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SYNTHESIS OF TYPES II AND III CYANOLIPIDS[1]

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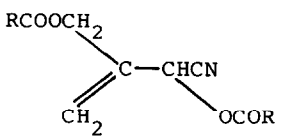
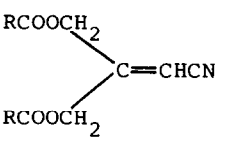
Abstract: Types II and III cyanolipids, which show an insecticidal activity, are synthesized by a very simple procedure. Esterification of fatty acid salts with 1,3-dibromoacetone or bromoacetone using a phase-transfer catalyst in non-polar solvent, followed by Wittig condensation, provided a variety of cyanolipids in high yield.

Cyanolipids are a unique class of plant lipids classified into four types I—IV[2], characteristic to seed oil of Sapindaceous plants. Recently, we have established full structures of three kinds of type II cyanolipids, N-IIb (1b), N-IIc (1c), and N-IId (1d), after complete purification by careful fractionation with the reverse-phase HPLC technique[1]. Mikolajczak et. al. have reported the structural study of cyanolipids and assigned the major fatty acid constituents to be C_{18}- and C_{20}-monoenoic and C_{20}-saturated acids for type III lipids[3]. However, their discussions have always been performed with mixture of cyanolipids, because of the very close similarity on the chromatographic and spectroscopic properties of each of the lipid component. Recent discovery of the insecticidal activity of cyanolipids[4] prompted us to design a general synthesis of this class of natural products. Described herein is the first synthesis of three kinds of type II (1b, 1c, and 1d) and three kinds of type III (2b, 2e, and 2f) cyanolipids in a following efficient procedure.



I



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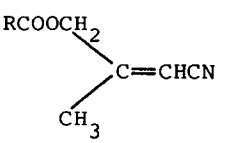
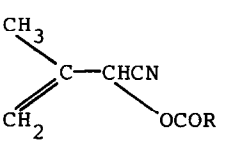


III



IV

Since usual esterification of 1,3-dihydroxyacetone dimer with oleyl chloride in the presence of base was unsuccessful, 1,3-dibromoacetone was employed as a starting material. By using tetrabutylammonium bromide (TBAB) as a catalyst, stepwise substitution reaction with proper sodium carboxylate took place very smoothly in non-polar solvent[5]. The intermediary half ester was isolable by using a calculated amount (1 equiv) of the carboxylate. Thus, preparation of the mixed diester was easily achieved. Subsequent Wittig condensation afforded a variety of cyanolipids in high yield.

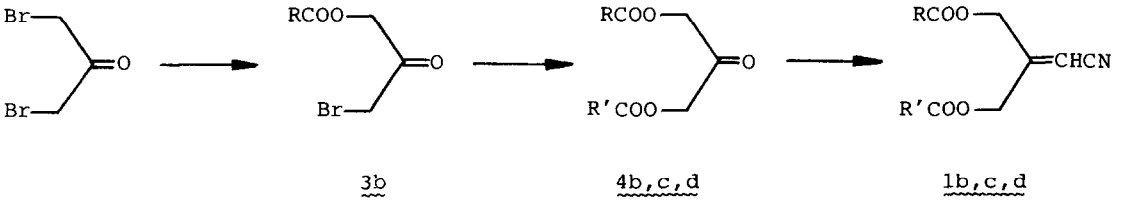
Synthesis of N-IIb (1b) is a representative of this procedure. A suspension of 1,3-dibromoacetone (200 mg, 0.92 mmol), sodium oleate (844 mg, 2.78 mmol), and TBAB (30 mg, 0.093 mmol) in toluene (3 ml)[6] was stirred vigorously at room temperature for 24 h. The filtrate through cotton-Celite pad was subjected to column chromatography on silica gel with a 1:1 mixture of dichloromethane and benzene to give 550 mg (96% yield) of 4b as a colorless syrup. A solution of 4b (239 mg, 0.39 mmol) and cyanomethylenetriphenylphosphorane (234 mg, 0.78 mmol)[7] in anhydrous benzene (4 ml) was heated at reflux under argon atmosphere for 24 h. The cooled solution was directly subjected to column chromatography on silica gel with a 4:1 mixture of petroleum ether and ether, affording N-IIb (1b) (234 mg, 94% yield) as a semi-solid. The IR, ^{1}H NMR, and ^{13}C NMR were superimposable with those of the natural product. This product was also indistinguishable from the natural lipid in HPLC analysis[8].

When the esterification was conducted with 1 equiv of sodium oleate, a mono-ester 3b (33% yield) was isolated together with the diester 4b (15% yield) after silica gel column chromatography (8:1 mixture of petroleum ether and ether). Repeated condensation of the mono-ester bromide 3b with sodium 11-Z-eicosenoate in the presence of TBAB (0.1 equiv) in toluene afforded a mixed diester 4c in 77% yield. The latter was converted to N-IIc (1c) in 74% yield. In the same way, 3b was converted to N-IId (1d) through esterification with sodium eicosanoate (60% yield) and Wittig condensation (93% yield). The synthetic N-IIc (1c) and N-IId (1d) were obtained as a stereoisomeric mixture of isobutenyl cyanide moiety, however, the spectral and HPLC data were indistinguishable with those of natural products[9].

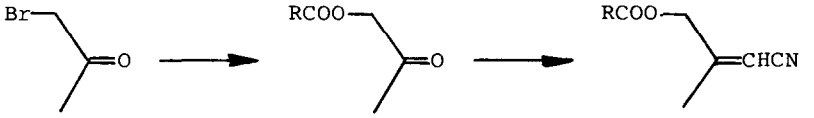
By using bromoacetone as the starting material, TBAB-catalyzed esterification of sodium oleate, sodium 11-Z-eicosenoate, or sodium eicosanoate smoothly gave ketones 5b, 5e, and 5f in quantitative yield. These products were then converted to type III cyanolipids 2b[10], 2e[10], and 2f[11] in 82%, 64%, and 77% yield, respectively, by the treatment with cyanomethylenetriphenylphosphorane. These three lipids were obtained as a stereoisomeric mixture of E and Z (6:1) of isobutenyl cyanide moiety[12]. Anyhow, these three compounds are first fully characterized type III cyanolipids.

By developing this simple and general preparative method, the type II and

III artificial cyanolipids with various chain length of the fatty acid parts became available in a large quantity. Biological examinations with hatched larvae of several insects and determination of the structure-activity relationship are in progress.



3b 4b,c,d 1b,c,d



5b,e,f 2b,e,f

b, R = (R' =) $CH_3(CH_2)_7CH{=}CH(CH_2)_7$

c, R = $CH_3(CH_2)_7CH{=}CH(CH_2)_7$; R' = $CH_3(CH_2)_7CH{=}CH(CH_2)_9$

d, R = $CH_3(CH_2)_7CH{=}CH(CH_2)_7$; R' = n-$C_{19}H_{39}$

e, R = $CH_3(CH_2)_7CH{=}CH(CH_2)_9$

f, R = n-$C_{19}H_{39}$

(Geometries of fatty acid double bonds are Z)

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References and Notes

1. Cyanolipid Part II, Part I See: M. Nishizawa, K. Adachi, S. Sastrapradja, and Y. Hayashi, Phytochemistry, in press.
2. K. L. Mikolajczak, Prog. Chem. Fats Other Lipids, 15, 97 (1977).
3. K. L. Mikolajczak, C. R. Smith, Jr., and L. W. Tjarks, Lipids, 5, 672 (1970).
4. Private communication from Professor I. Kubo of University of California, Berkeley.

5. J. Wildeman and A. M. van Leusen, Synthesis, 733 (1979).
6. Of a variety of solvent examined, such as hexane, dichloromethane, tetrahydrofuran, ether, and dimethylformamide, toluene afforded the best result. By using non-polar solvent, workup procedures of the reaction mixture became very simple.
7. J. W. Wilt and A. J. Ho, J. Org. Chem., 36, 2026 (1971).
8. The HPLC analysis was carried out using JASCO TRIROTAR-II instrument, ALTEX RI detector, Develosil C8-5 column, and acetonitrile as eluent in 2 ml/min flow rate. See also ref 1.
9. Not only the stereochemistry but also the stereochemical homogeneity of natural N-IIc and N-IId were not determined yet.
10. Analysis for 2b: Calcd for $C_{23}H_{39}NO_2$; C, 76.40; H, 10.87; N, 3.87. Found; C, 76.43; H, 10.89; N, 3.89. Analysis for 2e: Calcd for $C_{25}H_{43}NO_2$; C, 77.07; H, 11.13; N, 3.60. Found; C, 76.93; H, 11.11; N, 3.50. The spectral data of 2b and 2e are almost superimposable. Cited below are those for the major component of 2b[12] as the representatives. IR (neat) 3040, 2240, 1750, 1640 cm^{-1}. ^1H NMR (δ, $CDCl_3$) 0.87 (3H, t, J = 7Hz), 1.26 (br), 1.62 (2H, m), 2.00 (4H, m), 2.04 (3H, d, J = 0.8 Hz), 2.36 (2H, t, J = 7 Hz), 4.59 (2H, br), 5.30 (2H, t, J = 4 Hz), 5.34 (1H, br). ^{13}C NMR (δ, $CDCl_3$) 14.1, 18.0, 22.7, 24.9, 27.2, 29.1, 29.3, 29.5, 29.7, 29.8, 31.9, 34.0, 65.4, 95.8, 116.1, 129.7, 130.0, 157.7, 172.6.
11. Analysis for 2f: Calcd for $C_{25}H_{45}NO_2$; C, 76.67; H, 11.58; N, 3.58. Found; C, 76.63; H, 11.76; N, 3.54. IR (neat) 3060, 2220, 1740, 1640 cm^{-1}. ^1H NMR (δ, $CDCl_3$) 0.87 (3H, t, J = 7 Hz), 1.25 (br), 1.62 (2H, m), 2.05 (3H, d, J = 0.8 Hz), 2.36 (2H, t, J = 7 Hz), 4.58 (2H, br), 5.34 (1H, br). ^{13}C NMR (δ, $CDCl_3$) 14.2, 18.1, 22.8, 25.0, 29.2, 29.3, 29.4, 29.5, 29.8, 32.0, 34.1, 65.4, 95.9, 116.1, 157.7, 172.7.
12. The mixture were not separable on HPLC analysis. Nothing about the stereochemistry of the isobutenyl cyanide moiety of the type III cyanolipids has been recorded in the literature, but the following ^{13}C NMR analysis with 2f suggested the major isomer to be E. The allylic methyl signal of the major isomer (δ 18.1) and the allylic methylene signal of the minor isomer (δ 64.3) appear at the higher field than the corresponding carbon signals of the other isomer (δ 20.7 and 65.4) due to the steric compression effect.

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