SCIREA Journal of Chemistry

https://www.scirea.org/journal/Chemistry

August 9, 2019

Volume 4, Issue 3, June 2019

The Practical Synthesis and Purification of *cis*-11-Octadecenoic Acid: A Component of Inhibition of Endotoxin Response

Yoshifumi Yuasa and Akiko Horizoe

Kasai Chemical Laboratory, 7-7-402 Akashicho, Hiratsuka, Kanagawa, 254-0042, Japan.

Correspondence should be addressed to Y.Yuasa; Kasaiyuasay@gmail.com

Abstract

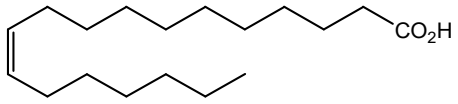
cis-11-Octadecenoic acid **1**, which is known to be a useful chemical for the component of drugs, has been synthesized by Wittig reaction with *n*-heptanal and 10-methoxycarbonyldecyltriphenylphosphonium bromide using potassium *t*-butoxide at –50 °C to give methyl *cis*-11-octadecenoate **2** in 79% yield with 95% *cis*-selectivity, followed by hydrolysis and then recrystallizated by MeOH at –20 °C to give a high purity of **1** in 33% yield.

Keywords: *cis*-11-Octadecenoic acid; Asclepic acid; Wittig reaction; Potassium *t*-butoxide; *cis*-Selectivity.

1. Introduction

cis-11-Octadecenoic acid **1** (Fig. 1); asclepic acid, which was identified by Morton et al. [1] with the haemolytic factor of horse brain, and it was later shown by Hofmann [2,3] to be the principal unsaturated fatty acid in *Lactobacillus arabinosus* and *L. casei*. Morever, **1** has been

reported by Mullarkey et al. [4] as a component of Inhibition of Endotoxin Response (Eritoran; E5564, Fig. 2).



1

FIGURE 1: The Structure of *cis*-11-Octadecenoic acid 1

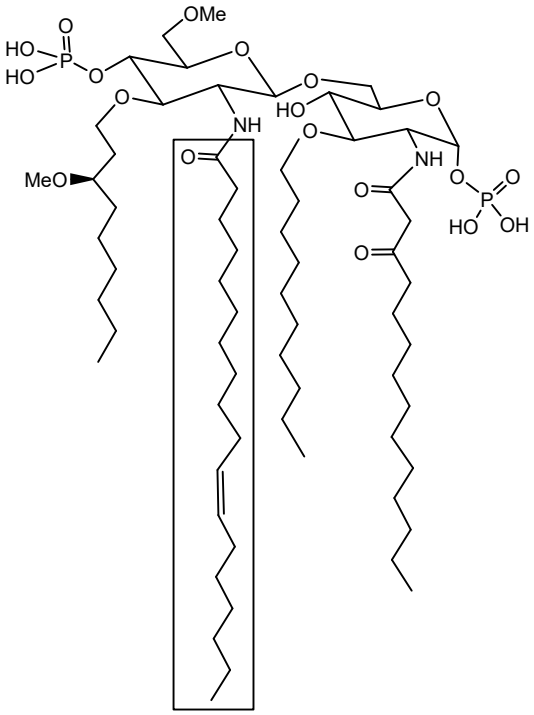


FIGURE 2: The Structure of Eritoran

Many syntheses of **1** have been reported [3, 5-11], however, it is difficult to obtain **1** as a facial and cost effect method in these syntheses. In particular, Weedon et al. [9] have reported that the Wittig type condensation of *n*-heptanal and 10-ethoxycarbonyldecyltriphenylphoshonium iodide, followed by hydrolysis to give **1** with 37% yield contained 5–7% of the *trans*-isomer. This method is used a readily available material and a short step, however, it is not the effective method concerning the *cis*-selectivity of Wittig reaction [11], a purity of *cis*-isomer in the product and the yield. As the similar method, Dzhemiev et al. [12] have reported the synthesis of methyl ester of **1** which was the Wittig reaction of *n*-heptanal and 10-methoxycarbonyldecyltriphenylphoshonium bromide used by potassium *t*-butoxide as base. However, these reports have not described about the purification of *cis*-isomer. In this viewpoint, we have re-examined the Wittig reaction of

n-heptanal and 10-methoxycarbonyl- decyltriphenylphoshonium bromide with base on large scales, and then the alkali hydrolysis followed by recrystallization for the purity-up. As the result of study, we now report the practical and effective synthesis of **1** with respect to provide a high purity of this useful chemical.

2. Materials and Method

2.1 General

All reagents and solvents were obtained from commercial sources and used without further purification. Boiling points are uncorrected values. Melting points were prepared using a Yanagimoto apparatus and are uncorrected. The NMR was a Bruker DRX-500. IR: Nicolet Avatar 360 FT-IR. The GC was done using a Shimadzu GC-18A with an FID detector (Column, TC-1 produced by GL Sciences, Inc., Japan, df = 0.25 m, 0.25 mm ID 30 m; carrier gas N_2, 0.1MPa, oven temperature, 150–230 °C programmed at 5 °C /min; injection temperature, 230 °C, detector temperature, 250 °C. **3** *tr*: 11.0 min., *cis*-**2** *tr*: 17.5 min., *trans*-**2** *tr*: 18.2 min. The GC was done using a Shimadzu GC-18A with an FID detector (Column, TC-WAX produced by GL Sciences, Inc., Japan, df = 0.25 m, 0.25 mm ID 30 m; carrier gas N_2, 0.1MPa, oven temperature, 150–230 °C programmed at 5 °C /min; injection temperature, 230 °C, detector temperature, 250 °C. *trans*-**1**: 17.5 min., *cis*-**1**: 18.3 min., HPLC: Hitachi L-6200: Column YMC-Pack ODS-AL313 (df = 5 m, 4.6 mm × 250 mm.) eluent: CH_3CN/0.15% aqueous H_3PO_4 = 8/2, Temp. 35 °C. Flow rate: 1.5 ml/min. Detector: Hitachi L-4000 (210 nm). *cis*-**1**: t*r* 11.9 min., *trans*-**1**: t*r* 15.8 min.

2.2 Synthetic procedures

Methyl *cis*-11-octadecenoate (2): In a 5-L glass vessel, methyl 11-bromoundecanoate **3** (693 g, 2.48 mol), triphenylphosphine (716 g, 2.73 mol) and CH_3CN (1.4 L) were added and the reaction mixture was stirred at 80 °C for 24 h. After the solvent was recovered under reduced pressure (80 °C/30–1 Torr.), 10-methoxy- carbonyldecylphosphonium bromide (1,409 g, 100%) was obtained as a solid (Mp. 110–112 °C). In a 20-L glass vessel, the phosphonium bromide (1,254 g) and THF (7.5 L) were added. The mixture was cooled at –50 °C and then potassium *t*-butoxide (253 g, 2.26 mol) in THF (6.3 L) was dropped for 1 h. The reaction mixture was stirred at the same temperature for 3 h and then *n*-heptanal (259 g, 2.26 mol) in THF (520 mL) was dropped for 1.5 h. The reaction mixture was stirred at –20 °C for 16 h. The conversion was 97% by GC. The solvent was recovered under reduced pressure

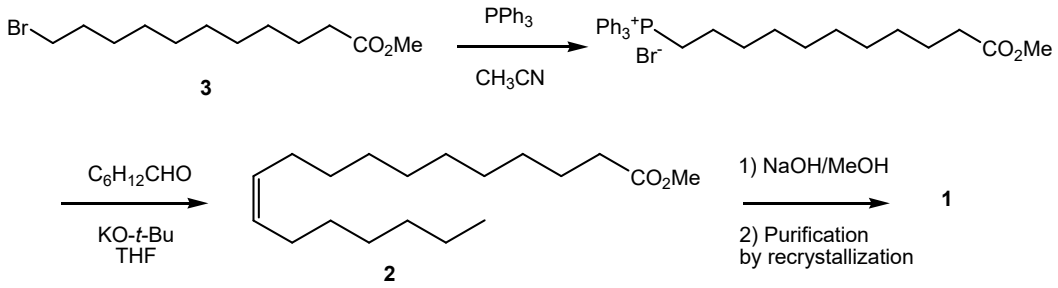
(70 °C/30 Torr.) and toluene (2.5 L) was added to the residue (1,709 g) and washed with 10% NaCl solution (2.5 L 2). Toluene was recovered under reduced pressure (70 °C/30 Torr.) and the solid residue was washed several times with *n*-heptane and filtered off. The heptane solution was concentrated under reduced pressure (50 °C/30 Torr.) and then the crude product was distilled by Claisen-type distillation to give methyl *cis*-11-octadecenoate 2 (580 g, p. 89%, Yield 79%) as an oil. bp 145–146 °C/0.15 Torr. {lit. [9] bp.134–136°C /0.2 mm.} IR (neat) 3004, 2926, 2855, 1743, 1459, 1436, 1171 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 0.88 (t, J = 6.9, 3H), 1.28–1.34 (m, 20H), 1.59–1.63 (m, 2H), 1.99–2.03 (m, 4H), 2.30 (t, J = 7.4, 2H), 3.66 (s, 3H), 5.35 (m, 2H). ^{13}C-NMR ($CDCl_3$) 14.08 (CH_3), 22.65 (CH_2), 24.95 (CH_2), 27.19 (CH_2), 27.21 (CH_2), 28.97 (CH_2), 29.14 (CH_2), 29.24 (CH_2), 29.25 (CH_2), 29.40 (CH_2), 29.46 (CH_2), 29.73 (CH_2), 31.77 (CH_2 2), 34.11 (CH_2), 51.41 (CH_3), 129.84 (CH), 129.92 (CH), 174.32 (CO). MS m/z: 296 (M^+, 8.5), 265 (28.3), 264 (43.4) 235 (6.7), 222 (21.7), 207 (3.8), 193 (2.8), 180 (16.0), 166 (8.5), 152 (10.4), 138 (11.3), 125 (16.0), 111 (24.5), 97 (50.9), 83 (51.9), 69 (73.5), 55 (100), 41 (54.7).

cis-11-Octadecenoic acid (1): In a 5-L glass vessel, MeOH (2.5 L) and 50%NaOHaq. (200mL) were added. After dissolved, methyl *cis*-11-octadecanoate **2** (570 g, 1.92 mol) was added dropwise and stirred at 70°C for 3 h. MeOH was recovered under reduced pressure (70°C/40 Torr.) and then 10% HCl (1L), wather (1L) and toluene (1.25 L) were added, washed with water (1.8 L). Toluene was recovered under reduced pressure (80°C/ 40 Torr.) to give crude *cis*-11-octadecenoic acid 1 (530 g, *cis*-purity 95% by HPLC, Yield 98%).

In a 5-L glass vessel, crude 1 (530 g) and MeOH (1.6 L) were added and cooled at –20 °C. After 3h, the precipitated solid was filtered. The procedure was repeated one more time, and then dried in vacuum (40 °C/1 Torr.) to give a high purity *cis*-11-octadecenoic acid **1** (162 g, *cis*-purty 99.8% by HPLC, Yield 33%). mp 14–15 °C. {lit. [5], mp 10.5–12 °C} IR (neat) 3004, 2926, 2855, 1710, 1462, 1413, 1287 cm^{-1}. ^{1}H NMR ($CDCl_3$) : 0.88 (t, J = 6.9, 3H), 1.25–1.34 (m, 20H), 1.60–1.66 (m, 2H), 1.99–2.03 (m, 4H), 2.35 (t, J = 7.4, 2H), 5.35 (m, 2H). ^{13}C NMR ($CDCl_3$) 14.08 (CH_3), 22.65 (CH_2), 24.67 (CH_2), 27.18 (CH_2), 27.21 (CH_2), 28.97 (CH_2), 29.05 (CH_2), 29.22 (CH_2), 29.25 (CH_2), 29.39 (CH_2), 29.46 (CH_2), 29.73 (CH_2), 31.77 (CH_2 2), 33.99 (CH_2), 129.83 (CH), 129.93 (CH), 179.79 (CO). MS m/z: 282 (M^+, 3.8) 264 (16.9), 235 (3.7), 222 (5.7), 207 (5.4), 193 (1.9), 180 (4.0), 165 (3.7), 151 (5.6), 138 (7.5), 123 (11.3), 111 (22.6), 97 (49.0), 83 (54.7), 69 (94.3), 55 (100), 41 (66.0).

3. Results and Discussion

Initially, we attempted the Wittig reaction of *n*-heptanal and 10-methoxycarbonyldecyltriphenylphoshonium bromide, which is derived from methyl 11-bromoundecanoate **3** and triphenylphosphine, in DMF with NaOEt as a base similarly to the above described literature [9], however, the satisfactory result of a high selectivity of *cis*-isomer was not obtained. (Table 1, run 1, 2). The *cis*-selectivity was determined by GC and HPLC after the hydrolysis of ester.



SCHEME 1: Synthetic Route of cis-11-Octadecenoic Acid

We investigated the *cis*-selectivity of methyl *cis*-11-octadecenoat **2** by using some bases, thus sodium ethoxide (NaOEt), sodium bistrimethylsiliylamide [$NaN(SiMe_3)_2$] and potassium *t*-butoxide (KO*t*-Bu) as a base similarly to the above described literature [12], and then the best result was obtained in a case of using KO*t*-Bu (Table 1, run 6). Thus, *n*-heptanal and 10-methoxy- carbonyldecyltriphenyl phoshonium bromide were reacted in THF at –50 °C with KO*t*-Bu to give **2** in 79% yield with 95% *cis*-selectivity.

TABLE 1: The results of Wittig reaction in some reaction conditions.

	Base	Temp. (°C)	Solvent	*Cis*-selectivity (%)	Yield of **2** [b] (%)
1	NaOEt	–50 to 20	DMF	81	30
2	NaOEt	–50 to 20	THF	83	34
3	$NaN(SiMe_3)_2$	–50 to 20	THF	90	48
4	KOt-Bu	–50 to 20	DMF	93	45
5	KOt-Bu	–50 to 20	CH_3CN	88	50
6	KOt-Bu	–50 to –20	THF	95	79

[a]*cis*-Selectivity of ester **2** was determined by GC (TC-WAX) and/or HPLC as acid **1** after hydrolysis of **2**.

[b]No purificated yield.

The ester **2** was hydrolyzed by 10% NaOHaq./MeOH solution at 70 °C for 3 h to give crude acid **1** according to an usual method. The purity-up of **1** has been reported by recrystallization using acetone at –30 °C [7].

We investigated about the inexpensive recrystallization solvent and the 99.8% purity of **1** was obtained by using MeOH at –20 °C (Table 2, run 7). It is difficult that the purity-up of crude **1** could not be performed by one time recrystallization in case of the purity of crude product is under 95%. Because the *trans*-11-octadecanoic acid having a high melting point as an impurity, the purity of *cis*-form **1** could not be raised. Furthermore, the recrystallization temperature under –20 °C can not raised to the purity of *cis*-form **1**, because the *trans*-11-octadecanoic acid which is a high melting point was easily crystallized more than *cis*-form.

TABLE 2: The results of variable solvents on recrystallization of 1

	Solvent	*cis*-Purity (%)	Yield (%)
1	Acetone	98.0	25
2	Toluene	95.8	18
3	MeOH	99.8	33

[a]The crude **1** obtained in run 6 of table 1 was used as the starting material for recrystallization.

[b]The recrystallization was carried out at –20 °C.

4. Conclusion

In conclusion, we succeed in the practical and purification of **1** by Wittig reaction with *n*-heptanal and 10-methoxycarbonyldecyltriphenylphosphonium bromide using potassium *t*-butoxide at –50 °C and then recrystallizated by MeOH at –20 °C. This method is suitable for large-scale synthesis of **1**.

References

[1] I. D. Morton and A. Todd, “The Haemolytic Acid present in Horse Brain” R. *Biochem. J.*, Vol. 47, pp. 327-330**,** 1950.

[2] K. Hofmann, R. A. Lucas and S. M. Sax, “The Chemical Nature of The Fatty Acids of Lactobacilus Arabinosus” *J. Biol. Chem.,* Vol. 195, pp. 473-485, 1952.

[3] K. Hofmann and S. Sax, “The Chemical Nature of the Fatty Acids of Lactobacilus Casei” *J. Biol. Chem.,* Vol. 205, pp. 55-66, 1953.

[4] M. Mullarkey, J. R. Rose, J. Bristol, T. Kawata, A. Kimura, S. Kobayashi, M. Przetak, J. Chow, F. Gusovsky, J. William,. W. J. Christ, P. Daniel and D. P. Rossignol, “Inhibition of Endotoxin Response by E5564, a Novel Toll-Like Receptor 4-Directed Endotoxin Antagonist” *J. Pharmacol. Exp. Ther.***,** Vol. 304, pp. 1093-1102, 2003, W. J. Christ, D. P. Rossignol, S. Kobayashi and T. Kawata, US Patent 5935938, 1999.

[5] K. Ahmad, F. M. Bumpus and F. M. Strong, “Synthesis of cis-11-Octadecenoic and trans-11-ctadecenoic (Vaccenic) Acids” *J. Amer. Chem. Soc.,* Vol. 70, pp. 3391-3394, 1948.

[6] S. A. Fusari, K. W. Greenlee and J. B. Brown, “Synthesis of Cis- and Trans-7- and 8-Octadecenoic Acids: Comparison of the Properities of Cis- and Trans-6-, 7-, 8-, 9-, and 11-Octadecenoic Acids” *J. Amer. Oil. Chem.,* Vol. 28, pp. 416-420, 1951.

[7] W. F. Huber, “A Study of *n*-Octadecenoic Acids. Synthesis of *cis*- and *trans*-7- through 12- and of 17-Octadecenoic Acids” *J. Amer. Chem. Soc.,* Vol. 73, pp. 2730-2735, 1951.

[8] D. G. Bounds; R. P. Linstead, and B. C. L. Weedon, “Anodic Synthesis. Part XII. Synthesis of *cis*- and *trans*-Octadec-11-enoic Acid, with a Note on the Nature of Vaccenic Acid.” *J. Chem. Soc.,* pp. 4219-4224, 1954.

[9] G. Pattenden and B. C. L. Weedon, “Carotenoids and Related Compounds. Part XVIII. Synthesis of *cis*- and Di-*cis*-Polyenes by Reactions of the Wittig Type” *J. Chem. Soc. (C),* pp. 1984-1992, 1968.

[10] S. Ranganathan, V. Maniktala, R. Kumar and G. P. Singh,”Metamorphosis of Gastor Oil to Inset Sex-pheromones & Useful Synthons ” *Indian J. Chem.,* Vol. 23B, pp. 1197-1207, 1984.

[11] A. Maercker, “The Wittig Reaction”*Organic Reaction,* Vol. 14, pp. 270-490, 1965.

[12] U. M. Dzhemilev, G. G. Balezina, L. A. Volkova, V. P. Krivonogov and G. A. Tolstikov, “Insect Pheromones and Their Analogs III. Synthesis of the Sex Attractants of Some Lepidoptera” *Chemistry of Natural Compounds*, Vol. 16, pp. 82-85, 1980, *Khimiya Prirodnykh Soedinenii,* Vol. 16, pp. 97-102, 1980.