

Synthesis of (*Z*)-9,10-Epoxy-nonacosane, a Long-Chain Epoxide Isolated from Stem Wax of *Rubus thibetanus*

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(*Z*)-9,10-Epoxy-nonacosane has been synthesized in four steps starting from oleic acid.

Rubus thibetanus Franck (Rosaceae) is a blackberry species originating from West China. Its erect branches, up to 180 cm high, are glaucous, the waxy coating often being so conspicuous that it appears to be chalky. This feature makes these blackberry bushes decorative, even in winter. Chemical examination of the wax revealed that, previously undescribed, (*Z*)-9,10-epoxy-nonacosane (**1**) was the major component.¹

Many epoxides have demonstrated important biological activity.² We wish to report here the synthesis of (*Z*)-9,10-epoxy-nonacosane starting from oleic acid (**2**).

Oleic acid was converted to Weinreb's amide (**3**) following the standard procedure.³ The amide was treated with undecylmagnesium bromide, and the resulting (*Z*)-nonacosan-9-en-18-one (**4**) was converted to (*Z*)-9,10-nonacosene (**5**) by reduction of the tosylhydrazone intermediate with NaBH₄ at reflux.⁴ Treatment of (*Z*)-9,10-nonacosene with 3-chloroperoxybenzoic acid (*m*-CPBA)⁵ gave (*Z*)-9,10-epoxy-nonacosane (**1**) (56% overall yield). Physical properties of the synthetic sample agree well with those reported by the original authors.¹

Experimental Section

General Experimental Procedures. IR spectra were recorded with a Perkin-Elmer 1310 spectrophotometer. The ¹H- and ¹³C-NMR spectra were recorded in CDCl₃ at 200 MHz on a Varian Gemini 200 spectrometer. Chemical shifts were recorded relative to internal TMS. Mass spectra were determined on a Hewlett-Packard GC/MS 5970 (EI, 70 eV). Reactions were monitored with a Carlo Erba Fractovap 4160 gas chromatograph using a capillary column of Duran glass (0.32 mm × 25 m), stationary phase OV1 (film thickness 0.4–0.45 nm) or by TLC. Flash chromatography was performed⁶ on Merck SiO₂ gel (0.040–0.063 mm) with hexane–EtOAc as eluent. Microanalyses were performed by using a Fisons Model EA 1108 C, H, N, S analyzer. THF was dried by refluxing it over sodium wire until the blue color of benzophenone ketyl persisted and distilling it into a receiver under a nitrogen atmosphere. EOH-free CHCl₃ was obtained by washing the CHCl₃ with H₂O, drying, and distilling immediately before use.

(*Z*)-*N*-Methoxy-*N*-methyloctadec-9-enamide (3**).** To a mixture containing 0.5 g (1.77 mmol) of oleic acid (**2**) and 10 mL of dry benzene was added thionyl chloride (0.42 g, 3.54 mmol). The mixture was stirred for 24 h at 50 °C. The solvent and excess reagent were removed

under reduced pressure, and the crude acid chloride was dried under vacuum. The crude compound was dissolved in 20 mL of EtOH-free CHCl₃, and *N,O*-dimethylhydroxylamine hydrochloride (0.19 g, 1.95 mmol) was added. The mixture was cooled at 0 °C, and pyridine (0.31 g, 3.89 mmol) was added dropwise via syringe. Stirring was continued for 2 h at room temperature, and then the mixture was evaporated under reduced pressure. The residue was partitioned between brine and a 1:1 mixture of Et₂O and CH₂Cl₂. The organic layer was dried with Na₂SO₄ and concentrated to afford an oil that was purified by flash chromatography (hexane–EtOAc, 8:2) to give the amide **3**, 0.48 g (83%), as a colorless oil: IR (dry film) ν_{\max} 3010, 1665, 1455, 1380, 1170, 995 cm⁻¹; ¹H NMR δ 0.87 (t, 3H, *J* = 6.5 Hz, CH₃C), 1.24–1.41 (m, 20H), 1.61 (m, 2H), 1.98–2.01 (m, 4H, CH₂C=CCH₂), 2.40 (t, 2H, *J* = 7.3 Hz, CH₂CO), 3.16 (s, 3H, NCH₃), 3.67 (s, 3H, OCH₃), 5.53 (m, 2H, CH=CH); EIMS (70 eV) *m/z* [M]⁺ 325, 265, 247, 135, 109, 97, 95, 83, 61 (100%), 57, 55, 41, 39; anal. C 73.78%, H 12.10%, N 4.29%, calcd for C₂₀H₃₉NO₂. C 73.79%, H 12.07%, N 4.30%.

(*Z*)-Nonacos-9-en-18-one (4**).** To a solution of *N*-methoxy-*N*-methyloctadec-9-enamide (**3**) (0.3 g, 0.85 mmol) in 5 mL of dry THF was added, dropwise, a solution of undecylmagnesium bromide [prepared from 0.6 g (2.55 mmol) of commercial 1-bromoundecane and 66 mg (2.72 mmol) of magnesium turnings in 3 mL of dry THF] at 0 °C under argon. After stirring for 3 h at 0 °C, the mixture was poured into 5% HCl–ice H₂O and then extracted with Et₂O. The combined organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane–EtOAc, 98:2) to give 0.34 g (95%) of (*Z*)-nonacos-9-en-18-one (**4**) as a colorless oil: IR (dry film) ν_{\max} 3010, 1710, 1450, 1370, 715 cm⁻¹; ¹H NMR δ 0.88 (t, 6H, *J* = 6.3 Hz, 2 × CH₃C), 1.05–1.54 (m, 40H), 1.95–2.25 (m, 8H), 5.33 (m, 2H, CH=CH); EIMS (70 eV) *m/z* [M]⁺ 420, 265, 237, 211, 183, 109, 97, 83, 61, 57, 55 (100%), 43, 41, 39; anal. C 82.76%, H 13.40%, calcd for C₂₉H₅₆O. C 82.78%, H 13.41%.

(*Z*)-9-Nonacosene (5**).** A solution of (*p*-tolylsulfonyl)hydrazine (0.18 g, 0.96 mmol) in EtOH (7 mL) was added to a solution of (*Z*)-nonacos-9-en-18-one (**4**) (0.37 g, 0.87 mmol), and the mixture was stirred for 15 h until the formation of tosylhydrazones was completed. Then, NaBH₄ (0.49 g, 12.9 mmol) was added in small portions, and the mixture was refluxed for 8 h, then treated carefully with cold H₂O (15 mL), acidified with 2 N HCl (pH 4–5), and extracted with *n*-pentane (3 × 10 mL). The organic layer was dried (Na₂SO₄), the solvent was removed by distillation, and the crude product was

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purified by short flash chromatography (hexane–EtOAc, 98:2) to afford 287 mg (80%) of the pure (*Z*)-9-nonacosene **5**: $^1\text{H NMR}$ δ 0.88 (t, 3H, $J = 7.2$ Hz, CH_3), 0.89 (t, 3H, $J = 7.2$ Hz, CH_3), 1.25–1.65 (m, 46H), 1.9–2.1 (m, 4H, $\text{CH}_2\text{C}=\text{CCH}_2$), 5.32–5.45 (m, 2H, $\text{CH}=\text{CH}$); EIMS (70 eV) m/z $[\text{M}]^+$ 406, 139, 111, 97 (100%), 57, 43; anal. C 85.76%, H 14.24%, calcd for $\text{C}_{29}\text{H}_{58}$, C 85.62%, H 14.37%.

(Z)-9,10-Epoxy-nonacosane (1). To a solution of (*Z*)-9-nonacosene **5** (90 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) was added 70% 3-chloroperoxybenzoic acid (*m*-CPBA, 59 mg, 0.24 mmol). The solution was stirred for 10 h after which 10% aqueous Na_2SO_3 (10 μL) was added. The layers were separated, and the aqueous layer was extracted two times with CH_2Cl_2 . After the combined organic layers were washed with saturated aqueous NaHCO_3 and brine, they were dried and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 98:2) to give 83 mg (89%) of the corresponding wax epoxide **1**: IR (dry film) ν_{max} 1410, 1360, 1108, 720 cm^{-1} ; $^1\text{H NMR}$ δ 0.860 (t, 3H, $J = 6.3$ Hz, CH_3C), 0.861 (t, 3H, $J = 6.3$

Hz, CH_3C), 1.10–1.70 (m, 50H), 2.85–2.95 (m, 2H, $2 \times \text{CHC}$); $^{13}\text{C NMR}$ δ 14.6 (CH_3), 23.2 (CH_2), 23.21 (CH_2), 27.0 (CH_2), 28.3 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 30.2 (CH_2), 30.6 (CH_2), 32.3 (CH_2), 32.4 (CH_2), 57.4 (CH); EIMS (70 eV) m/z $[\text{M}]^+$ 422, 309, 278, 155, 124, 97, 83, 69, 57, 55, 43 (100%), 41, 39; anal. C 82.36%, H 13.79%, calcd for $\text{C}_{29}\text{H}_{58}\text{O}$, C 82.38%, H 13.82%.

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References and Notes

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