A Stereocontrolled Synthesis of Trisubstituted Cyclohexanes and Cyclopentanes. Its Application to the Synthesis of 11-Deoxyprostaglandins

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1,4-Addition of organocopper reagents to γ-substituted α,β-unsaturated γ-lactones followed by intramolecular trapping of the resulted enolates afforded *cis,cis*-1,2,3-trisubstituted cyclopentanes and cyclohexanes in a stereocontrolled manner. This new cyclization reaction to cyclopentanes provides a new synthetic route to the key intermediate in the synthesis of 11-deoxyprostaglandins.

Keywords 1,4-addition; organocuprate; intramolecular cyclization; trisubstituted cyclopentane; trisubstituted cyclohexane; 11-deoxyprostaglandin

1,4-Addition of organocopper reagents[1] to α,β-unsaturated carbonyl compounds constitutes one of the most versatile reactions in syntheses of natural products. In general addition of an organometallic reagent to α,β-unsaturated carbonyl compounds, Grignard reagents give a mixture of 1,2- and 1,4-adducts.[2] It is well known that 1,4-addition with greater stereoselectivity[3] is achieved by using organocopper reagents.

We describe the stereocontrolled synthesis of *cis,cis*-trisubstituted cyclopentanes and cyclohexanes, based on 1,4-addition of copper reagents to α,β-unsaturated lactones followed by intramolecular trapping of the resulted enolates, and its application to the synthesis of 11-deoxyprostaglandins. The tosylate (**2**, X=OTs), the iodide (**2**, X=I), and the sulfonate (**2**, X=(±)-10-camphorsulfonyloxy) in Table I were prepared from γ-(2-hydroxyethyl)-α,β-unsaturated γ-lactone (**1**, $n=1$)[4] by the conventional methods (Chart 1). Treatment of **2** with R_2CuLi (3 eq), prepared from $CuBr\cdot Me_2S$[5] and RLi,[6] under the reaction conditions shown in Table I afforded stereoselectively the bridged lactones (**3**) in moderate yields. Structures of **3** were supported by the presence of common signals in the proton nuclear magnetic resonance (^{1}H-NMR) spectra [δ 2.7 (1H, s, C_4-H), 4.6 (1H, s, C_1-H)], in addition to absorption bands at 1770, 1760 cm^{-1} in the infrared (IR) spectra. The stereochemistry at C_7 was deduced, based on 1,4-addition of R_2CuLi to favor the *anti*-addition to the C_5-substituent. In this 1,4-addition leading to the stereoselective construction of the cyclopentane ring, the reaction temperature seems to play an important role. As shown in Table I, reactions at −25 °C afforded cyclized products in good yields among the tested reactions. However, reaction at −78 °C (entry 2a) resulted in the formation of only the 1,4-adduct (**4**), and the cyclized product was not obtained at all. On the other hand, reaction at room temperature reduced the yield of bridged lactone, and the substitution product (**5**) was isolated in 25% yield (entry 2e, Table I). As shown in entry 1a (Table II),[7] 1,4-addition reaction to form the cyclohexane ring at −25 °C resulted in the recovery of **2** (X=OTs), in addition to a small amount of the 1,4-adduct (**4**, R=Ph, X=OTs). The cyclization reaction to the cyclohexane ring required a higher temperature (0—25 °C) than in the case of $n=1$, and proceeded in a lower yield. Organocuprate, prepared from $CuBr\cdot Me_2S$ and RLi, gave better yields than did the "ate"-complex from CuI and RLi (entries 1b and 1c, Table I) in accord with the report of Bertz *et al.*[5] on 1,4-addition to cyclohexenone.

The above ring formation based on intramolecular trapping of the resultant enolate with the leaving group in the molecule suggests the occurrence of intramolecular acyl rearrangement from the γ-(2-acyloxyethyl)-α,β-unsaturated

Chart 1

TABLE I. Reaction of **2** ($n=1$) with $(R)_2CuLi$

Entry	$(R)_2CuLi$ (R=)	Substrate **2** (X=)	Temp. (°C)	Yield (%)		
				3	**4**	**5**
1a	Me	OTs	−25	76.2		
1b	Me	OTs	−25	47.2		
1c	Me	I	−25	41.1		
1d	Me	(±)-10-Camphor-sulfonyloxy	−25	64.5		
2a	Bu	OTs	−78		35.3	
2b	Bu	OTs	−25	70.3		
2c	Bu	I	−25	76.6		
2d	Bu	(±)-10-Camphor-sulfonyloxy	−25	74.5		
2e	Bu	OTs	Room temp.	40.0		25.0
3a	Ph	OTs	−25	71.2		
3b	Ph	I	−25	80.5		
4a	7-Octenyl	OTs	−25	72.3		

In entries 1b and 1c, CuI instead of $CuBr\cdot Me_2S$ was used. The reaction time in each entry was 0.5—1 h.

TABLE II. Reaction of **2** ($n=2$) with $(R)_2CuLi$

Entry	$(R)_2CuLi$ (R=)	Substrate **2** (X=)	Temp. (°C)	Yield (%)		
				3	**4**	**5**
1a	Ph	OTs	−25		8.0	
1b	Ph	OTs	0	24.8	12.1	
1c	Ph	OTs	20	27.5		16.3
1d	Ph	I	0	53.4		

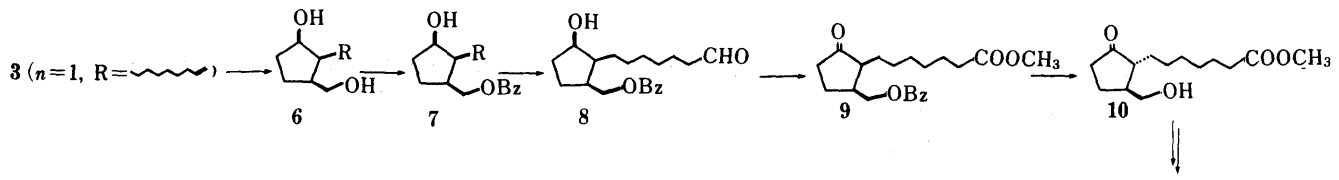

Chart 2

lactone to the α-acyl-α,β-unsaturated lactone. In accord with our expectation, 1,4-addition of $(Me)_2CuLi$ to **2** ($n=1$, X=OAc) at −25 °C afforded the acetyl lactone (**11**) in 35% yield. The structure of **11** was supported by the signals in the ^{1}H-NMR spectrum at δ 1.13 (3H, d, $J=6.6$ Hz, Me), 2.45 (3H, s, COMe) and 3.41 (1H, d, $J=10.8$ Hz, COCHCO), in addition to the absorption bands at 3400, 1765 and 1720 cm^{-1} in the IR spectrum and a positive $FeCl_3$ color test. This finding suggests a facile introduction of the acyl substituent in a stereocontrolled manner at the α-position to the γ-lactone.

The key intermediate for the synthesis of 11-deoxyprostaglandin was prepared, starting with the product (**3**) in entry 4a (Table I) (Chart 2). Reduction of **3** (R=7-octenyl) with $LiAlH_4$ in ether at 0 °C afforded the diol (**6**) in 90% yield. The monobenzoate (**7**) was obtained in 63% yield by selective benzoylation of **3** (1 mmol) with benzoyl chloride (1.01 mmol)/pyridine in CH_2Cl_2 at 0 °C. Ozone oxidation of **7** afforded the aldehyde (**8**), which was subjected to concurrent oxidation of the alcohol and aldehyde functions with Jones reagent to give the keto-acid, followed by esterification with CH_2N_2. By treatment with K_2CO_3/MeOH, the ester (**9**) could be converted to the key intermediate (**10**)[8] for the synthesis of 11-deoxyprostaglandin *via* C_2-epimerization to the *trans*-isomer and methanolysis of the benzoate.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer, and ^{1}H-NMR spectra were recorded on a JEOL JNM-PS-100 or JEOL JNM-FX-100 spectrometer. Mass spectra (MS) were taken 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 F_{254} plates (Merck). All organic solvent extracts were dried over anhydrous sodium sulfate. The percentage composition of solvent systems in column chromatography refers to v/v.

General Procedure (Entry 1a, Table I) Methyl lithium (1 M solution in ether, Kanto Chemicals) (2.84 ml, 2.98 mmol) was added dropwise with stirring to a suspension of $CuBr\cdot Me_2S$ (356 mg, 1.73 mmol, Aldrich) in ether (5 ml) under an Ar atmosphere at −25 °C, and the whole was stirred for 15 min. Compound **2** ($n=1$, X=OTs) (70 mg, 0.248 mmol) in tetrahydrofuran (THF) (2 ml) was added dropwise at −25 °C, and stirring was continued for 30 min. The reaction mixture was diluted with 15% aqueous NH_4Cl (10 ml), and extracted with ether. The ether extract was washed with brine, and dried, then concentrated *in vacuo* to leave an oily residue, which was subjected to silica-gel column chromatography. The fraction eluted with 30% AcOEt in hexane afforded **3** ($n=1$, R=Me) (24 mg, 76.7%) as a colorless oil.

Substrates (2) $n=1$, X=OTs: Colorless oil. IR ($CHCl_3$): 1750, 1600, 1170, 1090. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s, Me), 4.18 (2H, dd, $J=6.6$, 5.3 Hz, CH_2OTs), 5.05—5.22 (1H, m, CHOCO), 6.14 (1H, dd, $J=5.6$, 2.1 Hz, =CHCO), 7.37 (2H, d, $J=8.3$ Hz, aromatic-H), 7.48 (1H, dd, $J=5.6$, 1.5 Hz, CH=), 7.79 (2H, d, $J=8.3$ Hz, aromatic-H). MS *m/z*: 282 (M^+), 218, 111, 91.

$n=1$, X=I: Colorless oil. IR (neat): 1750, 1600, 1160, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.32 (2H, dd, $J=6.1$, 7.5 Hz, CH_2I), 5.11—5.28 (1H, m, CHOCO), 6.16 (1H, dd, $J=5.6$, 2.0 Hz, =CHCO), 7.50 (1H, dd, $J=5.6$, 1.5 Hz, CH=). MS *m/z*: 238 (M^+), 155, 111, 83.

$n=1$, X=(±)-10-Camphorsulfonyloxy: Colorless oil. IR (neat): 1750, 1740, 1350, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, s, Me), 1.11 (3H, s, Me), 4.49 (2H, dd, $J=6.6$, 5.1 Hz, CH_2OSO_2), 5.15—5.29 (1H, m, CHOCO), 6.16 (1H, dd, $J=5.6$, 2.0 Hz, =CHCO), 7.59 (1H, dd, $J=5.6$, 1.7 Hz, CH=). MS *m/z*: 342 (M^+), 233, 151, 109.

$n=1$, X=OAc: Colorless oil. IR (neat): 1740, 1600, 1240, 1160, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, COMe), 4.16—4.31 (2H, m, CH_2OAc), 5.08—5.26 (1H, m, CHOCO), 6.15 (1H, dd, $J=6.0$, 2.0 Hz, =CHCO), 7.51 (1H, dd, $J=6.0$, 1.5 Hz, CH=). MS *m/z*: 171 (M+1), 128, 110, 83.

$n=2$, X=OTs: Colorless oil. IR (neat): 1745, 1600, 1350, 1160, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s, Me), 4.08 (2H, t, $J=5.1$ Hz, CH_2OTs), 4.98—5.06 (1H, m, CHOCO), 6.17 (1H, dd, $J=5.6$, 2.0 Hz, =CHCO), 7.36 (2H, d, $J=8.5$ Hz, aromatic-H), 7.41 (1H, dd, $J=5.6$, 1.5 Hz, CH=), 7.78 (2H, d, $J=8.5$ Hz, aromatic-H). MS *m/z*: 296 (M^+), 172, 125.

$n=2$, X=I: Colorless oil. IR (neat): 1750, 1600, 1160, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.24 (2H, t, $J=6.2$ Hz, CH_2I), 5.02—5.10 (1H, m, CHOCO), 6.14 (1H, dd, $J=5.6$, 2.0 Hz, =CHCO), 7.50 (1H, dd, $J=5.6$, 1.5 Hz, CH=). MS *m/z*: 252 (M^+), 125, 83.

Products (3) $n=1$, R=Me: Colorless oil. IR (neat): 1760, 1460, 1330, 1170, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, $J=6.8$ Hz, Me), 2.63 (1H, s, CHCOO), 4.56 (1H, s, CHOCO). MS *m/z*: 126 (M^+), 98, 82.

$n=1$, R=Bu: Colorless oil. IR (neat): 1770, 1460, 1330, 1170, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83—1.54 (9H, m, $CH_2\times3$, Me), 2.70 (1H, s, CHCOO), 4.64 (1H, s, CHOCO). MS *m/z*: 168 (M^+), 139, 124, 111.

$n=1$, R=Ph: mp 108—110 °C (from hexane–AcOEt). IR (Nujol): 1775, 1605, 1455, 1150, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.76—2.27 (4H, m, $CH_2\times2$), 3.13—3.15 (1H, m, CHCOO), 3.27 (1H, s, CHPh), 5.03 (1H, s, CHOCO), 7.16—7.56 (5H, m, aromatic-H). MS *m/z*: 188 (M^+), 160, 144.

$n=1$, R=7-Octenyl: Colorless oil. IR (neat): 1775, 1635, 1460, 1330, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21—2.07 (17H, m, $CH_2\times8$, –CH), 2.70 (1H, s, CHCOO), 4.63 (1H, s, CHOCO), 4.88—5.10 (2H, m, $=CH_2$), 5.62—6.03 (1H, m, CH=). MS *m/z*: 222 (M^+), 193, 178, 111.

$n=2$, R=Ph: mp 82—84 °C (from hexane–AcOEt). IR (Nujol): 1760, 1605, 1455, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.71—2.21 (6H, m, $CH_2\times6$), 2.83—2.85 (1H, m, CHCOO), 3.10 (1H, s, CHPh), 4.91 (1H, d, $J=3.7$ Hz, CHOCO), 7.14—7.45 (5H, m, aromatic-H). MS *m/z*: 202 (M^+), 174, 158, 130.

Products (4) $n=1$, R=Bu, X=OTs: Colorless oil. IR (neat): 1775, 1600, 1170, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84—2.20 (12H, m), 2.46 (3H, s, Me), 4.04—4.24 (3H, m, CHOCO, CH_2OTs), 7.35 (2H, d, $J=8.3$ Hz, aromatic-H), 7.79 (2H, d, $J=8.3$ Hz, aromatic-H). MS *m/z*: 341 (M+1), 340 (M^+), 258, 169, 127.

$n=2$, R=Ph, X=OTs: Colorless oil. IR (neat): 1780, 1600, 1500, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s, Ph-Me), 3.99—4.05 (2H, m, CH_2O), 4.34—4.41 (1H, m, CHOCO), 7.20—7.42 (7H, m), 7.74 (2H, d, $J=8.3$ Hz, aromatic-H). MS *m/z*: 375 (M+1), 374 (M^+), 356, 203, 202, 161.

Products (5) $n=1$, R=Bu: Colorless oil. IR (neat): 1780, 1460, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85—2.12 (23H, m), 4.06—4.13 (1H, m, CHOCO). MS *m/z*: 226 (M^+), 141.

$n=2$, R=Ph: Colorless oil. IR (neat): 1780, 1600, 1500, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59—1.89 (4H, m, $CH_2\times2$), 2.53—2.65 (2H, m, CH_2Ph), 2.69 (1H, dd, $J=17.6$, 10.7 Hz, CH_aCO), 2.95 (1H, dd, $J=17.6$, 8.1 Hz, CH_bCO), 4.42—4.51 (1H, m, CHOCO). MS *m/z*: 280 (M^+), 104, 91.

(1*RS*,2*SR*,3*SR*)-3-Hydroxymethyl-2-(7-octenyl)-1-cyclopentanol (6) Compound **3** ($n=1$, R=7-octenyl) (861 mg, 3.87 mmol) in ether (7 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (168 mg, 4.45 mmol) in ether (4 ml) at 0 °C under an Ar atmosphere. After 1 h, usual work-up afforded a crude oil, which was subjected to column chromatography on

silica gel. The fraction eluted with 25% AcOEt in hexane gave **6** (791 mg, 90%) as a colorless oil. IR (neat): 3300, 1640, 1450, 1020, 905 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.26—2.08 (18H, m), 3.21 (2H, s, OH × 2), 3.46 (1H, dd, J=10.7, 2.9 Hz, CH_aOH), 3.69 (1H, dd, J=10.7, 2.2 Hz, CH_bOH), 4.05—4.25 (1H, m, CHO–), 4.83—5.10 (2H, m, $=CH_2$), 5.62—6.03 (1H, m, CH=). MS m/z: 227 (M+1), 226 (M^+), 208, 177, 97.

(1*RS*,2*SR*,3*SR*)-3-Benzoyloxymethyl-2-(7-octenyl)-1-cyclopentanol (7) A mixture of pyridine (0.25 ml, 3.05 mmol) and benzoyl chloride (143 mg, 1.01 mmol) in CH_2Cl_2 (3 ml) was added dropwise to a stirred solution of **6** (230 mg, 1.01 mmol) in CH_2Cl_2 (15 ml) at 0 °C. After 1 h, the reaction mixture was diluted with brine, and extracted with ether. The ether extract was successively washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, then dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 15% AcOEt in hexane afforded **7** (210 mg, 63%) as a colorless oil. IR (neat): 3500, 1720, 1600, 1270, 1025 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.17—4.56 (3H, m, CH_2OCO, CHO–), 4.85—5.09 (2H, m, $=CH_2$), 5.61—6.02 (1H, m, CH=), 7.34—7.64 (3H, m, aromatic-H), 7.99—8.12 (2H, m, aromatic-H). MS m/z: 330 (M^+), 312, 208, 190, 122, 105, 79.

(1*RS*,2*SR*,3*SR*)-3-Benzoyloxymethyl-2-(6-formylhexyl)-1-cyclopentanol (8) Ozone gas was bubbled into a solution of **7** (210 mg) in CH_2Cl_2 (20 ml) at −78 °C, and the reaction was monitored by TLC. The resulting ozonide was decomposed with Zn powder (450 mg) and AcOH (3 ml) at 10 to 20 °C. The Zn powder was filtered off, and the filtrate was concentrated *in vacuo*, diluted with brine (20 ml), and then extracted with AcOEt. The AcOEt extract was washed, and dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% AcOEt in hexane gave **8** (143 mg, 68%) as a colorless oil. IR (neat): 3500, 1715, 1600, 1270, 1110, 1020 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.16—4.57 (3H, m, CH_2OCO, CHO–), 7.34—7.65 (3H, m, aromatic-H), 8.04 (2H, m, aromatic-H), 9.75 (1H, t, J=1.7 Hz, CHO). MS m/z: 333 (M+1), 332 (M^+), 105.

(2*SR*,3*SR*)-3-Benzoyloxymethyl-2-(6-methoxycarbonylhexyl)-1-cyclopentanone (9) Oxidation of **8** (143 mg) in acetone (3 ml) with Jones reagent at −5 °C afforded the corresponding keto-acid, which was converted to the keto-ester by treatment with CH_2N_2, and then purified by silica-gel column chromatography to give **9** (119 mg, 77%) as a colorless oil. IR (neat): 1740, 1720, 1600, 1280, 1175, 1030 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.66 (3H, s, COOMe), 4.23 (1H, dd, J=10.3, 5.8 Hz, CH_aOCOAr), 4.45 (1H, dd, J=10.3, 4.1 Hz, CH_bOCOAr), 7.42—7.60 (3H, m, aromatic-H), 7.93—7.97 (2H, m, aromatic-H). MS m/z: 361 (M+1), 360 (M^+), 180, 120, 105.

(2*RS*,3*SR*)-3-Hydroxymethyl-2-(6-methoxycarbonylhexyl)-1-cyclopentanone (10) A mixture of **9** (20 mg) and K_2CO_3 (50 mg) in MeOH (3 ml) was stirred for 10 h, diluted with brine, and then extracted with ether. The ether extract was washed with brine, dried, and then concentrated *in vacuo* to afford an oily residue, which was purified by silica-gel column chromatography to give **10** (10 mg, 78%) as a colorless oil. The ^1H-NMR spectrum and IR spectrum of **10** were identical with those of a standard sample.[8]

(3*RS*,4*SR*,5*RS*)-3-Acetyl-5-(2-hydroxyethyl)-4-methyltetrahydro-2-furanone (11) Methyl lithium (1 M solution in ether, Kanto Chemicals) (8.23 ml, 8.81 mmol) was added dropwise to a stirred suspension of CuI (838 mg, 4.40 mmol) in ether (15 ml) at −25 °C. After 15 min, **2** (n=1, X=OAc) (150 mg, 0.882 mmol) in ether (2 ml) was added dropwise at −25 °C, and the whole was stirred for 4 h. The reaction mixture was diluted with 10% aqueous HCl (4 ml), and extracted with ether. The ether extract was washed with brine, and dried, then concentrated *in vacuo* to afford a oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 50% AcOEt in hexane afforded **11** (60 mg, 32%) as a colorless oil. IR (neat): 3400, 1765, 1720, 1050 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=6.6 Hz, Me), 2.45 (3H, s, COMe), 3.41 (1H, d, J=10.7 Hz, COCHCO), 3.82 (2H, dd, J=6.8, 5.1 Hz, CH_2OH), 4.23 (1H, m, CHOCO). MS m/z: 186 (M^+), 168, 98.

References and Notes

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6) Commercially available MeLi (1 M in ether, Kanto Chemicals), BuLi (1.6 M in hexane, Nakarai Chemicals), and PhLi (2 M in cyclohexane–ether, Aldrich) were used. 7-Octenyl lithium was prepared from 8-bromo-1-octene and lithium dispersion (see ref. 8).
7) Compound **2** (n=2) was prepared from **1** (n=2). For the preparation of **1** (n=2), see S. Hanessian, P. J. Hodges, P. J. Murray and S. P. Sahoo, *J. Chem. Soc., Chem. Commun.*, **1986**, 754.
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