[Chem. Pharm. Bull. 36(4)1550—1553(1988)]

Preparation of 2,6-Dioxabicyclo[3.3.0]octan-3,7-dione and Its Application to the Synthesis of (±)-Eldanolide

MICHIYO HIZUKA, NORIYUKI HAYASHI, TOMOKO KAMASHITA, HIROSHI SUEMUNE and KIYOSHI SAKAI*

Faculty of Phamaceutical Sciences, Kyushu University, Fukuoka 812, Japan

(Received October 16, 1987)

2,6-Dioxabicyclo[3.3.0]octan-3,7-dione seems to be a promising compound for the synthesis of natural products such as epoxyeicosatrienoic acid, laurediol, and eldanolide. This compound, consisting of two γ-lactones, could be prepared by double lactonization of the silver salt of *trans*-3-hexenedioic acid using iodine. Starting with this bis-lactone, (±)-eldanolide could be synthesized in a stereocontrolled manner.

Keywords——2,6-dioxabicyclo[3.3.0]octan-3,7-dione; eldanolide; α,β-unsaturated lactone; lactonization; 1,4-addition; *trans*-3-hexenedioic acid

There are a number of natural products with the partial structure of bis-homoallyl alcohols such as *cis*- and *trans*-laurediol[1] (**3**) in red algae, bis-homoallyl oxides such as epoxyeicosatrienoic acid[2] (**4**) produced from arachidonic acid *via* epoxidation with cytochrome P-450, and the disubstituted monolactones such as eldanolide[3] (**5**), the wing gland pheromone of the African sugar-cane borer *Eldana saccharina* (WLK.). Syntheses of these biologically active compounds might be achieved by using the bis-lactone (**2**) as an intermediate, because i) the ring junction of this compound should have *cis* configuration, ii) carbon chains required for the synthesis of laurediol (**3**) and epoxyeicosatrienoic acid (**4**) may be introduced by Wittig reaction of the corresponding lactol, iii) eldanolide (**5**) may be synthesized *via* 1,4-addition in a stereocontrolled manner after conversion to the α,β-unsaturated lactone. The bis-lactone (**2**) was expected to be obtainable by the double lactonization of *trans*-3-hexenedioic acid (**1**). However, it has been reported that the lactonization of **1** using iodine resulted in the formation of the monolactone,[4] and **2** was not

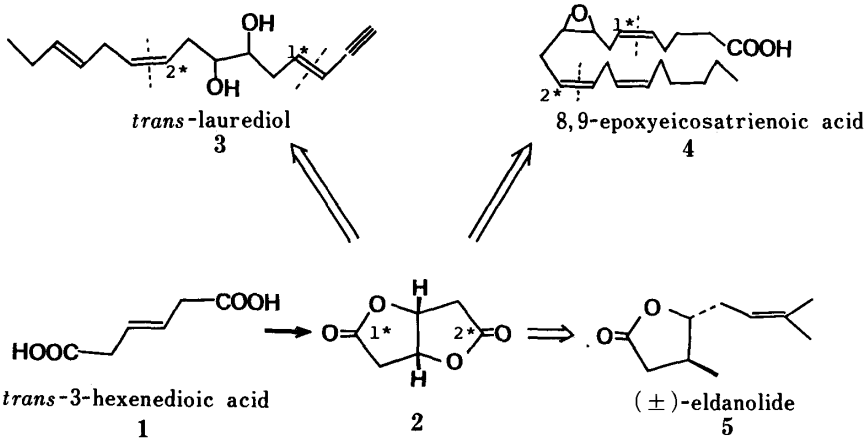
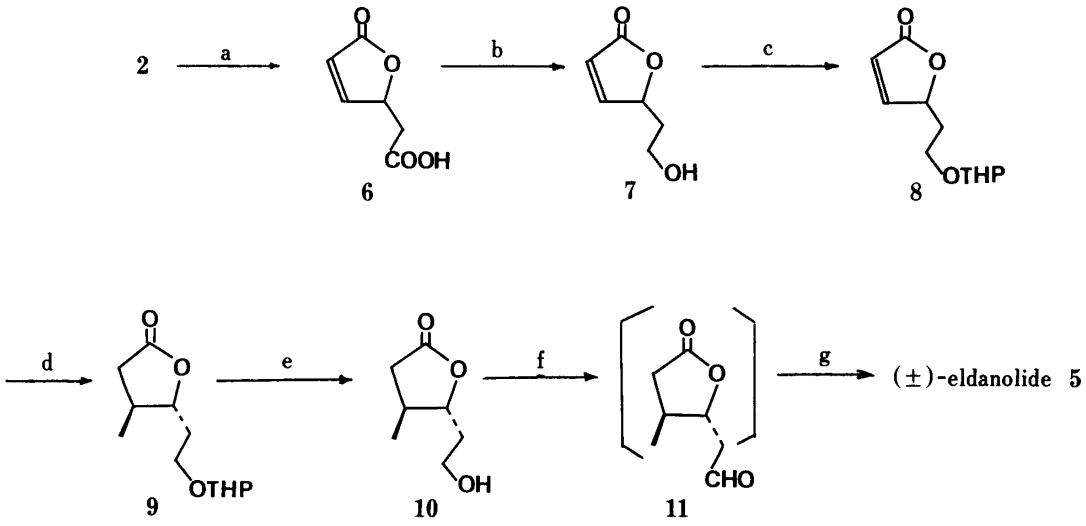


Chart 1

isolated.

In a re-examination of this double lactonization, expected to provide the basis for a simple, short synthesis of **2**, we have found that treatment of the well-dried silver salt of **1** with iodine in CH_2Cl_2 affords **2**, in excellent yield, as colorless needles (recrystallized from acetone–hexane), mp 132 °C. The structure of **2** was supported by the signals of δ 5.38 (2H, CHOCO) 3.16 (2H, $CH_\beta CO$) and 2.76 (2H, $CH_\alpha CO$)[5] in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, in addition to the absorption band of 1775 cm^{-1} in the infrared (IR) spectrum. Compound **2** has two interesting features. One is that this compound is very unstable to bases. On treatment with a very weak base such as $NaHCO_3$, AcOK, or amine base, **2** is susceptible to cleavage of one lactone ring to afford an α,β-unsaturated lactone, and the hydrolyzed product is not obtained at all. This eliminative cleavage of one lactone ring may occur *via* the facile enolization of the other lactone ring. The other feature is that the solubility[6] in organic solvents such as ether, tetrahydrofuran (THF), alcohol, and benzene is extremely low, except for acetone.



a) K_2CO_3/MeOH b) BH_3–Me_2S/THF c) DHP/*p*-TsOH d) Me_2CuLi e) *p*-TsOH/MeOH
f) PCC g) isopropyltriphenylphosphonium bromide/BuLi

Chart 2

As an example of the application of **2** to the synthesis of natural products, we have undertaken a stereospecific synthesis of (±)-eldanolide (**5**). Treatment of **2** with K_2CO_3/acetone–MeOH at room temperature afforded the α,β-unsaturated lactone (**6**), in 78% yield, as colorless needles, mp 112 °C. The structure of **6** was confirmed by the signals of δ 5.29—5.47 (1H, m, =C–CHOCO), 6.23 (1H, dd, CO–CH=), and 7.77 (1H, dd, =CH–) in the ^{1}H-NMR spectrum, and the absorption bands at 3300—3400, 1740, and 1708 cm^{-1} in the IR spectrum. Reduction of the carboxyl function in **6** with BH_3–Me_2S afforded the alcohol (**7**), which could be converted to the tetrahydropyranyl ether (**8**), in 50% yield from **6**, by treatment with 3,4-dihydro-2*H*-pyran in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in CH_2Cl_2. 1,4-Addition of $(Me)_2CuLi$ to **8** at −25 °C proceeded smoothly to afford the addition product (**9**), in 56% yield, as a single product. The stereochemistry of **9** was established to be *trans* by analysis of the nuclear Overhauser effect difference spectrum[7] of the alcohol (**10**), which was obtained by treatment with *p*-TsOH/MeOH. Oxidation of **10** with pyridinium chlorochromate (PCC), followed by Wittig reaction with isopropylidenetriphenylphosphorane afforded (±)-eldanolide (**5**), whose spectroscopic data were identical with the reported values.[3b]

Experimental

IR spectra were measured with a JASCO A-202 spectrometer, ^{1}H-NMR spectra on a JEOL JNM-FX 100, and mass spectra (MS) on a JEOL JMS-D 300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates (Merck). Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. All organic solvent extracts were washed with saturated brine and dried on anhydrous sodium sulfate.

1*βH*,5*βH*-2,6-Dioxabicyclo[3.3.0]octan-3,7-dione (2)——$AgNO_3$ (60.0 g, 353 mmol) in H_2O (500 ml) was added dropwise with stirring to a mixture of *trans*-3-hexenedioic acid (**1**) (25.0 g, 174 mmol) and $NaHCO_3$ (29.2 g, 348 mmol) in H_2O (500 ml) at room temperature. The resulting white precipitate was filtered off, washed with water, and then dried *in vacuo* under protection from light to give the silver salt (60.0 g, 97%).

Iodine (1.43 g, 5.6 mmol) in CH_2Cl_2 (10 ml) was added to a stirred suspension of the well-dried silver salt (2.00 g, 5.6 mmol) in CH_2Cl_2 (30 ml) at room temperature. After 2 h, the precipitate was filtered off, and the filtrate was successively washed with 10% aqueous $NaHSO_3$, 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded the crystalline residue (**1**) (0.76 g, 95%), which was recrystallized from acetone and hexane, mp 132 °C. IR (Nujol): 1775, 1195, 1050 cm^{-1}. ^{1}H-NMR (CD_3COCD_3) δ: 2.76 (2H, d, J=18.0 Hz, COCH (α)), 3.16 (2H, dd, J=4.5, 18.0 Hz, COCH (β), 5.38 (2H, m, COOCH). MS *m/z*: 142 (M^+), 71. *Anal.* Calcd for $C_6H_6O_4$: C, 50.71; H, 4.26. Found: C, 50.65; H, 4.21.

5-(Carboxymethyl)-2,5-dihydro-2-furanone (6)——K_2CO_3 (243 mg, 1.76 mmol) was added to a stirred solution of **5** (500 mg, 3.52 mmol) in 50% acetone in methanol (v/v) (12 ml) at room temperature, and the whole was stirred for 3 h, then for 20 h in the presence of Amberlite IR-120B (1 g). The reaction mixture was filtered off, and the filtrate was concentrated *in vacuo* to leave an oily residue, which was subjected to column chromatography. The fraction eluted with 65% AcOEt in hexane (v/v) gave **6** (389 mg, 78%) as colorless needles, recrystallized from CH_2Cl_2–hexane, mp 112 °C. IR (Nujol): 3300—3400, 1740, 1708 cm^{-1}. ^{1}H-NMR (*d*-DMSO) δ: 5.29—5.47 (1H, m, CHOCO), 6.23 (1H, dd, J=2.2, 6.5 Hz, COCH=), 7.77 (1H, dd, J=2.1, 6.5 Hz, CH=), 10.2 (1H, br, COOH). MS *m/z*: 142 (M^+), 96, 71. *Anal.* Calcd for $C_6H_6O_4$: C, 50.71; H, 4.26. Found: C, 50.82; H, 4.24.

5-(2-Hydroxyethyl)-2,5-dihydro-2-furanone (7)——Borane–methyl sulfide complex (10.0 M in BH_3) (0.56 ml, 5.6 mmol) was added dropwise to a stirred solution of the acid (**6**) (389 mg, 2.74 mmol) in THF (15 ml) at 0 °C. The whole was stirred for 3 h at 0 to 5 °C, and for an additional 3 h at room temperature. The reaction mixture was diluted with MeOH (6 ml), and the solvent was removed *in vacuo* to leave an oily residue, which was subjected to silica-gel column chromatography. The fraction eluted with 40% AcOEt in hexane (v/v) afforded **7** (211 mg, 60%) as a colorless oil. IR (neat): 3400, 1740, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (2H, t, J=5.2 Hz, CH_2O), 5.26 (1H, m, CHOCO), 6.10 (1H, dd, J=2.0, 5.8 Hz, COCH=), 7.58 (1H, dd, J=2.0, 5.8 Hz, =CH). MS *m/z*: 128 (M^+), 110, 82.

5-[2-(Tetrahydropyran-2-yl)oxyethyl]-2,5-dihydro-2-furanone (8)——3,4-Dihydro-2*H*-pyran (262 mg, 3.12 mmol) in CH_2Cl_2 (2 ml) was added dropwise to a stirred solution of the alcohol (**7**) (160 mg, 1.26 mmol) and *p*-TsOH (trace) in CH_2Cl_2 (2 ml) at 0 °C. After 1 h, the reaction mixture was diluted with ether (50 ml). The organic layer was successively washed with 5% $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was chromatographed on silica gel (5.0 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **8** (220 mg, 83%) as a colorless oil. IR (neat): 1755, 1600, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.58 (1H, m, OCHO), 5.24 (1H, m, CHOCO), 6.10 (1H, dd, J=1.9, 5.8 Hz, COCH=), 7.60 (1H, dd, J=1.4, 5.8 Hz, =CH). MS *m/z*: 212 (M^+), 211, 157, 128.

***trans*-4-Methyl-5-[2-(tetrahydropyran-2-yl)oxyethyl]-tetrahydro-2-furanone (9)**——MeLi (1.07 M solution in ether) 4.4 ml, 4.72 mmol) was added dropwise with stirring to a suspension of CuI (447 mg, 2.36 mmol) in ether (5 ml) at −25 °C under an N_2 atmosphere. After 10 min, the tetrahydropyranyl ether (**8**) (100 mg, 0.472 mmol) in ether (2 ml) was added dropwise at −25 °C. The whole was stirred for 1 h, and diluted with 5% aqueous NH_4Cl (15 ml), then extracted with ether. The ether extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (3.0 g). The fraction eluted with 30% ether in hexane (v/v) afforded **9** (60 mg, 56%) as a colorless oil. IR (neat): 1775, 1450, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6.5 Hz, CH_3), 4.11—4.31 (1H, m, CHOCO). MS *m/z*: 228 (M^+), 227, 173, 155.

***trans*-5-(2-Hydroxyethyl)-4-methyl-tetrahydro-2-furanone (10)**——A mixture of the lactone (**9**) (60 mg, 0.26 mmol) and *p*-TsOH (trace) in MeOH (2 ml) was stirred for 12 h at room temperature, then pyridine (1 drop) was added, and the solvent was removed *in vacuo* to afford an oily residue, which was chromatographed on silica gel. The fraction eluted with 25% hexane in AcOEt (v/v) afforded **10** (36 mg, 95%) as a colorless oil. IR (neat): 3410, 1765, 1420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=6.0 Hz, CH_3), 3.85 (2H, dd, J=6.3, 5.1 Hz, CH_2O), 4.18—4.26 (1H, m, CHOCO). MS *m/z*: 144 (M^+), 126, 99.

(±)-Eldanolide——PCC (210 mg) in CH_2Cl_2 (3 ml) was added with stirring to a stirred solution of the alcohol (**10**) (77 mg, 0.53 mmol) in CH_2Cl_2 (2 ml) at room temperature. After 2 h, the reaction mixture was diluted with ether, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford a crude aldehyde (**11**) (63 mg), which was subjected to the next Wittig reaction without purification. The aldehyde (**11**) was added to the ylide [prepared from isopropyltriphenylphosphonium bromide (340 mg, 0.88 mmol) and BuLi (1.56 M solution in

hexane) (0.60 mmol) in THF (6 ml) in the usual manner], at −78 °C under an N_2 atmosphere. The whole was stirred for 2 h, and diluted with H_2O (5 ml), then extracted with ether. The ether extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was chromatographed on silica gel. The fraction eluted with 10% AcOEt in hexane (v/v) afforded **5** (20 mg, 22% from **10**) as a colorless oil. IR (neat): 1780, 1675, 1450, 1208 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=6.4 Hz, CH_3), 1.64 (3H, s, C=C–CH_3), 1.73 (3H, d, J=1.3 Hz, C=C–CH_3), 4.06 (1H, q, J=6.2 Hz, CHOCO), 5.17 (1H, t, J=7.4 Hz, CH=C). MS m/z: 168 (M^+), 99, 71, 43.

References and Notes

1) B. Anorbe, V. S. Martin, J. M. Palazone, and J. M. Trujillo, *Tetrahedron Lett.*, **27**, 4991 (1986).
2) *a*) C. A. Moustakis, J. Viala, J. Capdevila, and J. R. Falck, *J. Am. Chem. Soc.*, **107**, 5283 (1985); *b*) P. Mosset, P. Yadagiri, S. Lumin, J. Capdevila, and J. R. Falck, *Tetrahedron Lett.*, **27**, 6035 (1986); *c*) M. D. Ennis and M. E. Base, *ibid.*, **27**, 6031 (1986).
3) *a*) C. W. Jefford, A. W. Sledeski, and J. Boukouvalas, *Tetrahedron Lett.*, **28**, 949 (1987), and references cited therein; *b*) T. K. Chakraborty and S. Chandrasekaran, *ibid.*, **25**, 2891 (1984).
4) M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, and A. Yoshikoshi, *J. Org. Chem.*, **40**, 1932 (1975).
5) 4αH(8αH) and 4βH(8βH) were assigned on the basis of the coupling constant predicted from each bond angle between 1βH–8αH(5βH–4αH) or 1βH–8βH(5βH–4βH).
6) In a preliminary experiment, we have succeeded in the synthesis of homoallylic alcohol from **2** by Wittig reaction of the corresponding monolactol. However, the low solubility of **2** in organic solvents inhibited further studies.
7) Irradiation of C_4-CH_3 in **10** enhanced the intensity of the C_5-H signal by 20%.