Synthesis of *dl*-3-Hydroxydihydro- β -damascone and Dihydro- β -damascone[†]

Kenji MORI, Masahiko OHKI, Katsuhide OKADA,
Yoko TAKEI and Masanao MATSUI

*Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113*

Received August 21, 1973

The Rupe rearrangement of the appropriate acetylenic alcohols afforded dihydro- β -damascone (XII) and its 3-hydroxy derivative (I). The latter is an aroma component of Manila leaf tobacco.

Recently Kaneko and Harada isolated a hydroxy ketone as an aroma component of Manila leaf tobacco and proposed its structure as 3-hydroxydihydro- β -damascone (I, without stereochemical assignment at C-3)* on spectral evidences.¹⁾ This proposal has now been confirmed by an unambiguous synthesis reported herein.

Inspection of the target molecule made us to believe that the simplest synthetic route to it would be the coupling of two synthons—a cyclohexanone (II) and a side chain in the form of ethylacetylene (X) as a latent *n*-butyryl group. The necessary transformation would then be made possible by the Rupe rearrangement³⁾ as exemplified in the preparation of α -acetylcyclohexene (B) from 1-ethynylcyclohexanol (A).⁴⁾

In contrast with the ready availability of ethylacetylene (X), 4-tetrahydropyranyloxy-2,2,6-trimethylcyclohexanone (II) was not so easy to prepare. Horii *et al.* synthesized α -acetoxy-2,2,6-trimethylcyclohexanone (Va) starting from 2,2,6-trimethylcyclohexanone (III).⁵⁾ However, the final step in their synthesis, hydrogenation of IV to Va, afforded Va only in a moderate yield (50% or less). Although several other routes to II were conceivable (*cf.* 6), we attempted a conversion of

4-hydroxy-3,3,5-trimethylcyclohexanone (VIIa) into the ketone (II). This served as a model experiment for the conversion of an optically active ketone (II) useful for other purposes.⁷⁾ The ketol (VIIa) was readily available from a diketone (VI) by catalytic hydrogenation.⁷⁾ On acetylation, the ketol (VIIa) gave a crystalline acetate (VIIb). This was reduced with lithium tri-*t*-butoxyaluminum hydride to give a crystalline diol monoacetate (VIIIa) in 52% yield. The newly generated hydroxyl group was axial, for the CHOH proton showed a quintet with $W_{1/2} = 7$ Hz ($J_{\text{Hc}} = 3.5$ Hz, $J_{\text{Hd}} = 3.5$ Hz), while the acetoxyl group was equatorial as could be seen from the large coupling constant ($J = 11$ Hz) exhibited by the CHOAc proton. The corresponding tetrahydropyranyl ether (VIIIb) was prepared in the standard manner and reduced with lithium aluminum hydride to afford a diol mono-tetrahydropyranyl ether (IX) in 80% yield from VIIIa. This was oxidized with chromic anhydride in pyridine to give the desired ketone (II) in 98% yield. As this was thermolabile, it could not be purified by distillation. A portion of the tetrahydropyranyl ether (II) was hydrolyzed to the ketol (Vb) which was acetylated to give 4-acetoxy-2,2,6-trimethylcyclohexanone (Va). This was identical with an authentic sample prepared by Horii's method.⁵⁾

The remaining steps were the preparation of an ethynyl alcohol (XIII) and its rearrange-

[†] Carotenoids and Degraded Carotenoids. Part I, K. Mori, *Agr. Biol. Chem.*, **37**, 2899 (1973).

* The numbering-system employed here is that of carotenoid nomenclature. See Ref. 2).

EXPERIMENTAL

All mps and bps were uncorrected. IR spectra refer to films for liquids and nujol mulls for solids and were recorded on a JASCO IRA-1 spectrometer. NMR spectra were recorded at 100 or 60 MHz with TMS as an internal standard.

4-Acetoxy-3,3,5-trimethylcyclohexanone (VIIb)

Acetic anhydride (9 ml) was added to a soln of 4-hydroxy-3,3,5-trimethylcyclohexanone (VIIa, 4.5 g) in dry pyridine (9 ml) and the mixture was left to stand overnight at room temp. Then it was concentrated *in vacuo*, poured into ice and dil. HCl and extracted with ether. The ether extract was washed with water, NaHCO₃ soln and NaCl soln, dried (MgSO₄) and concentrated to give 4.8 g (83% yield) of crystalline VIIb. Recrystallization from ether-pet. ether gave prisms, mp 46~47°C. IR ν_{max} cm⁻¹: 1735, 1370, 1240, 1040. NMR (60 MHz, CCl₄) δ : 0.90 (3H, s), 0.94 (3H, d, *J*=6 Hz), 0.95 (3H, s), 2.08 (3H, s), 4.91 (1H, d, *J*=11 Hz). Anal. Found: C, 66.77; H, 9.01. Calcd. for C₁₁H₁₈O₃: C, 66.64; H, 9.15%.

4-Acetoxy-3,3,5-trimethylcyclohexan-1-ol (VIIIa)

A soln of LiAlH (OBu^t)₃ was prepared by dropwise addition of *t*-BuOH (10 g) to a suspension of LiAlH₄ (1.7 g) in dry THF (75 ml) followed by 1 hr stirring at 0°C. A soln of VIIb (4.8 g) in dry THF (30 ml) was added to the stirred soln of the hydride at 0°C and the mixture was stirred for 2 hr at 0°C. Then it was poured into ice-dil. HCl-NH₄Cl soln and extracted with ether. The ether extract was washed with sat. NH₄Cl soln and NaCl soln, dried (MgSO₄) and concentrated *in vacuo* to give 4.6 g (96% yield) of crude VIIIa. Recrystallization from ether-pet. ether gave 2.5 g (52% yield) of pure VIIIa, mp 81~82°C. IR ν_{max} cm⁻¹: 3400, 1720, 1370, 1240, 1040. NMR (60 MHz, CDCl₃) δ : 0.85 (3H, s), 0.86 (3H, d, *J*=6 Hz), 1.16 (3H, s), 2.10 (3H, s), 4.10 (1H, quintet, *W*_{1/2}=7 Hz, *J*_{ea}=3.5 Hz, *J*_{ee'}=3.5 Hz), 4.52 (1H, d, *J*=11 Hz). Anal. Found: C, 66.16; H, 10.02. Calcd. for C₁₁H₂₀O₃: C, 65.97; H, 10.07%.

4-Acetoxy-3,3,5-trimethylcyclohexan-1-ol tetrahydropyranyl ether (VIIIb)

Dihydropyran (6 g) and *p*-toluenesulfonic acid (0.5 g) were added to a soln of VIIIa (4.5 g) in dry ether (60 ml) and the soln was left to stand overnight at room temp. Then it was washed with K₂CO₃ soln, dried (K₂CO₃) and concentrated *in vacuo* to give 6.4 g (quantitative) of VIIIb. An attempted distillation at 110~113°C (0.2 mm) resulted in the partial pyrolysis of VIIIb giving crude VIIIb contaminated with VIIIa

(*n*_D²⁸ 1.4630). IR ν_{max} cm⁻¹: 1735, 1370, 1245, 1130, 1110, 1080, 1030, 980. TLC (silica gel G, C₆H₆-EtOAc 15:1): *R*_f 0.42. This crude VIIIb was used for the next step without distillation.

4-Tetrahydropyranyloxy-2,2,6-trimethylcyclohexan-1-ol (IX)

A soln of VIIIb (3.5 g) in dry ether (20 ml) was added to an ice-cooled and stirred suspension of LiAlH₄ (0.6 g) in dry ether (50 ml). The mixture was stirred for 4 hr at 0~5°C. Then the excess LiAlH₄ was destroyed by cautious addition of water under cooling. The mixture was filtered through Celite and extracted with ether. The ether extract was washed with NaCl soln, dried (MgSO₄) and concentrated *in vacuo* to give 3.1 g (89% yield) of IX. IR ν_{max} cm⁻¹: 3450, 1200, 1155, 1130, 1080, 1025, 980. TLC (silica gel G, C₆H₆-EtOAc 15:1): *R*_f 0.26. This was employed for the next step without further purification.

4-Tetrahydropyranyloxy-2,2,6-trimethylcyclohexanone (II)

A soln of IX (3.1 g) in dry pyridine (10 ml) was added to the Sarett reagent prepared from CrO₃ (2.5 g) in dry pyridine (25 ml) and the mixture was left to stand for 2 days at room temp. Then it was poured into ice-water and extracted with ether. The ether extract was washed with water and NaCl soln, dried (MgSO₄) and concentrated *in vacuo* to give 3.0 g (98%) of oily II. IR ν_{max} cm⁻¹: 1700, 1120, 1060, 1020, 970. TLC (silica gel G, C₆H₆-EtOAc 15:1): *R*_f 0.45.

4-Hydroxy-2,2,6-trimethylcyclohexanone (Vb)

A 0.5 g portion of II was dissolved in MeOH (4 ml) containing 0.2% of *p*-toluenesulfonic acid. After 16 hr at room temp, K₂CO₃ was added to neutralize the acid and the solvent was removed *in vacuo*. Water was added to the residue and the mixture was extracted with ether. The ether extract was washed with NaCl soln, dried (MgSO₄) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 0.2 g of pure Vb, bp 89~92°C (0.1 mm), *n*_D²⁵ 1.4688. IR ν_{max} cm⁻¹: 3400, 1700, 1380, 1080, 1050, 1030. NMR (60 MHz, CDCl₃) δ : 0.99 (3H, d, *J*=6 Hz), 1.04 (3H, s), 1.18 (3H, s), ~4.1 (1H, m, *W*_{1/2} 16 Hz). Anal. Found: C, 68.89; H, 10.32. Calcd. for C₉H₁₆O₂: C, 69.19; H, 10.32%.

4-Acetoxy-2,2,6-trimethylcyclohexanone (Va)

The ketol Vb was acetylated by acetic anhydride and pyridine. The acetate Va boiled at 100~104°C (5 mm), *n*_D³³ 1.4570. IR ν_{max} cm⁻¹: 1740, 1705, 1250, 1130, 1060, 1035, 1000. NMR (60 MHz, CCl₄) δ : 1.02 (3H, d, *J*=6 Hz), 1.07 (3H, s), 1.26 (3H, s), 1.97 (3H, s), 5.25 (1H, tt, *J*_{aa'}=12 Hz, *J*_{ae'}=6 Hz). This

data implies that the acetoxyl group is equatorial. *Anal.* Found: C, 66.58; H, 9.02. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%. This was identical with an authentic sample (IR and NMR).

1-But-1'-ynyl-2,2,6-trimethylcyclohexan-1-ol (XI)

A suspension of $NaNH_2$ was prepared from Na (44.3 g) and liquid NH_3 (11). A soln of 1,2-dibromobutane (139 g) in dry ether (40 ml) was added during 30 min to the stirred suspension at $-50^\circ C$. The stirring was continued for 3 hr at $-40^\circ C$. The ketone (III, 30 g) was added to the stirred mixture at $-40^\circ C$ during 30 min. The stirring was continued for 2 hr. The mixture was left to stand overnight at room temp to remove NH_3 . Water (50 ml) was cautiously added to the mixture to destroy remaining Na derivatives. The mixture was then acidified with dil H_2SO_4 and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over neutral alumina. Elution with *n*-hexane and benzene gave 36.1 g (87% yield) of XI. An analytical sample boiled at $64\sim 68^\circ C$ (0.6 mmHg), n_D^{19} 1.4780. IR ν_{max} cm^{-1} : 3450, 1455, 1030, 955. NMR (60 MHz, CCl_4) δ : 1.00 (3H, s), 1.02 (3H, d, $J=6$ Hz), 1.10 (3H, s), 1.15 (3H, t, $J=7$ Hz), 1.35 $\sim$ 1.60 (7H, m), 1.8 (1H), 2.25 (2H, q, $J=7$ Hz). MS m/e : 194 (M^+ , 35%), 123 (100%).

Dihydro- β -damascone (XII)

The acetylene (XI, 27.3 g) was dissolved in 90% HCO_2H (100 ml) and the mixture was heated under reflux for 1 hr. Then it was concentrated *in vacuo*, diluted with water and extracted with ether. The ether extract was washed with water, $NaHCO_3$ soln and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 26.4 g (97%) of crude XII. This was chromatographed over silicic acid. Elution with *n*-hexane followed by distillation gave pure XII, bp $81\sim 83^\circ C$ (3 mmHg), n_D^{20} 1.4750 (lit.⁸⁾ 1.4745). IR ν_{max} cm^{-1} : 1685, 1460, 1370, 1160, 1035. NMR (60 MHz, CCl_4) δ : 0.95 (3H, t, $J=7$ Hz), 1.04 (6H, s), 1.10 (3H, s), 1.54 (3H, s). MS m/e : 194 (M^+ , 13%), 151 (100%), 123 (39%), 81 (26%). *Anal.* Found: C, 79.94; H, 11.41. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41%.

1-But-1'-ynyl-4-tetrahydropyranyloxy-2,2,6-trimethylcyclohexan-1-ol (XIII)

A suspension of $NaNH_2$ was prepared from Na (2.66 g) and liquid NH_3 (100 ml). A soln of 2-bromobut-1-ene (8.6 g) in dry ether (20 ml) was added to the stirred suspension at $-35^\circ C$. The mixture was stirred for 2 hr at $-35^\circ C$ to complete the formation of sodium ethylacetylide. A soln of 4-tetrahydropyranyloxy-2,2,6-trimethylcyclohexanone (II, 1.4 g) in dry ether (10 ml) was added to it at $-35^\circ C$ and the stirring was continued for 2 hr. NH_4Cl was added to destroy

excess sodium ethylacetylide and the mixture was left to stand overnight to evaporate NH_3 . Water was added to the reaction product. The resulting soln was saturated with NaCl and extracted with ether. The ether layer was washed with NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.10 g (65% yield) of crude XIII. IR ν_{max} cm^{-1} : 3400, 1140, 1085, 1040, 975, 920, 885, 820. NMR (60 MHz, CCl_4) δ : 1.00 (3H, s), 1.10 (3H, t, $J=8$ Hz), 1.10 (3H, s), 1.14 (3H, d, $J=7$ Hz). MS m/e : 194 (4%), 149 (8%), 123 (10%), 85 (100%). This was employed for the next step without further purification.

dl-3-Hydroxydihydro- β -damascone (I)

A soln of XIII (1.05 g) in 100% HCO_2H (10 ml) was heated under reflux for 30 min. After cooling, it was poured into water, made slightly alkaline by addition of Na_2CO_3 soln, saturated with NaCl and extracted with ether. The dark-colored ether extract was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (activity grade II). Elution with C_6H_6 -EtOAc (7:3) gave crude I (120 mg). This was further purified by TLC (silica gel GF₂₅₄, C_6H_6 -EtOAc 7:3, R_f 0.73) to give 74 mg (10% yield) of pure I. IR ν_{max} cm^{-1} : 3400, 1690, 1170, 1060. NMR (100 MHz, CCl_4) δ : 0.91 (3H, t, $J=7$ Hz), 0.98 (3H, s), 1.10 (3H, s), 1.52 (3H, s), 3.85 (1H, m). MS m/e : 210 (M^+ , 13%), 168 (40%), 167 (100%), 149 (25%), 121 (53%). These spectral properties were compared with those of the natural product by Dr. H. Kaneko and found to be identical. *Anal.* Found: C, 73.44; H, 10.43. Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54%.

Acknowledgement. We are indebted to Dr. H. Kaneko, Japan Monopoly Corporation, for spectral comparisons. A large portion of the ketones III and VI used in this work was kindly prepared by Messrs S. Saito and K. Takakusaki, to whom we express our thanks. We gratefully acknowledge the help of Mr. K. Aizawa and his associates in spectroscopic and analytical works.

REFERENCES

- 1) H. Kaneko and M. Harada, *Agr. Biol. Chem.*, **36**, 168 (1972).
- 2) O. Isler, "Carotenoids," Birkhäuser Verlag, Basel and Stuttgart, 1971, pp. 22~24.
- 3) P. B. de la Mare, "Molecular Rearrangements, Part I," ed. by P. de Mayo, Interscience Publishers, New York, 1963, pp. 87~88.
- 4) a. J. H. Saunders, *Org. Synth. Col. Vol.* **3**, 22 (1955).
b. H. B. Henbest and G. Woods, *J. Chem. Soc.*, **1952**, 1150.

- 5) Z. Horii, T. Yagami, M. Ito and M. Hanaoka, *Chem. Pharm. Bull.*, **16**, 848 (1968).
 - 6) T. Oritani and K. Yamashita, *Agr. Biol. Chem.*, **37**, 1215 (1973).
 - 7) K. Mori, *Tetrahedron Lett.*, **1973**, 723.
 - 8) E. Demole, P. Enggist, U. Säuberli, M. Stoll and E. sz. Kováts, *Helv. Chim. Acta*, **53**, 541 (1970).
-