Tetrahedron Letters No. 30, pp 2813 - 2816.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0722-2813$02.00/0

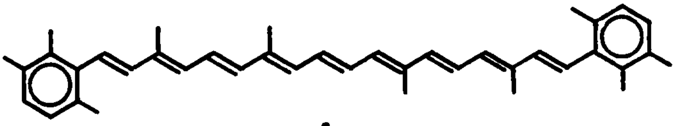
CAROTENOID SYNTHESIS WITH 4-(*t*-BUTYLTHIO)-3-BUTEN-2-ONE. A NEW SYNTHESIS OF ISORENIERATENE

Shuzo Akiyama, Shin'ichi Nakatsuji, and Shohei Eda
Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyomachi, Nagasaki 852, Japan
Motohiro Kataoka and Masazumi Nakagawa*
Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan

Summary: Isorenieratene has been efficiently synthesized using 4-(*t*-butylthio)-3-buten-2-one as chain lengthening agent.

Isorenieratene is an interesting natural carotenoid containing aromatic terminal groups isolated from a kind of sea sponge, *Reniera japonica* by Yamaguchi,[1)] and the structure has been elucidated by the same author.[2)] The structure (I) has been confirmed by syntheses.[3)]

As reported in the preceding paper,[4)] 4-(*t*-butylthio)-3-buten-2-one (III) seemed to be a convenient synthon for the construction of isoprenoid polyene chain. Now, we wish to report a new synthesis of I using III.



I

The reaction sequence leading to I is shown in Scheme. The aldol condensation of 2,3,6-trimethylbenzaldehyde (II)[5)] with III in the presence of sodium ethoxide gave IV as yellow needles, mp 47.5∿48.5°C (65%). Treatment of IV with a large excess of methyllithium followed by 1M sulphuric acid yielded a stereoisomeric mixture of dienal (V, 75%, E:Z = 9:1). Treatment of the mixture of V in benzene with iodine gave pure E-V in a moderate yield.[6)] A mixture of V and III in ethanol was treated with an aqueous solution of sodium hydroxide. Chromatographic purification of the product on silica gel afforded tetraene ketone (VI) as an orange red liquid (67%). The alkylation of VI with methyllithium followed by treatment with an aqueous sulphuric acid yielded a stereoisomeric mixture of tetraene aldehyde (VII), which gave E-VII on treatment with iodine in benzene-ether. VII was obtained as an orange red liquid in a moderate yield. A solution of VII in THF was added to a mixture of titanium(III) chloride and lithium aluminium hydride in the same solvent,[7)] and the resulting liquid was chromatographed on alumina to give a red solid (96%) which was recrystallized from benzene to give red crystals, mp 200°C.

The mixed melting point with natural isorenieratene[1)] exhibited no depression, and also a mixed TLC of the synthetic and natural pigments showed no separation (Merck, Kieselgel 60, hexane-benzene (2:1), R_f 0.61). As summarized in Table 1, the properties of the red pigment thus prepared were found to be identical in every respects with those of natural and the reported synthetic isorenieratenes.3)

Scheme

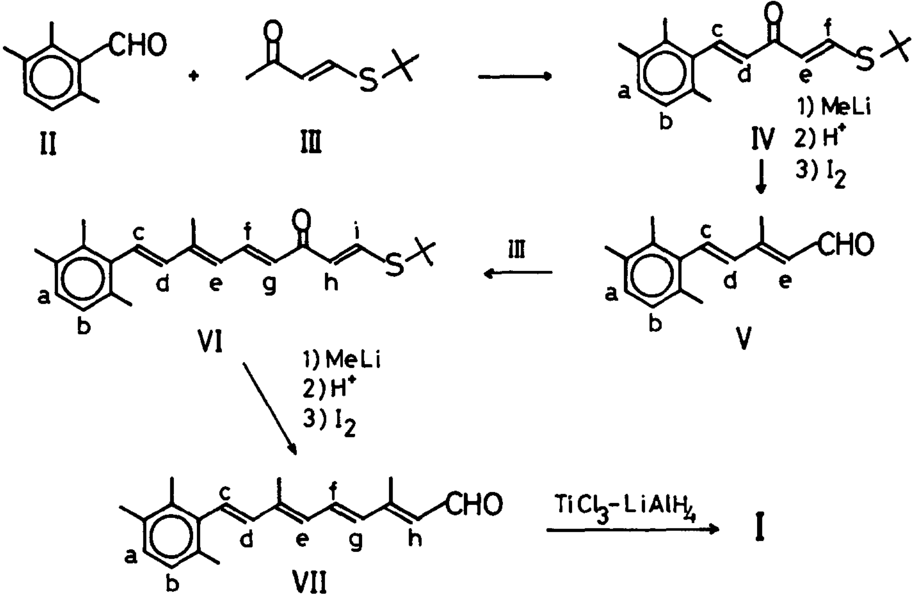


Table 1. Comparison of Physical Properties of Natural and Synthetic Isorenieratenes

Properties	Natural	Synthetic present work	3a	3b	3c
mp	199∿200°C	200°C	199∿200°C	199∿200°C	207∿208°C(corr.)
NMR*		8.00, 7.92 7.77, 7.74			8.02, 7.93 7.78, 7.73
UV in benzene nm($\varepsilon \times 10^{-4}$)	463(12.3)$^+$ 492(10.4)$^+$	464(11.4) 493(9.71)	463(12.3) 492(10.4)	464(11.9) 492(9.95)	465(12.3) 492(10.6)

* Only methyl signals are quoted in τ-values in $CDCl_3$. + Wavelength and intensities were estimated from the reported curve.2)

The spectroscopic and analytical data of the intermediates (IV, V, VI and VII) and the carotenoid (I) are tabulated in Table 2.

Table 2. Spectroscopic and Analytical Data of IV, V, VI, VII and I

IV: IR(KBr-disk): 1634 s (C=O), 1615 s (C=C), 965 m (*trans* -CH=CH-) cm^{-1}; NMR($CDCl_3$): δ 1.47 (9H, s, *t*-Bu), 2.23 (3H, s, Me), 2.28 (6H, s, 2Me), 6.37 (1H, d, J=16, H^d), 6.60 (1H, d, J=15, H^e), 6.89 (1H, d, J=8, H^a or H^b), 7.00 (1H, d, J=8, H^b or H^a), 8.03 (1H, d, J=15, H^f); Mass(m/e): 288 (M$^+$), 231 (M$^+$-57); Anal. Found: C, 74.69; H, 8.41; S, 10.96%. Calcd. for $C_{18}H_{24}OS$: C, 74.95; H, 8.39; S, 11.12%.

V: IR(neat): 1667 vs (C=O), 1620 s (C=C), 978 m (*trans* -CH=CH-) cm^{-1}; NMR($CDCl_3$): δ 2.18 (3H, s, Me), 2.21 (6H, s, 2Me), 2.38 (3H, s, Me), 5.90 (1H, d, J=8, H^e), 6.26 (1H, d, J=16, H^d), 6.91 (d, J=8, H^a or H^b), 6.93 (1H, J=8, H^b or H^a), 7.11 (1H, d, J=16, H^c), 10.10 (1H, d, J=8, CHO); Mass(m/e): 214 (M^+), 199 (M^+-15). 2,4-Dinitrophenylhydrazone: red crystals, mp > 190°C (dec.), Anal. Found: C, 64.05; H, 5.62; N, 13.95%. Calcd. for $C_{21}H_{22}O_4N_4$: C, 63.94; H, 5.62; N, 14.21%.

VI: IR(neat): 1660 s (C=O), 1575 s (C=C), 980 m (*trans* -CH=CH-) cm^{-1}; NMR(CCl_4): δ 1.46 (9H, s, *t*-Bu), 2.18 s, 2.19 s, 2.21 s (12H, 4Me), 6.19 d, 6.21 d, 6.25 d (3H, J=16, H^c, H^d, H^g), 6.39 (1H, d, J=16, H^h), 6.76 (1H, d, J=12, H^e), 6.86 (2H, s, H^a, H^b), 7.66 (1H, dd, J=12, 16, H^f), 7.83 (1H, d, J=16, H^i); Mass(m/e): 354 (M^+), 297 (M^+-57).

VII: IR(neat): 1665 vs (C=O), 1590 m (C=C), 975 m (*trans* -CH=CH-) cm^{-1}; NMR(CCl_4): δ 2.11 s, 2.19 s, 2.22 s, 2.32 s (15H, 5Me), 5.85 (1H, d, J=8, H^h), 6.13 d, 6.18 d, 6.30 d (3H, J=16, H^c, H^d, H^g), 6.64 (1H, d, J=11, H^e), 6.81 (2H, s, H^a, H^b), 7.02 (1H, dd, J=11, 16, H^f), 10.11 (1H, d, J=8, CHO); Mass(m/e): 280 (M^+), 265 (M^+-15). 2,4-Dinitrophenylhydrazone: dark red needles, mp 195.0∿195.5°C. Anal. Found: C, 67.68; H, 5.86; N, 11.90%. Calcd. for $C_{26}H_{28}O_4N_4$: C, 67.81; H, 6.13; N, 12.17%.

I: IR(Kbr-disk): 966 s (*trans* -CH=CH-) cm^{-1}; NMR($CDCl_3$): δ 2.00 (6H, s, 2Me), 2.08 (6H, s, 2Me), 2.23 (6H, s, 2Me), 2.26 (12H, s, 4Me), 6.1 ∿ 6.8 (14H, m, olefinic-H), 6.95 (4H, s, aromatic-H); Mass(m/e): 528 (M^+); Anal. Found: C, 90.92, H, 9.36%. Calcd. for $C_{40}H_{48}$: C, 90.85; H, 9.15%.

Experimental procedures are described below:

1-(*t*-Butylthio)-5-(2,3,6-trimethylphenyl)-1,4-pentadien-3-one (IV).

To a solution of the aldehyde (II, 7.90 g, 53.4 mmol) and the thiovinyl ketone (III, 8.66 g, 54.8 mmol) in ethanol (35 ml) was added at -15°C under nitrogen atmosphere over a period of 1.5 hrs. a solution of sodium ethoxide (Na, 1.4 g, 60 mmol in ethanol, 35 ml). After being stirred for 4 hrs. at -10 ∿ 0°C, the reaction mixture was worked up in the usual way. The product in hexane-benzene (3:7) was chromatographed on silica gel (75 g). A reddish orange liquid (14.8 g) thus obtained could be crystallized from ether at a low temperature, yellow needles, 9.99 g.

3-Methyl-5-(2,3,6-trimethylphenyl)-1,3-pentadienal (V).

A solution of IV (6.96 g, 24.2 mmol) in ether (50 ml) was added to an ice-cooled solution of methyllithium (prepared from Li, 1.6 g, 0.5 mol, methyl bromide and ether 100 ml) under nitrogen atmosphere. After being stirred for 4 hrs. at room temperature, 1M sulphuric acid (100 ml) was added to the mixture under ice-cooling, and stirring was continued overnight at room temperature. The reaction mixture was worked up in the usual way, and the product was dissolved in benzene containing trace of iodine. The mixture was kept at room temperature under diffused sunlight for 8 hrs. The product obtained on working up the mixture was dissolved in hexane-benzene (2:8) and chromatographed on silica gel (100 g) to give E-V as a yellow liquid, 2.34 g.

1-(*t*-Butylthio)-7-methyl-9-(2,3,6-trimethylphenyl)-1,4,6,8-nonatetraen-3-one (VI).

A solution of the dienal (V, 2.8 g, 13 mmol) and the ketone (III, 2.0 g, 12.7 mmol) in ethanol (20 ml) was mixed with a solution of sodium hydroxide (1.2 g, 30 mmol) in ethanol-water (2 ml-2 ml). After being stirred for 1 hr. at room temperature, the reaction mixture was worked up, and the product in hexane-benzene (1:1) was chromatographed twice on silica gel (60 g and 30 g) to give VI as an orange red liquid, 3.03 g.

3,7-Dimethyl-9-(2,3,6-trimethylphenyl)-1,3,5,7-nonatetraenal (VII).

To an ethereal solution of methyllithium (prepared from Li, 0.8 g, 114 mmol, methyl bromide and ether, 100 ml) was added at 0°C a solution of VI (2.02 g, 5.70 mmol) in the same solvent (20 ml). The mixture was stirred for 2 hrs. at room temperature, and then worked up in the usual manner. The product dissolved in benzene-ether (1:1) was passed through a column of alumina (30 g). Evaporation of the eluate gave a stereoisomeric mixture of VII. Trace of iodine was added to a solution of VII in the same solvent (100 ml), and the solution was stood for 4 hrs. at room temperature under diffused sunlight. The mixture was worked up, and again chromatographed on silica gel (30 g, hexane-benzene, 1:1) to give E-VII as an orange red liquid, 613 mg.

Isorenieratene (I).

Powdered lithium aluminium hydride (47 mg, 1.24 mmol) was added under nitrogen atmosphere to a solution of titanium(III) chloride (327 mg, 2.12 mmol) in THF (20 ml). After the mixture had been stirred for 1 hr., a solution of the nonatetraenal (VII, 223 mg, 0.796 mmol) in the same solvent (10 ml) was added. After being stirred for 20 min., the mixture was refluxed for 5 hrs. A red liquid obtained on working up the reaction mixture was chromatographed on alumina (20 g) to give a red crystalline solid, 201 mg. Recrystallization of the material from benzene yielded analytical pure I.

Acknowledgement: The authors are deeply grateful to Professor M. Yamaguchi, Department of Chemistry, Faculty of Science, Kyushu University, Fukuoka, Japan for supplying the specimen of natural isorenieratene.

References

1) M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 30, 111 (1957).
2) M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 31, 51 (1958).
3) a) M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 32, 1171 (1959); b) M. C. Kosla and P. Karrer, *Helv. Chim. Acta*, 43, 453 (1960); c) R. D. G. Cooper, J. B. Davis, and B. C. L. Weedon, *J. Chem. Soc.*, 5637 (1963).
4) S. Akiyama, S. Nakatsuji, T. Hamamura, M. Kataoka, and M. Nakagawa, the preceding paper.
5) G. Lowe, F. G. Torto, and B. C. L. Weedon, *J. Chem. Soc.*, 1855 (1958).
6) T. Mukaiyama and A. Ishida, *Chem. Lett.*, 1201 (1975).
7) J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, 96, 4708 (1974) and the following papers.

(Received in Japan 25 April 1979)