Synthesis of 3Z-Nonenal and 3Z,6Z-Nonadienal

Tadahiko KAJIWARA, Yoshinobu ODAKE and Akikazu HATANAKA

Department of Agricultural Chemistry, University of Yamaguchi, Yamaguchi

Received March 31, 1975

3Z-Nonenal and 3Z, 6Z-nonadienal, potential biosynthetic precursors of 2E-nonenal and 2E, 6Z-nonadienal, were for the first time synthesized stereoselectively.

In the previous paper,¹⁾ the biosynthetic pathway of 2E, 6Z-nonadienal (IV-a), 2E-nonenal (IV-b), and the corresponding alcohols was proposed as implicit in Scheme 1, on the basis of biochemical and chemical evidence; linolenic (I-a), linoleic acid (I-b), 3Z, 6Z-nonadienal (II-a) and 3Z-nonenal (II-b) were found in cucumbers, the latter aldehydes having been enzymatically derived from I-a and I-b, respectively. These aldehydes were easily isomerized to the 2E-counterparts, IV-a and IV-b, respectively, which were further hydrogenated by alcohol dehydrogenase to the corresponding alcohols.

In the present paper, the first stereoselective synthesis of 3Z, 6Z-nonadienal (II-a), 3E, 6Z-(XXIV), 2E,6Z-nonadienal (IV-a) and 3Z-nonenal (II-b) was described with special emphasis on the IR-, NMR- and MAS-spectral evidence for the structure and stereochemistry.

[I] 3Z, 6Z-Nonadienal

The stereoselective synthesis of 1Z, 4Z-pentadienes of potential biological significance has not been established. Thus, 1Z, 4Z-pentadienals have not been known so far. We succeeded for the first time in a highly stereoselective synthesis of 3Z, 6Z-nonadienal (II-a) by means of stereoselective hydrogenation of diynol (XIV) followed by oxidation of 3Z, 6Z-nonadienol (III-a). This route of synthesis (Scheme 2) offers the advantage that sterically pure isomers can be obtained without contamination of other geometrical isomers by facile procedures.

The Grignard coupling of 3-butyryl-

tetrahydropyranyl ether (VIII)²⁾ with bromopentyne (XI) gave nona-3, 6-diynyl-tetrahydropyranyl ether (XIII) in good yield, which was contaminated by a small amount of isomeric impurities such as allens, and the product ether was used for further synthesis without purification. After removal of tetrahydropyranyl protective group, the resulting nonadiynol (XIV) was carefully rectified repeatedly on an effective column *in vacuo*.

Attempted stereoselective hydrogenation of nonadiynol (XIV) into 3Z, 6Z-nonadienol (III-a) by the use of W-1 Raney nickel and the Lindlar catalyst in ethanol, methanol or ethyl acetate under various conditions was doomed to failure, since the resulted dienol (III-a) was contaminated with considerable amounts of geometrical isomers as indicated by VPC.

With P-2 nickel³⁾ prepared from nickel acetate and sodium borohydride, the diynol (XIV) was hydrogenated in ethanol containing a small amount of ethylenediamine, to afford the desired sterically pure 3Z, 6Z-nonadienol (III-a) in nearly quantitative yield.

In the final stage, the unique oxidation of 3Z, 6Z-nonadienol (III-a) with chromium trioxide-pyridine complex in methylene chloride and with DMSO-DCC-P₂O₅ afforded the corresponding aldehyde, 3Z, 6Z-nonadienal (II-a) without shifting the double bonds into conjugation, and the yield was satisfactory. The products (II-a and III-a) thus obtained were practically free from any stereoisomers as evidenced by VPC, NMR and IR analyses.

The structural confirmation was obtained

SCHEME 3. Synthesis of 3Z-Nonenal and 2E, 6Z-Nonadienal.

also obtained with the naturally occurring aldehyde (II-b) from cucumbers.

[III] 3E, 6Z-, and 2E, 6Z-Nonadienal

2E, 6Z-Nonadienal (IV-a) was obtained by successive dihydrooxazine homologations starting from 2Z-pentenyl chloride (XIX) according to Scheme 3.

The carbanion (XX) generated by the action of butyl lithium was alkylated with (XIX) to give the oxazine (XXI) without rearrangement, which was then subjected to borohydride reduction. Subsequent acid-hydrolysis of the dihydrooxazine gave 4Z-heptenal (XXII), which was free from contamination, in high yield. The aldehyde with the 2 carbon-elongated chain was again condensed with oxazoline lithiate (XX) to give the corresponding hydroxyderivative (XXIII), which was not isolable by distillation. Fortunately, purification of the compound was not a necessary prerequisite to success of the overall sequence and this step was readily circumvented by the reduction of (XXIII) to the tetrahydro-1,3-oxazine. In the final stage, the mild hydrolysis of the reduced oxazine with oxalic acid yielded

violet leaf aldehyde, 2E, 6Z-nonadienal (IV-a), which was then reduced with lithium aluminium hydride to cucumber alcohol (V-a). The process proceeded in a stereospecific manner and the yield was satisfactory. The structure was fully substantiated by NMR, IR and MAS spectral comparison, and the synthetic aldehyde was identified with the naturally occurring violet leaf aldehyde.

3E, 6Z-Nonadienal (XXIV) was prepared by the condensation of XXII with malonic acid in triethanolamine, followed by decarboxylation, lithium aluminium hydride reduction and chromium trioxide-pyridine complex oxidation in methylene chloride. The structure was confirmed by comparison with 3Z, 6Z-nonadienal (II-a) obtained by unequivocal route (Scheme 2) as well as by NMR, IR and MAS spectral evidence. In accordance with expectation, the E, Z-geometry was supported by the absorption at 973 and 730 cm^{-1}

EXPERIMENTAL

IR-spectra were recorded with a Hitachi EPI-G2. NMR-spectra were taken on a Varian Associates Model A-60 (60 MHz). MAS-spectra were on a Japan spectroscopic Model TAM-OISG spectrometer.

[I] 3Z, 6Z-Nonadienal (II-a)

2-(3'-Butynyloxy)-tetrahydropyran (VIII). To a solution of 3-butynol (VII; 11.3 g; 0.16 mole) containing small amounts of HCl was dropwise added 2, 3-dihydropyran (16.0 g; 0.19 mole) with stirring. The reaction mixture was worked-up in an usual manner to give VIII (24.0 g; 97%), bp 90°C (14 mmHg). $\text{IR}_{\text{max}}^{\text{film}}$ cm^{-1} : 3250 ($\equiv\text{CH}$), 2100 ($-\text{C}\equiv\text{CH}$), 1120 ($\text{C}-\text{O}-\text{C}$).

2-Pentynol (X). a) 4-Chloro-2-butanol (IX; 77 g; 0.74 mole) obtained by mono-chlorination of butyne-1, 4-diol was added to Grignard reagent prepared from methyl bromide (154 g; 1.62 mole) and magnesium (39.4 g; 1.62 mole) in a mixed solvent of dry ether (500 ml) and dry THF (100 ml). After refluxing for 3 hr, the mixture was allowed to stand overnight. The reaction mixture was worked-up in an usual manner to afford X (50 g; 78%), bp 65~75°C (20 mmHg). $\text{IR}_{\text{max}}^{\text{film}}$ cm^{-1} : 3300 ($-\text{OH}$), 2250, 2200 ($-\text{C}\equiv\text{C}-$).

b) To a stirred solution of pyranyl ether (XII; 28.0 g; 0.2 mole) in dry THF (50 ml) and dry HMPA (50 ml) was added *n*-butyllithium (0.22 mole) in *n*-hexane keeping the temperature below 5°C. After the

mixture was stirred for 15 min, ethyl bromide (24.0 g; 0.22 mole) in dry THF was added rapidly. After stirring for an additional 30 min, the mixture was poured into a large volume of cold water and extracted with *n*-hexane. Pyranyl ether obtained thus was hydrolyzed with TsOH (1.0 g) in methanol under refluxing for 2 hr. The mixture was poured into water and extracted with ether. After evaporation of ether, distillation of the residue gave X (5.2 g; 31%), bp 65~70°C (20 mmHg).

2-Pentynyl bromide (XI). To a stirred solution of X (15.5 g; 0.19 mole) and pyridine (0.4 g) in dry ether was added PBr₃ (18.3 g; 0.068 mole). After refluxing for 2 hr, the mixture was cooled and upper layer was poured into ice. The reaction mixture was worked-up to give XI (19.5 g; 72%), bp 50°C (20 mmHg). IR_{max}^{film} cm⁻¹: 2200 (—C≡C—), 610 (C—Br).

3,6-Nonadiynol (XIV). A stirred solution of Grignard compound prepared from ethylmagnesium bromide (0.088 mole) and VIII (13.6 g; 0.088 mole) in dry THF was refluxed for 3 hr. The solution was cooled to 20°C and then cuprous chloride (0.02 g) was added with stirring. Bromide (XI; 11.8 g; 0.08 mole) in dry THF was added to the mixture, which was stirred for 3 hr at 20°C, then refluxed for an additional 16 hr. The reaction mixture was quenched and extracted with ether. Evaporation of solvent gave the crude compound (XIII), which was hydrolyzed with TsOH (0.6 g) in methanol under refluxing for 2.5 hr, to yield XIV (6.8 g; 62%), bp 115°C (15 mmHg). IR_{max}^{film} cm⁻¹: 3350 (—OH), 2200 (—C≡C—).

3Z, 6Z-Nonadienol (III-a). Diynol (XIV; 1.36 g; 0.01 mole) was hydrogenated by flashing with hydrogen in the presence of p-2 nickel catalyst prepared from nickel acetate (2.5 g; 0.01 mole) and the required quantity of NaBH₄ in dry methanol containing ethylene diamine (2.0 ml). The reaction mixture was worked-up in an usual manner to give dienol (III-a; 0.76 g; 54%), bp 110°C (13 mmHg). IR_{max}^{film} cm⁻¹: 3300 (—OH), 730 (Z, —CH=CH—). NMR (CDCl₃): δ 3.5 (2H, *t*, CH—CH₂—CH), 5.3 (4H, *m*, —CH=CH—CH₂—CH=CH—).

3Z, 6Z-Nonadienal (II-a). Chromium trioxide (6.0 g; 0.06 mole) was added to a magnetically stirred solution of pyridine (9.5 g; 0.12 mole) in methylene chloride (150 ml). The solution was stirred for 15 min at room temperature, at the end of this period, a solution of dienol (III-a; 1.25 g; 0.009 mole) in a small volume of methylene chloride was added in one portion. After stirring for an additional 15 min at room temperature, the solution was decanted from the residue, which was washed with 200 ml of ether. The combined organic solution was applied to a column of silica gel (Woelm) for dry-column chromatography and the eluate

was washed with 1 N HCl to remove a pyridine. The solvent was evaporated under nitrogen and the residue was distilled to give dienal (II-a; 1.2 g; 98%), bp 86~91°C (14 mmHg). IR_{max}^{film} cm⁻¹: 1725 (—CHO), 725 (Z, —CH=CH—). MAS: M⁺; 138 *m/e*. 2, 4-DNPH*; NMR (CDCl₃): δ 0.95 (3H, *t*, CH₃—CH₂—), 2.03 (2H, *p*, CH₃—CH₂—CH=), 2.80 (2H, *t*, —CH—CH₂—CH=), 3.15 (2H, *t*, —CH—CH₂—CH=N—), 5.28, 5.45 (4H, *m*, —CH=CH—CH₂—CH=CH—), 7.36 (1H, *t*, —CH₂—CH=N—), 7.75 (1H, *d*, Ho), 8.13 (1H, *d, d*, Hm'), 8.95 (1H, *d*, Hm), 10.88 (1H, *s*, =N—NH—).

[II] 3Z-Nonenal (II-b)

2Z-Octenol (XVI). The coupling of 4-chloro-2Z-butenol (XV; 26.6 g; 0.25 mole) with Grignard compound prepared from butyl bromide (82.2 g; 0.6 mole) and magnesium (14.4 g; 0.6 mole) afforded 2Z-octenol (XVI; 20.0 g; 80%), bp 105°C (20 mmHg). IR_{max}^{film} cm⁻¹: 3300 (—OH), 730 (Z, —CH=CH—).

Ethyl-3Z-nonenoate (XVII). 2Z-Octenyl chloride (6.3 g; 0.05 mole) prepared by chlorination of XVI was added to a solution of DMSO (50 ml) containing sodium cyanide (5.0 g; 0.10 mole). The reaction mixture was worked-up in an usual manner to give 3Z-octenonitrile (3.5 g; 60%), which was dissolved in ethanol and hydrogen chloride was slowly passed through the solution for 1 hr. The mixture was brought to gentle reflux for an additional 12 hr. The reaction mixture was filtered and diluted with water, and then neutralized with 5% Na₂CO₃, extracted with ether. Drying and concentration left a crude oil, which was distilled to give XVII (2.7 g; 78%), bp 102°C (20 mmHg). IR_{max}^{film} cm⁻¹: 1725 (—COOEt), 720 (Z, —CH=CH—).

3Z-Nonenol (III-b). Reduction of XVII with LiAlH₄ (2.7 g; 0.04 mole) in an usual manner gave the corresponding alcohol (III-b; 1.5 g; 57%), bp 97°C (17 mmHg). IR_{max}^{film} cm⁻¹: 3300 (—OH), 725 (Z, —CH=CH—).

3Z-Nonenal (II-b). According to the same manner mentioned above, III-b (1.0 g; 0.007 mole) was oxidized with chromium trioxide-pyridine complex in methylene chloride to the corresponding aldehyde (II-b; 0.95 g; 97%), bp 91°C (20 mmHg), IR_{max}^{film} cm⁻¹: 1725 (—CHO), 720 (Z, —CH=CH—).

[III] 2E, 6Z- (IV-a) and 3E, 6Z-Nonadienal (XXIV)

2Z-Pentenyl chloride (XIX). According to the procedure previously reported,⁴⁾ 2Z-pentenyl chloride (XIX) was prepared by methylation of 4-chloro-2Z-butenol (XV) via Grignard compound followed by

* DNPH: Dinitrophenyl hydrazone. 2, 4-DNPH of II-a was prepared according to the procedure previously reported.⁴⁾

chlorination of 2Z-pentenol (XIII), bp 55°C (60 mmHg).

4Z-Heptenal (XXII). To a stirred solution of 2, 4, 4, 6-tetramethyl-5, 6-dihydro-1, 3-oxazine (14.1 g; 0.10 mole) in dry THF was added dropwise *n*-butyllithium (0.11 mole) in *n*-hexane at -78°C. After stirring for 1 hr, the mixture was formed yellow precipitate, which was indicative of lithio anion (XX) formation. 2Z-Pentenyl chloride (XIX; 11.3 g; 0.11 mole) in dry THF was added to the mixture. The reaction mixture was allowed to slowly warm to room temperature. After standing for 1 hr, the mixture was poured into ice-water and was acidified (pH 2) with 6 N HCl. The acidic solution was extracted with *n*-hexane (discarded) and made basic by the careful addition of 40% NaOH solution. The resulting oil was extracted with ether and the extract was dried over anhydrous K₂CO₃. Evaporation of ether gave crude XXI, which was dissolved in ethanol (100 ml) and THF (100 ml) without further purification. The solution was cooled to -40°C and then NaBH₄ (4.15 g; 0.11 mole) solution and 6 N HCl solution were introduced to the stirred solution alternately so that pH 6~8 was maintained. After stirring for an additional 1 hr at -40°C, the contents were poured into water and made basic by the addition of 25% NaOH solution. The mixture was extracted with ether and the extracts were washed with sat. NaCl, and dried over anhydrous K₂CO₃. After removal of solvent, a mixture of the residue and hydrated oxalic acid (12.5 g) dissolved in water was steam-distilled until the distillate was free from organic materials. The distillate was saturated with NaCl and extracted with ether. The extracts were dried over anhydrous Na₂SO₄ and distillation gave XXII (2.5 g; 22.3%), bp 54~58°C (21 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1725 (-CHO), 730 (Z, -CH=CH-).

2E, 6Z-Nonadienal (IV-a). Oxazine derivative (XXIII) was prepared by condensation of aldehyde (XXII; 2.5 g; 0.022 mole) and lithio anion (XX; 0.02 mole) according to the procedure mentioned above. Hydroxyloxazine (XXIII) was reduced with NaBH₄ and hydrolysis of the reduced oxazine with oxalic acid

gave 2E, 6Z-nonadienal (IV-a; 0.83 g; 30%), bp 94~98°C (11 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1725 (-CHO), 990 (E, -CH=CH-), 730 (Z, -CH=CH-).

2E, 6Z-Nonadienal (IV-a) was reduced to cucumber alcohol, 2E, 6Z-nonadienol (V-a), with LiAlH₄ in an usual manner.

3E, 6Z-Nonadienal (XXIV). According to the procedure of Jutz,⁶ 3E, 6Z-nonadienoic acid (4.2 g; 88%) was prepared by condensation of 4Z-heptenal (XXII; 3.5 g; 0.031 mole) with malonic acid (3.2 g; 0.031 mole) in triethanolamine (4.17 g; 0.028 mole) followed by decarboxylation. 3E, 6Z-Nonadienol (2.9 g; 76.7%) was obtained by esterification of 3E, 6Z-nonadienoic acid (4.2 g; 0.027 mole) with CH₂N₂ followed by reduction with LiAlH₄. The alcohol (1.4 g; 0.01 mole) was oxidized by chromium trioxide-pyridine complex in methylene chloride to the corresponding aldehyde (XXIV; 0.8 g; 60%). bp 94~95°C (22 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1725 (-CHO), 973 (E, -CH=CH-), 730 (Z, -CH=CH-).

Acknowledgement. The authors wish to express their thanks to Prof. Y. Inouye, Institute for Chemical Research Kyoto University for NMR and MAS spectra throughout this work.

REFERENCES

- 1) A. Hatanaka, T. Kajiwarra and T. Harada, *Phytochem.*, **14**, (1975), in press.
- 2) M. Schwartz and R. M. Waters, *Synthesis*, **1972**, 567.
- 3) C. A. Brown and V. K. Ahuja, *J. C. S. Chem. Comm.*, **1973**, 533.
- 4) T. Kajiwarra, T. Harada and A. Hatanaka, *Agr. Biol. Chem.*, **39**, 243 (1975).
- 5) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
- 6) C. Jutz, *Chem. Ber.*, **92**, 1983 (1959).