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A New Approach to (9*Z*)-Dodec-9-en-12-olide (Yuzu Lactone) via Phase Transfer Catalysis Cyclization

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Abstract:

(9*Z*)-Dodec-9-en-12-olide (**1**), also known as "Yuzu lactone", a volatile ingredient of Yuzu fruit was prepared in a three step synthesis via *Z*-selective Wittig olefination, a deprotection and activation protocol and subsequent cyclization by solid-liquid phase transfer catalysis under avoidance of high dilution conditions.

Keywords: Cyclization; Flavours and fragrances; Macrolides; Natural products; Phase transfer; Wittig reactions

Introduction

Yuzu is a kind of citrus tree (*Citrus junos* Tanaka) which is widely cultivated in the western parts of Japan. Flesh and peel of Yuzu fruits, that ripen at the beginning of November, have a characteristic flavour clearly different from other citrus fruits. Owing to their strong sour taste, Yuzu fruits are not eaten themselves but they have economic importance for flavouring purposes of vinegars and seasonings. In order to find substances imparting the Yuzu note Sakai, Abe et al. [1] investigated the constituents of volatile parts of cold pressed Yuzu oil. These authors isolated and identified (9*Z*)-dodec-9-en-12-olide (**1**) (Scheme 1), also called Yuzu lactone. **1** with its camphor-like and minty odour was considered to be responsible for the characteristic flavour of Yuzu. The same compound was also identified as a constituent of a steam volatile fraction from *Medicago rugosa* leaves and stems [2].

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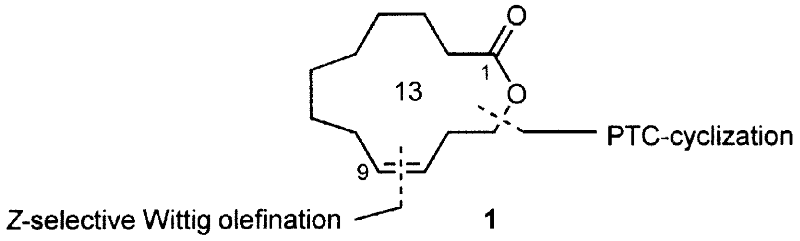
1 stands for the first macrocyclic lactone with a *Z*-configurated double bond isolated from a citrus oil and could be useful as quality improver for perfumes. Thus, there is a need for detailed evaluation of its flavour and fragrance. However, to our knowledge there is only one synthesis of **1** published until now [3] and further synthetic approaches would be interesting. In the course of our studies of fragrant macrolides [4] we also worked out a new approach to the title compound **1** via solid-liquid phase transfer catalysis [5].



Scheme 1: Retrosynthetic analysis of Yuzu lactone (**1**) from *Citrus junos* Tanaka

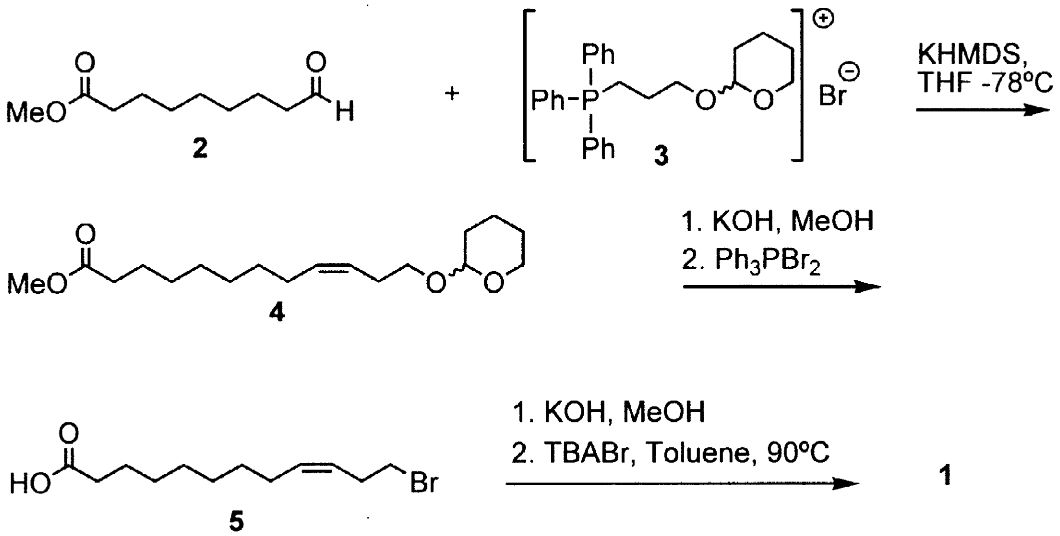
Results and Discussion

Our synthesis of **1** started with a *Z*-selective Wittig reaction of components **2** and **3** under salt free conditions in accordance to ref. [6]. Starting compound **2** was obtained by ozonolysis of methyl oleate [7] and the phosphonium salt **3** was synthesized in two steps by the procedure described in ref. [8]. Reaction of **2** and **3** with potassium hexamethyldisilazide (KHMDS) as base furnished olefin **4** in 61%. The coupling constant of olefinic protons (10.8 Hz) clearly indicates a *Z*-configuration. The *E*-isomer was not isolated.

Methyl ester **4** was cleaved by saponification with potassium hydroxide in methanol furnishing the crude acid in 97% which was used in the next step without further purification. Subsequent transformation of this acid (**4**, COOH instead of $COOCH_3$) into the bromide **5** combines deprotection and activation in one step and was performed with triphenylphosphine dibromide [9] in 91% yield.

For the cyclization of **5** we chose the phase transfer catalyzed method of Regen et al. [10] that enabled us to avoid high dilution conditions. First step of the cyclization protocol required the synthesis of the potassium salt of **5** which was subsequently cyclized in toluene with tetrabutylammonium bromide (TBABr) as PTC-catalyst in 62% yield. Even in a concentration of 64 mmol/l **1** was obtained in 57% yield. Gas chromatographic analysis revealed that **1** was generated in a purity of $\geq$ 97% with a ratio of $Z : E = 80 : 1$. All spectroscopic data were identical to those reported in ref. [1]. With the aid of gradient COSY and HSQC NMR experiments all signals of aliphatic protons and carbons were assigned unambiguously.

1 has a very complex and intensive odour that can be described as earthy, dry and dusty, woody, fresh and camphoraceous-minty. It has a fruity under-tone and some wax-stearin-like accents. But in contrast to its interesting olfactory properties the flavour was perceived as comparatively unpleasant, perfume like, reminding of textile finishing.



Scheme 2: Synthesis of **1**

Conclusion

We presented a highly *Z*-selective synthesis of Yuzu lactone (**1**) via a salt free Wittig reaction. After combined deprotection and activation steps we could show that macrolactonization of a 13-membered ring is possible by solid-liquid phase transfer catalyzed cyclization under avoidance of high dilution. Although its olfactory properties are very interesting, the contribution of Yuzu lactone to the typical Yuzu flavour seems to be of limited importance.

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1600 FTIR spectrometer. $^{1}H/^{13}C$ NMR spectra (reference: TMS int) were taken on Bruker AC 200 P, Bruker AM 300 or Bruker DRX 500 spectrometers, respectively. The assignment of related data marked with * may be exchanged. EI (70 eV) and CI (*i*BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Gas chromatography (GC) was performed on a Varian 3400 gas chromatograph equipped with a capillary column, MN Permabond® SE 30, (25 m), using nitrogen as carrier gas; the detector and injector temperatures were 250 °C. Ozonization was performed with

Sander 301 (0.45 A, 30 l/h O_2). Column chromatography was performed on Baker Silicagel 30-60 µm and analytical TLC on Macherey-Nagel SIL G/UV_{254} plates.

Methyl (9Z)-12-(tetrahydro-2′H-pyran-2′-yl-oxy)-1-dodec-9-enoate (**4**): Into a vigorously stirred solution of **3** (7.75 g, 16.5 mmol) [8] in 40 ml anhydrous THF at -80°C a 15% solution of KHMDS in toluene (22.0 mL, 17.0 mmol) under argon atmosphere was injected. The mixture was allowed to warm up to room temp and again cooled down to -80°C. After injection of **2** (3.00 g, 16.1 mmol) [7] the solution warmed up to room temp overnight. The reaction mixture was treated with water (10 mL), stirred for 15 min and poured into water/Et_2O (1:1, 100 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed twice with water, once with brine and dried over Na_2SO_4. The solvents were removed in vacuo and triphenylphosphine oxide was separated by crystallization. Column chromatography on silicagel (Et_2O/*n*-pentane, 1:5, R_f = 0.24) furnished 3.08 g (61%) of **4** as a colourless liquid. The *E*-configurated isomer was not detected by spectroscopical methods.

IR (film, cm^{-1}): $\tilde{\nu}$ 1741 (s, OC=O); - ^1H NMR ($CDCl_3$): δ = 1.25 - 1.37 (m, 8H, 4-H_2 - 7-H_2), 1.50 - 1.65 (m, 6H, 3-, 4′-, 5′-H_2), 1.71 (tdd, J = 8.8 Hz, 3.7 Hz, 3.1 Hz, 1H, 3′-H_a), 1.78 - 1.87 (m, 1H, 3′-H_b), 2.04 (td, J = 6.8 Hz, 6.8 Hz, 2H, 8-H_2), 2.30 (dd, J = 7.7 Hz, 7.7 Hz, 2H, 2-H_2), 2.34 (tdd, J = 7.1 Hz, 7.1 Hz, 1.4 Hz, 2H, 11-H_2), 3.40 (dt, J = 9.6 Hz, 7.1 Hz, 1H, 12-H_a), 3.48 - 3.53 (m, 1H, 6′-H_a), 3.66 (s, 3H, OCH_3), 3.72 (dt, J = 9.6 Hz, 7.2 Hz, 1H, 12-H_b), 3.88 (ddd, J = 11.3 Hz, 7.6 Hz, 3.5 Hz, 1H, 6′-H_b), 4.59 (dd, J = 4.5 Hz, 2.7 Hz, 1H, 2′-H), 5.38 (dtt, J = 10.8 Hz, 6.6 Hz, 1.5 Hz, 1H, 9-H^*), 5.45 (dtt, J = 10.8 Hz, 7.2 Hz, 1.5 Hz, 1H, 10-H^*); - ^{13}C NMR ($CDCl_3$): δ = 19.30 (t, C-4′), 24.66 (t, C-3), 25.26 (t, C-3′), 27.01 / 27.70 / 28.79 / 28.83 / 28.89 / 29.29 (t, C-4 - C-8, C-11), 30.44 (t, C-5′), 33.75 (t, C-2), 51.06 (q, OCH_3), 61.86 (t, C-6′), 66.77 (t, C-12), 98.35 (d, C-2′), 125.36 (d, C-10^*), 131.52 (d, C-9^*), 173.80 (s, C-1); - MS (CI): *m/z* (%): 313 (1) [M^+ + H], 229 (75) [M^+ - C_5H_8O +H], 85 (100) [C_5H_8O +H]; - Anal calcd for $C_{18}H_{32}O_4$ (312.5), C 69.20, H 10.32; found C 69.18, H 10.35.

(9Z)-12-Bromo-1-dodec-9-enoic acid (**5**): **4** (2.60 g, 8.34 mmol) was treated with KOH (2.24 g, 20.0 mmol) in anhydrous MeOH (20 mL) for about 6 h at reflux. The solvent was removed in vacuo. The crude product was dissolved in sat. NH_4Cl solution (50 mL) and the mixture was extracted six times with Et_2O (50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporating of the solvent furnished 2.44 g (97%) the crude acid (**4**, COOH instead of $COOCH_3$) as a colourless solid that was used for the synthesis of **5** without further purification.

A solution of Br_2 (1.53 mL, 29.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise to an ice cooled solution of triphenylphosphine (7.86 g, 30.0 mmol) in CH_2Cl_2 (150 mL) under nitrogen without exceeding a temperature of 5°C. The addition of pyridine (0.89 mL, 11.0 mmol) is followed by the above described acid (2.21 g, 7.42 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for about 1 h at 0°C and 1 h at room temp. For work up the reaction mixture was treated with of 5 N HCl (50 mL) and extracted four times with Et_2O (50 mL). The combined organic extracts were washed three times with brine and dried over Na_2SO_4. Triphenylphosphine oxide was removed by crystallization from Et_2O. Column chromatography on silicagel (Et_2O/*n*-pentane, 1:10) gave 1.7 g impure **5** and 480 mg (23%) of pure **5**. The first fraction was further purified by neutralization with 0.508 N KOH/MeOH solution (12.2 mL) and subsequent removal of the solvent. The remaining solid was suspended in 0.5 N NaOH solution (10 mL) and the aqueous phase was washed with Et_2O/*n*-pentane (1:1). The aqueous phase was acidified with 2 N HCl and extracted three times with Et_2O. The resulting organic phase was dried over Na_2SO_4 and evaporated in vacuo to give additional 1.40 g (68%) of pure **5**. The above described procedure led to a total total yield of 1.88 g (91%) **5** as colourless liquid.

IR (film, cm^{-1}): $\tilde{\nu}$ 3100 (br. s, OH), 1709 (s, OC=O); - ^1H NMR ($CDCl_3$): δ = 1.23 - 1.40 (m, 8H, 4-H_2 - 7-H_2), 1.63 (tt, J = 7.7 Hz, 7.7 Hz, 2H, 3-H_2), 2.04 (tdd, J = 7.2 Hz, 7.2 Hz, 1.4 Hz, 2H, 8-H_2), 2.35 (dd, J = 7.4 Hz, 7.4 Hz, 2H, 2-H_2), 2.62 (dtd, J = 7.2 Hz, 7.2 Hz, 1.5 Hz, 2H, 11-H_2), 3.37 (t, J = 7.2 Hz, 2H, 12-H_2), 5.36 (dtt, J = 10.8 Hz, 7.1 Hz, 1.5 Hz, 1H, 9-H^*), 5.53 (dtt, J = 10.8 Hz, 7.3 Hz, 1.5 Hz, 1H, 10-H^*), 11.0 (br, s, exchangeable, OH); - ^{13}C NMR ($CDCl_3$): δ = 24.61 (t, C-3), 27.35 / 28.97 / 29.01 / 29.09 / 29.40 (t, C-4 - C-8), 30.81 (t, C-11), 32.59 (t, C-12), 34.10 (t, C-2), 125.85 (d, C-10^*), 133.01 (d, C-9^*), 180.60 (s, C-1); - MS (CI): *m/z* (%): 277 (100) [M^+ + H], 259 (20) [M^+ + H - H_2O], 179 (39) [M^+ - H_2O - Br]; Anal calcd for $C_{12}H_{21}BrO_2$ (277.2), C 52.00, H 7.64; found C 51.98, H 7.67.

(9Z)-Dodec-9-en-12-olide (**1**): **5** (478 mg, 1.72 mmol) was titrated with 0.1037 N KOH/MeOH solution (15.25 mL) against phenolphthaleine. Afterwards MeOH was removed in vacuo and the resulting residue was dried for 2 h at 120°C and 0.1 torr. The resulting potassium salt (230 mg, 0.73 mmol) and TBABr (1.50 mg, 0.0046 mmol) in toluene (30 mL) were vigorously stirred at 90°C for 44 h. Afterwards TBABr (2.00 mg, 0.0062 mmol) was added followed by additional heating for 32 h. The reaction mixture was filtered over silicagel (0.063 - 0.2 μm, 5 g) and subsequently purified by column chromatography (Et_2O/*n*-pentane, 1:10) furnishing 89.0 mg (62%) of **1** as a colourless oil. Gas chromatography showed a purity of $\geq$ 97% with a ratio of $Z : E = 80 : 1$ (100(5)-2-150(10)). With the aid of gradient COSY and HSQC NMR experiments all signals of aliphatic protons and carbons were assigned unambiguously.

In a second run the potassium salt (1.00 g, 3.20 mmol) in toluene (50 mL) and TBABr (20.0 mg, 0.062 mmol) were heated for 16 h at 90°C furnishing 359 mg (57%) of **1** after column chromatography.

IR (film, cm^{-1}): $\tilde{\nu}$ 1733 (s, OC=O), 684 (m, H-C=, (*Z*) double bond); - ^1H NMR ($CDCl_3$): $\delta =$ 1.20 (m, 2H, 5-H_2), 1.29 (m, 2H, 6-H_2), 1.39 (tt, *J* = 6.9 Hz, 6.3 Hz, 2H, 4-H_2), 1.50 (tt, *J* = 6.4 Hz, 6.4 Hz, 2H, 7-H_2), 1.68 (m, 2H, 3-H_2), 2.10 (ddd, *J* = 7.3 Hz, 7.3 Hz, 5.4 Hz, 2H, 8-H_2), 2.29 (m therein dd, *J* = 6.1 Hz, 6.1 Hz, 2H, 2-H_2), 2.44 (ddd, *J* = 6.2 Hz, 6.2 Hz, 4.8 Hz, 2H, 11-H_2), 4.24 (m therein dd, *J* = 6.5 Hz, 6.5 Hz, 2H, 12-H_2), 5.39 Part A of an ABX_2Y_2-System (ddd, *J* = 10.8 Hz, 5.7 Hz, 1.3 Hz, 1H, 10-H), 5.42 Part B of an ABX_2Y_2-System (ddd, *J* = 10.8 Hz, 5.8 Hz, 1.1 Hz, 1H, 9-H); - ^{13}C NMR ($CDCl_3$): δ = 23.52 (t, C-3), 24.61 (t, C-8), 25.91 (t, C-5), 26.04 (t, C-6), 27.55 (t, C-7), 27.59 (t, C-11), 29.73 (t, C-4), 35.37 (t, C-2), 64.16 (t, C-12), 127.16 (d, C-10), 132.27 (d, C-9), 174.64 (s, C-1); - MS (CI): *m/z* (%): 197 (100) [M^+ + H], 179 (36) [M^+ - H_2O + H], 161 (10) [M^+ - $2H_2O$ + H]; - $C_{12}H_{20}O_2$ (196.3).

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