Synthesis of Isolaurene and Its Related Compounds from Cyclotene

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Novel syntheses of isolaurene (**1**), an isomer of laurene (**2**) found in algae, and its related compounds were performed from cyclotene (**3**). Benzylated cyclotene (**4**) was allowed to react with *p*-tolyl-magnesium bromide to give 5-methyl-2-*p*-tolyl-2-cyclopentenone (**6**). Hydrogenation of **6** over palladium charcoal, followed by methylation with one equivalent of methyl iodide gave 2, 5-dimethyl-2-*p*-tolyl-cyclopentanone (**8**), whereas treatment with 3 equivalents of methyl iodide gave 2-*p*-tolyl-2, 5, 5-trimethylcyclopentane (**10**). Both **8** and **10** were treated with a large excess of methyl lithium to afford the corresponding alcohols (**9**) and (**11**), dehydration of which, in an acidic medium, gave **1** and 1-methylene-2-*p*-tolyl-2, 5, 5-trimethylcyclopentane (**12**), respectively. Compound **10** is a structural isomer of cuparenone (**15**) found in the wood of an Indian plant.

Isolaurene **1**, an isomer of laurene **2** which is the sesquiterpene hydrocarbon in some algae (*Laurencia glandulifera* Kutzing and *Laurencia nipponica* Yamada), has been well described by Irie¹⁾ and McMurry²⁾ in the discussion of the structural elucidation of **2**.

For the synthesis of **1**, a lengthy route including a tedious reaction was involved, when cyclopentanone was chosen as starting material.¹⁾ However, if cyclotene **3**, used as a artificial flavor in various food items, is employed for the synthesis of **1**, a simple and short route is expected.

The purpose of this report is to describe a simple synthesis of **1** and its related compounds **10** and **12**, from easily available **3**, as depicted in Scheme 1.

Benzylation of **3** with benzyl chloride and potassium hydroxide in methanol under reflux afforded **4** with a yield of 80%. Compound **4** was allowed to react with Grignard reagent prepared from an equivalent amount of magnesium and *p*-bromotoluene in ether for 10 hr at room temperature, followed by acidification to give a 1:1 mixture of **5** and **6**, 78% yield. This suggests that the reaction may proceed via tolylation of **3** and **4**, followed by spontaneous elimination of benzyl alcohol to give **5** and **6**. When **3** was directly treated with 2

equivalents of Grignard reagent, the yield of **5** and **6** was only 15%, leading to the suspicion that the magnesium complex of **3** is more insoluble than that of **4** in ether.

In order to obtain pure **6** with a good yield, the conversion from **5** to **6** was examined under various conditions as shown in Table I. The best yield was obtained by heating under reflux with toluene containing *p*-toluenesulfonic acid as a catalyst, using an azeotropic water removal system (Dean-Stark trap). Compound **6** thus obtained was further purified by silica-gel column chromatography. Catalytic hydrogenation of **6** over palladium charcoal afforded **7** which showed a single peak on GLC. However, **7** appeared as two spots on TLC suggesting the possibility of two diastereomers, **7a** and **7b**. In the NMR spectrum the methyl protons in **7a** (1.06 ppm) are shifted slightly higher field than those in **7b** (1.12 ppm) because of the anisotropic effect of the carbonyl group.

The alkylation of **7** with methyl iodide in THF using an equimolar amount of sodium hydride at room temperature afforded a mixture of two products showing almost only one spot on TLC. Distillation of the products gave a mixture showing two peaks (*R_t*=4.2, 4.4 min) on GLC, 55% yield. The GC-MS

Fig. 1.

Scheme 1

 TABLE I. CONVERSION OF 2-HYDROXY-5-METHYL-2-*p*-TOLYLCYCLOPENTANONE (5) TO 5-METHYL-2-*p*-TORYL-2-CYCLOPENTENONE (6) BY DEHYDRATION UNDER VARIOUS CONDITIONS

Expt. run	Reaction conditions	Conversion (%)
1	20% HCl reflux	30
2	<i>p</i> -TsOH/toluene reflux	80
3	$(\text{COOH})_2$ at $180^\circ\text{C}^{(4)}$	50
4	Pyridine- SOCl_2 at $0\sim 20^\circ\text{C}^{(5)}$	10

spectra of these products showed the molecular weight to be 202 and indicated that the products consisted of two diastereomers of **8** (**8a** and **8b**) or one diastereomer (**8a** or **8b**) and another possible compound, **14**. This was synthesized from **6** as shown in Scheme 2.

Moreover, there was no evidence from the physical properties determined from TLC, GLC, IR and NMR for the presence of **14** in the methylated product of **7**. Therefore, the two peaks on GLC were assigned to the dia-

stereomers **8a** and **8b**.

The mixture of **8a** and **8b** was treated with an excess of methyl lithium to give a mixture of the possible diastereomers **9**. Purification of the products using silica-gel column chromatography and preparative TLC afforded mainly two products having *R_f* 0.7 and 0.6 on TLC. These products showed the same retention time on GLC and similar patterns in the IR and NMR spectra. When they were refluxed in methanol containing a trace amount of hydrochloric acid, however, a single product **1** was obtained with a good yield. This can be well explained by the assumption that a water molecule was eliminated from **9** to form the possible product **1**. Spectroscopic data of **1** thus obtained were in clear accordance with the reported data.⁽¹⁾

On the other hand, **7** was treated with 3 equivalents of methyl iodide and 2.2 equivalents of sodium hydride to afford trimethyl com-

Fig. 2.

Scheme 2

pound **10**, which is the structural isomer of cuparenone **15** found in the essential oil from the wood of an Indian plant.^{6,7)} Further methylation of **10** with an excess of methyl lithium gave **11**, and subsequent dehydration by acid treatment afforded hydrocarbon **12**, corresponding to the structural isomer of **1**.

EXPERIMENTAL PROCEDURES

Infrared spectra were taken with a JASCO IRA-2 spectrometer. Nuclear magnetic resonance spectra were recorded with a JNM MH-60 spectrometer. Mass spectra were measured with a Hitachi RUM-6MG instrument.

2-Benzoyloxy-3-methyl-2-cyclopentenone (4). To a stirred mixture of cyclotene (**3**) (22.4 g, 0.2 mol) and potassium hydroxide (12.4 g, 0.22 mol) in 150 ml of methanol was added benzyl chloride (30.4 g, 0.24 mol) and then the mixture was refluxed for 3 hr. After removal of the solvent, the residue was extracted with ether; the extract was washed successively with 5% aqueous sodium hydroxide, water and brine, and dried over Na_2SO_4 . The ether solution was concentrated, and the residue was distilled *in vacuo* to afford 31 g of **4**, bp $134\sim 138^\circ\text{C}/3\text{ mm}$. IR ν_{max} cm^{-1} : 2900, 1690, 1640, 1490, 1440, 1390, 1330, 1200, 1100, 740. NMR $\delta_{\text{max}}^{\text{CCl}_4}$ ppm: 1.8 (3H, s), 2.24 (4H, s), 5.15 (2H, s), 7.25 (5H, s). MS m/e : 202 (M^+), 111, 91.

2-Hydroxy-5-methyl-2-p-tolylcyclopentanone (5) and 5-methyl-2-p-tolyl-2-cyclopentenone (6). To stirred Grignard reagent prepared from Mg (3.9 g, 0.16 mol) and *p*-bromotoluene (27.4 g, 0.16 mol) in 50 ml of ether was added **4** (24.2 g, 0.1 mol) in 50 ml of ether dropwise

and the mixture was stirred for 10 hr at room temperature. The reaction mixture was treated with cold diluted hydrochloric acid and the ether layer was washed with water and brine, and then dried over Na_2SO_4 . After removal of the solvent, the residue was distilled *in vacuo* to afford 10 g of benzyl alcohol, bp $103\sim 108^\circ\text{C}/20\text{ mm}$ and 18.3 g (78.2%) of a 1:1 mixture of **5** and **6** as a colorless oil, bp $125\sim 133^\circ\text{C}/3\text{ mm}$.

The above-mentioned mixture (**5** and **6**) with *p*-toluenesulfonic acid monohydrate in 150 ml of toluene was refluxed under stirring using a Dean-Stark trap for 9 hr. After removal of the solvent, the resulting mixture was extracted with 200 ml of ether and washed with 5% aqueous sodium hydroxide, water and brine, and then dried over Na_2SO_4 . Distillation *in vacuo* gave 12 g of **6** (purity; 90%), bp $143\sim 150^\circ\text{C}/3\text{ mm}$. Compound **6** thus obtained was subjected to silicagel column chromatography with hexane-ether (75:25) giving 9 g of pure **6**. IR ν_{max} cm^{-1} : 2900, 1700, 1600, 1505, 1440, 1300, 800. NMR $\delta_{\text{max}}^{\text{CCl}_4}$ ppm: 1.22 (3H, d, $J=7\text{ Hz}$), 2.33 (3H, s), 7.7.8 (5H, m). MS m/e : 186 (M^+), 171, 157, 143, 127, 117.

5-Methyl-2-p-tolylcyclopentanone (7). A solution of **6** (3.7 g, 0.02 mol) in 50 ml of methanol was shaken under 1 atm of hydrogen with 5% palladium on carbon until 1 equivalent of hydrogen was absorbed (ca. 2 hr). After removal of the solvent and catalyst, the residue was distilled *in vacuo* to afford 3.6 g of **7** as a colorless oil, bp $142\sim 147^\circ\text{C}/4\text{ mm}$. GLC: single peak $R_t=2.8\text{ min}$ (OV-1, $150\sim 200^\circ\text{C}$, programmed $8^\circ\text{C}/\text{min}$). TLC: two spots, $R_f=0.44$ and 0.52 [silica-gel, hexane-ether (9:1)]. IR ν_{max} cm^{-1} : 2950, 2850, 1740, 1500, 1450, 1140, 800. NMR δ_{max} ppm: 1.06 (7a), 1.12 (7b), (3H, d, $J=7\text{ Hz}$), 2.30 (3H, s), 7.1 7.2 (4H, s). MS m/e : 188 (M^+), 173, 145, 131, 117.

2,5-Dimethyl-2-p-tolylcyclopentanone (8). To a sus-

pension of sodium hydride (0.38 g of a 50% dispersion in mineral oil; 8 mmol) in 20 ml of THF was added **7** (1.5 g, 8 mmol) dropwise, and the mixture was cooled in an ice-bath for 10 min with mechanical stirring. To this reaction mixture was added methyl iodide (1.4 g, 10 mmol) and the resulting mixture was kept for 3 hr below 15°C. After removal of the solvent, the residue was extracted with ether and the ether extract was washed with 5% aqueous sodium hydroxide, water and brine, and then dried over Na₂SO₄. Distillation *in vacuo* gave 0.8 g of a 1:1 mixture of **8a** and **8b**, bp 125~130°C/6 mm GC-MS *m/e*: *R*_t=4.2; 202 (M⁺), 187, 175, 159, 145, 132, 117., *R*_t=4.4; 202 (M⁺), 187, 175, 159, 145, 132, 117. TLC: single spot *R*_f=0.6 [silica-gel, hexane-ether (9:1)] IR $\nu_{\max}$ cm⁻¹: 2950, 2870, 1730, 1500, 1450, 1370, 820. NMR $\delta_{\max}^{\text{CCl}_4}$ ppm: 1.02 (**8a**) and 1.13 (**8b**) (3H, d, *J*=7Hz), 1.3 (3H, s), 2.35 (3H, s), 7.2-7.3 (4H, s).

2-*p*-Tolyl-1, 2, 5-trimethyl-cyclopentanol (9). To a stirred solution of methyl lithium prepared from Li (0.3 g, 40 mmol) and methyl iodide (2.8 g, 20 mmol) in 30 ml of ether was added **8** (0.6 g, 3 mmol) dropwise at 0~5°C. The mixture was stirred for 10 hr at room temperature, and then quenched by the addition of saturated ammonium chloride solution. The separated ether layer was subjected to silica-gel column chromatography [hexane-ether (9:1)] to give 0.3 g of **9** as a colorless oil, which was further purified by preparative TLC, developed with the same solvent system as used for the column chromatography. The two zones of *R*_f=0.7 and 0.6 on TLC were collected separately and eluted with ether to afford 0.05 g and 0.1 g of an oil, respectively. **9** having *R*_f=0.7; IR $\nu_{\max}$ cm⁻¹: 3600, 2930, 1500, 1450, 1370, 1180, 920, 810. NMR $\delta_{\max}^{\text{CCl}_4}$ ppm: 1.0 (3H, d, *J*=7Hz), 1.06 (3H, s), 1.35 (3H, s), 2.35 (3H, s), 7.0~7.5 (4H, m). MS *m/e*: 218 (M⁺), 200, 185, 171, 146, 133, 119. **9** having *R*_f=0.6; IR $\nu_{\max}$ cm⁻¹: 3550, 2950, 1510, 1440, 1380, 1160, 1120, 1090, 810. NMR $\delta_{\max}^{\text{CCl}_4}$ ppm: 1.0 (3H, d, *J*=7Hz), 1.07 (3H, s), 1.35 (3H, s), 2.28 (3H, s), 7.0~7.5 (4H, m). MS *m/e*: 218 (M⁺), 185, 171, 157, 146, 133, 117.

2-*p*-Tolyl-1, 2, 5-trimethyl-5-cyclopentene (Isolaurene) (1). i) A solution of 30 mg of **9** (*R*_f=0.7) in methanol containing a trace amount of conc. hydrochloric acid was refluxed for 1 hr. After removal of the solvent, the residue was extracted with ether, and then the usual work-up afforded 15 mg of pure **1**. IR $\nu_{\max}$ cm⁻¹: 2900, 1510, 1440, 1370, 810. NMR $\delta_{\max}^{\text{CCl}_4}$ ppm: 1.36 (6H, s), 1.75 (3H, s), 7.06 (4H, s). MS *m/e*: 200 (M⁺), 185, 171, 158, 143.

ii) One-tenth of **9** (*R*_f=0.6) was treated as described above to afford 70 mg of **1**. This product was identical in all respects (IR, NMR and MS spectra) with that obtained in experiment i).

The spectroscopic data of **1** agreed also with those reported by Irie *et al.*¹⁾.

2-*p*-Tolyl-2, 5, 5-trimethylcyclopentanone (10). To a stirred suspension of sodium hydride (0.42 g of a 50% dispersion in mineral oil, 9 mmol) in 10 ml of THF was added **7** (0.75 g, 4 mmol) dropwise at 0~5°C for 15 min. To this mixture was added methyl iodide (1.7 g, 12 mmol) and the mixture was stirred for 4 hr at room temperature. The usual work-up gave **10** as a colorless oil, bp 98~102°C/3 mm. IR $\nu_{\max}$ cm⁻¹: 2950, 2860, 1735, 1510, 1460, 1380, 1020, 820. NMR $\delta_{\max}^{\text{CCl}_4}$ ppm: 0.9 (3H, s), 1.05 (3H, s), 1.3 (3H, s), 2.25 (3H, s), 6.9~7.0 (4H, m). MS *m/e*: 216 (M⁺), 201, 188, 173, 159, 144, 132.

1,2,5,5-Tetramethyl-2-*p*-tolylcyclopentanol (11). To a stirred solution of methyl lithium prepared from Li (0.7 g, 0.1 mol) and methyl iodide (7.1 g, 0.05 mol) in 20 ml of ether was added **10** (0.43 g, 2 mmol) dropwise at 0~5°C. After stirring for 30 hr at room temperature, the reaction was quenched by the addition of saturated ammonium chloride solution. The ether layer was separated and condensed *in vacuo*, the residue was purified by silica-gel column chromatography and preparative TLC to give 0.45g of pure **11**. IR $\nu_{\max}$ cm⁻¹: 3600, 2950, 1510, 1450, 1370, 810. NMR $\delta_{\max}^{\text{CCl}_4}$ ppm: 0.95 (3H, s), 1.05 (6H, s), 1.35 (3H, s), 7.0~7.3 (4H, s), MS *m/e*: 232 (M⁺), 214, 199, 189, 171, 145, 132, 112.

1-Methylene-2-*p*-tolyl-2, 5, 5-trimethylcyclopentane (12). Dehydration of **11** was similarly conducted as described for the preparation of **1**. A solution of **11** (150 mg, 0.65 mmol) in methanol containing a few drops of conc. hydrochloric acid was refluxed for 2 hr. After removal of the solvent, the residue was extracted with ether and the extract was washed with 5% aqueous sodium carbonate and brine, and then dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by TLC to afford 100 mg of pure **12**. IR $\nu_{\max}$ cm⁻¹: 2950, 1510, 1450, 1360, 810. NMR $\delta_{\max}^{\text{CCl}_4}$ ppm: 1.03 (6H, s), 1.3 (3H, s), 2.36 (3H, s), 5.56~5.6 (2H, m), 7.1 (4H, m). MS *m/e*: 214 (M⁺), 199, 185, 171, 156, 143, 132, 119.

5, 5-Dimethyl-2-*p*-tolyl-2-cyclopentenone (13). To a stirred suspension of sodium hydride (290 mg of a 50% dispersion in mineral oil, 6 mmol) in 15 ml of THF was added **6** (930 mg, 5 mmol) dropwise at 0~5°C for 15 min. To this mixture was added methyl iodide (1.4 g, 10 mmol) and the mixture was stirred for 2.5 hr at room temperature. After removal of the solvent, the residue was extracted with ether. The extract was dried and evaporated and the residue was distilled *in vacuo* to afford 150 mg of **13** as a colorless oil, bp 105~107°C/3 mm, mp 85~87°C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 2900, 1690,

1600, 1500, 1460, 1430, 1300, 820. NMR $\nu_{\text{max}}^{\text{CCl}_4}$ ppm: 1.12 (6H, s), 2.3 (3H, s), 6.9~7.6 (5H, m).

5, 5-Dimethyl-2-p-tolylcyclopentanone (**14**). A solution of **13** (0.2 g, 1 mmol) in 30 ml of methanol was hydrogenated with 0.3 g of 5% palladium on carbon by the same procedure used for the hydrogenation of **6**. After removal of the solvent and catalyst, the residue was purified by silica-gel column chromatography to yield 0.15 g of pure **14**. IR ν_{max} cm^{-1} : 2960, 1740, 1600, 1510, 1450, 1260, 1060, 800. NMR $\delta_{\text{max}}^{\text{CCl}_4}$ ppm: 0.95 (3H, s), 1.1 (3H, s), 2.28 (3H, s), 6.85 (4H, s). MS m/e : 202 (M^+), 187, 157, 142, 131, 118.

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