 10 min. Conventional workup resulted in **8** (0.19 g, 95 %) with m.p. 137–138 °C (hexane- Et_2O) and $[\alpha]_{580}^{20} +61.1^\circ$ (c 0.72). IR, ν/cm^{-1} : 1110, 1150, 1230 (C–O); 1725 (C=O); 3465 (OH, intramolecular H-bond). ^1H NMR (CDCl_3), δ : 0.60 (s, 3 H, C(20) H_3); 1.09 (dddd, 1 H, $^2J = ^3J_{7\alpha,6\beta} = 13$ Hz, $^3J_{7\alpha,6\alpha} = 4$ Hz, and $^4J_{7\alpha,17\beta} = 1.3$ Hz, C(7)- α -H); 1.13 (s, 3 H, C(18) H_3); 1.39 (m, 1 H, C(2)- α -H); 1.92 (d, 1 H, $^2J = 14$ Hz, C(17)- α -H); 1.91 (m, 1 H, C(7)- β -H (from correlated ^{13}C - ^1H spectrum)); 2.14 (m, 1 H, C(3)- β -H); 2.22 (dd, 1 H, $^2J = 14$ Hz and $^4J_{17\beta,7\alpha} = 1.3$ Hz, C(17)- β -H); 3.50 (dd, 1 H, $^2J = 14$ Hz and $^3J_{21\alpha,\text{OH}} = 5$ Hz, C(21)- α -H); 3.59 (s, 3 H, OMe); 3.60 (dd, 1 H, $^2J = 12$ Hz and $^3J_{21\beta,\text{OH}} = 7$ Hz, C(21)- β -H); 4.65 (d, 1 H, $^3J = 2.7$ Hz, C(14)H); 6.51 (d, 1 H, $^3J = 2.7$ Hz, C(15)H). The addition of a drop of D_2O in the NMR tube results in the conversion of the C(21)- α -H and C(21)- β -H signals into doublets with $J_{\text{AB}} = 12$ Hz. For ^{13}C NMR data see Table 2. MS, m/z : 360.2304 $[\text{M}]^+$. Calculated for $\text{C}_{22}\text{H}_{32}\text{O}_4$: 360.2300.

B. A solution of compound **5** (2.70 g, 7.55 mmol) in acetone (40 mL) was irradiated with a DRSh-1000 high-pressure mercury vapor lamp on cooling with a ventilator for 5 h. Then acetone was evaporated, and the residue was chromatographed to give the starting ester **5** (1.81 g), ester **8** (0.27 g), and a mixture of unidentified compounds (0.45 g), sequentially.

References

- W. G. Dauben and V. F. German, *Tetrahedron*, 1966, **22**, 679.
- N. K. Kashtanova, A. I. Lisina, A. K. Dzizenko, and V. A. Pentegova, *Izv. Sib. Otd. Akad. Nauk SSSR*, 1967, No. 2, 126.
- V. A. Pentegova, Zh. V. Dubovenko, V. A. Raldugin, and E. N. Shmidt, *Terpenoidy khvoynykh rastenii [Terpenoids of Coniferous Plants]*, Nauka, Novosibirsk, 1987, 97 pp. (in Russian).
- USSR Inventor's Certificate No. 1668352, *Byull. Izobret.*, 1992, 29 (in Russian).
- V. A. Raldugin, V. V. Grishko, Yu. V. Gatilov, M. M. Shakirov, I. Yu. Bagryanskaya, and L. I. Demenkova, *Sib. Khim. Zh. [Sib. Chem. J.]*, 1992, No. 5, 66 (in Russian).
- V. A. Raldugin, V. V. Grishko, I. Yu. Bagryanskaya, Yu. V. Gatilov, and M. M. Shakirov, *Sib. Khim. Zh. [Sib. Chem. J.]*, 1993, No. 1, 69 (in Russian).
- V. L. Minkin and N. E. Dorofeenko, *Usp. Khim.*, 1960, **29**, 1301 [*Russ. Chem. Rev.*, 1960, **29** (Engl. Transl.)].
- J. P. Kutney, H. W. Hanssen, and G. V. Nair, *Tetrahedron*, 1971, **27**, 3323.
- R. Roy, A. Mukhergea, and A. Bharduri, *Indian J. Chem.*, 1992, **31**, 608.

Received April 25, 1995