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Synthesis of ω-Chain-modified Analogues of 7-Oxaprostaglandins†

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ω-Methyl-11-deoxy-7-oxaprostaglandin (**5a–t**), ω-methyl-9,11-bisdeoxy-7-oxaprostaglandin (**6a–t**) and their related compounds having a *gem*-dimethyl, *gem*-methylethyl,*gem*-methylpropyl, *gem*-methylbenzyl or *gem*-methylallyl group as the ω-chain (**5b～5f**, **6b～6e**) were synthesized starting from cyclotene (**1**), 2-hydroxy-3-methyl-2-cyclopenten-1-one, which is a principal constituent of coffee aroma and maple flavor.

It has been reported that synthetic 7-oxa analogues of prostaglandin E_1 and $F_{1\alpha}$ were similar to their natural counterparts in biological activities,[1] while their 9,11-bisdeoxy-7-oxa analogues were predominantly antagonistic and ω-chain-shortened analogues of prostaglandin E_1 inhibited the secretion of gastric acid.[2]

Cyclotene (**1**), CT, a principal component of coffee aroma[3] and maple flavor,[4] is widely applied as a caramel-like flavoring in food. Since CT exists in the stable, chemically active enol form within the five-membered ring rather than as the unstable α-diketone, it was expected that CT could be utilized as a convenient starting material for the synthesis of biologically active compounds containing a five-membered ring in their skeleton. Nevertheless, there are few reports on the reaction of CT to date[5] except for the alkylation *via* the ketimine[6] and ketal[7] derivatives.

These facts prompted us to synthesize ω-chain-shortened 7-oxa analogues of prostaglandin E_1 and their related compounds from CT *via* the 1,3-dithiane derivative. These prostaglandins may exhibit biological activities as the antagonist of natural prostaglandins.

trans-ω-Methyl-11-deoxy-7-oxaprostaglandin (**5a–t**) and *trans*-ω-methyl- 9,11-bisdeoxy-7-oxaprostaglandin (**6a–t**) were synthesized first according to Scheme I. The keto group of CT was protected with 1,3-propanedithiol,[8] and the product **2a** was reduced with various reagents. Natural prostaglandin is a *trans* product. Reduction of **2a** with popular complex hydrides such as sodium borohydride, lithium aluminum hydride, lithium tri-*t*-butoxyaluminohydride, lithium trimethoxyaluminohydride or zinc borohydride gave the alcohol as a mixture of *cis*- and *trans*-isomers, while reduction with 9-borabicyclo[3.3.1]nonane (9-BBN) produced the desired *trans*-alcohol **3a–t** in a homogeneous state on GLC. Desulfurization of **3a–t** with metallic sodium gave *trans*-2-methylcyclopentanol in a homogeneous state, which was identical with the *trans*-alcohol derived from cyclopentanone[9] in GLC, and in IR, ^{1}H NMR and Mass spectra.

Etherification of **3a–t** was carried out with

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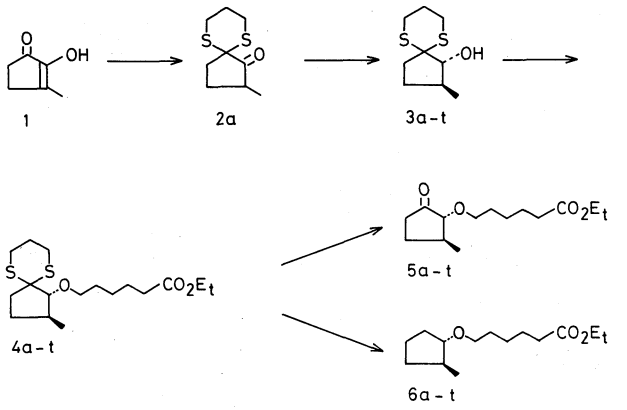
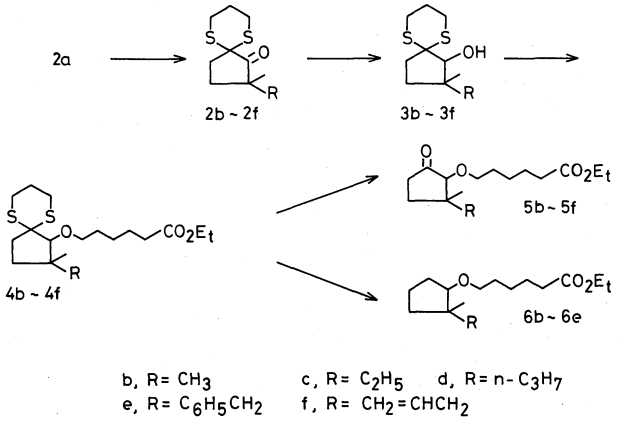


SCHEME I.



b, R= CH_3 c, R= C_2H_5 d, R= n-C_3H_7
e, R= $C_6H_5CH_2$ f, R= CH_2=$CHCH_2$

SCHEME II.

an excess of ethyl 6-iodohexanoate and sodium hydride in dimethylformamide in the presence of a trace of 18-crown-6. However, the yield of the ether **4a–t** was not satisfactory, approximately 24%, and a large amount of unreacted **3a–t** remained. The conditions under which the etherification of **3a–t** was carried out were studied. Satisfactory yields were obtained by using additional ethyl 6-iodohexanoate and sodium hydride, the yield of **4a–t** being raised to 64%. **4a–t** was subjected to oxidative hydrolysis with *N*-chlorosuccinimide and silver nitrate in an aqueous acetonitrile to give **5a–t** in an 85% yield. On the other hand, the desulfurization of **4a–t** with a large excess of Raney-nickel in ethanol gave **6a–t** in an 80% yield.

Synthesis of the 12-alkyl-12-methyl analogues was performed next (Scheme II). The dithiaspirodecane **2a** was treated with several alkyl halides to give the alkylated products **2b**~**2f**, which have methyl, ethyl, *n*-propyl, benzyl or allyl groups geminately on C-2 together with the methyl group.[8] These products were reduced with lithium aluminum hydride, sodium borohydride, lithium tri-*t*-butoxyaluminohydride and 9-BBN. Reductions with all of the tested reagents except 9-BBN gave the corresponding alcohols **3b**~**3f** in almost quantitative yields as an inseparable mixture of stereoisomers. The alcohols **3b**~**3f** were subjected to etherification followed by oxidative hydrolysis or desulfurization with Raney-nickel. The desired 7-oxaprostaglandin analogues **5b**~**5f** or **6b**~**6e** were obtained in reasonable yields as a mixture of

stereoisomers, except that the desulfurization of **4f** produced a 12-methyl-12-*n*-propyl analogue (**6d**) owing to the additional reduction of the allyl group.

EXPERIMENTAL

All melting points and boiling points were uncorrected. The IR spectra were recorded on a Hitachi 260-10 spectrometer. The ^{1}H NMR spectra were taken in $CDCl_3$ solutions on a Hitachi R-24B instrument with an internal standard of TMS and the ^{13}C NMR spectra in $CDCl_3$ solutions. Mass spectra were measured with a JEOL JMS-D300 spectrometer under electron impact (EI, 70 eV) and chemical ionization (CI, 200 eV, ammonia). The homogeneity of the reaction products was always checked with a glass column (3 mmϕ × 2 m) packed with 10% Silicone GE SE-30 on Chromosorb W (AW-DMCS, 60~80 mesh). Column chromatographies were carried out with silica gel (Merck Kieselgel 60 Art 7734, 70~230 mesh).

Reduction of 2-methyl-6,10-dithiaspiro[4.5]decan-1-one (**2a**) *with 9-BBN.* The dithiane derivative **2a** (6 g, 0.03 mol) of cyclotene[8] was dissolved in dry tetrahydrofuran (30 ml). The solution was added dropwise to 9-BBN (5.5 g, 0.045 mol) in dry tetrahydrofuran (60 ml) with stirring under a flow of nitrogen gas at room temperature, and the mixture was refluxed for 3 hr. After the reaction mixture had cooled to room temperature, an excess of 9-BBN was decomposed with methanol (3 ml) and the solvent was distilled off *in vacuo*. The viscous residue was dissolved in hexane (20 ml), and 2-aminoethanol (2 ml, 0.033 mol) was added dropwise to the solution. An ethanolamine derivative of 9-BBN which was deposited immediately was filtered and washed with hexane. The filtrate and washings were combined and concentrated under reduced pressure. The residue was chromatographed over silica gel with a mixed solvent of hexane–ether (15 : 1 in v/v) to give a *trans* isomer of dithiaspirodecan-1-ol **3a–t** (5.2 g, 85%) as a colorless liquid in a homogeneous state for the GLC. The compound was solidified during storage in a refrigerator; mp 26~26.5°C. EIMS *m/z*: 204 (M^+, 63), 186 (11), 171 (8), 145 (100), 132 (16), 119 (47), 106 (41), 71 (36), 55 (11), 41 (59). CIMS *m/z*: 222 [$(M+NH_4)^+$, 37], 205 [$(M+H)^+$, 2], 187 [$(M+H-H_2O)^+$, 100]. IR ν_{max}^{neat} cm^{-1}: 3440. ^{1}H NMR ($CDCl_3+D_2O$) δ: 1.09 (3H, d, J=7 Hz), 1.43~2.20 (5H, m), 2.40~3.05 (6H, m), 4.00 (1H, d, J=3.5 Hz, CHOD).

Reduction of **2a** *with sodium borohydride.* Sodium borohydride (0.3 g, 7.5 mmol) was added to a solution of **2a** (1 g, 5 mmol) in methanol (30 ml) with stirring at 0°C, and stirring was continued for 3 hr at room temperature. To the reaction mixture were added 5% hydrochloric acid (5 ml) and water (25 ml), and the mixture was concentrated under reduced pressure. The residue was again dissolved in water (10 ml) and the solution was saturated with NaCl for extraction with ether. The ethereal solutions were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue showed two peaks corresponding to the *trans* (t_R: 15.5 min, **3a–t**) and *cis* (t_R: 16 min, **3a–c**) isomers of dithiaspirodecan-1-ol in a ratio of 7 : 3 on GLC, using a 10% DEGS-ST column (3 mmϕ × 2 m) with 10°C/min programmed from 100°C to 210°C. These two isomers were separated by chromatography over a silica gel column with a mixed hexane–ether solvent (15 : 1). *trans*-Alcohol **3a–t** (0.69 g, 70%). *cis*-Alcohol **3a–c** (0.29 g, 29%); EIMS *m/z*: 204 (M^+, 72), 186 (17), 171 (14), 145 (100), 132 (17), 119 (52), 106 (49), 71 (36), 55 (24), 49 (60). CIMS *m/z*: 222 [$(M+NH_4)^+$, 33], 205 [$(M+H)^+$, 3], 187 [$(M+H-H_2O)^+$, 100]. IR ν_{max}^{neat} cm^{-1}: 3440. ^{1}H NMR ($CDCl_3+D_2O$) δ: 1.15 (3H, d, J=7 Hz), 1.88~2.35 (5H, m), 2.45~3.11 (6H, m), 3.70 (1H, d, J=6.5 Hz, CHOD).

Reduction of **2a** *with lithium aluminum hydride.* A solution of **2a** (1 g, 5 mmol) in dry ether (5 ml) was added dropwise to a slurry of lithium aluminum hydride (190 mg, 5 mmol) in dry ether (10 ml) at 0°C, and the mixture was refluxed gently for 2 hr. The reaction mixture was cooled in an ice bath, and mixed with a 10% aqueous solution of sulfuric acid (5 ml) to decompose an excess of the hydride. After the solution had been saturated with NaCl, the organic layer was separated and the aqueous layer extracted with ether. The ethereal solutions were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a mixture of the *trans*- and *cis*-dithiane alcohols, **3a**, (0.98 g, 98%) as a viscous liquid showing two peaks in a ratio of 2 : 3 on the GLC.

Reduction of **2a** *with lithium tri-t-butoxyaluminohydride.* To a solution of lithium tri-*t*-butoxyaluminohydride (0.64 g, 2.5 mmol)[10] in diglyme (10 ml) was added a solution of **2a** (0.1 g, 0.5 mmol) in diglyme (5 ml) under a flow of nitrogen gas and with ice cooling, and the mixture was refluxed for 5 hr. A normal work-up of the reaction mixture gave a mixture of the *trans*- and *cis*-alcohols, **3a**, (0.097 g, 97%) in a ratio of 7 : 3 on the GLC.

Reduction of **2a** *with lithium trimethoxyaluminohydride.* A mixture of methanol (97 mg, 3 mmol) and tetrahydrofuran (5 ml) was added dropwise to a slurry of lithium aluminum hydride (38 mg, 1 mmol) in tetrahydrofuran (19 ml) with stirring in an atmosphere of nitrogen and with ice cooling, and stirring was continued for 15 min. To the solution of lithium trimethoxyaluminohydride thus prepared was slowly added a solution of **2a** (0.1 g, 0.5 mmol) in tetrahydrofuran (5 ml) at 0°C, and stirring was continued for 1.5 hr at 0°C. A normal work-up of the reaction mixture gave a mixture of the *trans*- and *cis*-alcohols, **3a**, (0.098 g, 98%) in a ratio of 7 : 3 on the GLC.

Reduction of **2a** *with zinc borohydride.* A solution of zinc

borohydride (13 mmol)[11] in dry ether (70 ml) was added to a solution of **2a** (1 g, 5 mmol) in dry ether (20 ml), and the mixture was refluxed gently for 3 hr. After cooling, water (20 ml) and glacial acetic acid (4 ml) were added to the mixture to decompose the excess of zinc borohydride. The resulting mixture was worked up to give a mixture of the *trans*- and *cis*-alcohols, **3a**, (0.96 g, 96%) in a ratio of 1 : 1 on the GLC.

Desulfurization of trans 2-methyl-6,10-dithiaspiro[4.5]decan-1-ol (**3a–t**) *with metallic sodium.* The dithiane alcohol **3a–t** (1 g, 5 mmol) was dissolved in a mixed solvent of liquid ammonia (100 ml) and dry ether (20 ml) under a flow of nitrogen gas at −50°C and metallic sodium (0.29 g, 12.5 mmol) was then added to the solution. After stirring for 30 min, ethanol was added until the blue color of the solution had disappeared and the solvent was evaporated. The residue was extracted with ether, the ethereal solutions were concentrated and the residual materials were fractionated through a Vigreux-Claisen-type distillation column to give the *trans* methylcyclopentanol (**7-t**), bp 156~157°C (760 mmHg), 0.31 g (63%). EIMS *m/z*: 100 (M^+, 0), 56 (100), 43 (40), 41 (44). CIMS *m/z*: 118 $[(M+NH_4)^+$, 100], 101 $[(M+H)^+$, 18]. IR ν_{max}^{neat} cm^{-1}: 3300. ^1H NMR ($CDCl_3+D_2O$) δ: 0.96 (3H, d, J= 7 Hz, CH_3), 1.11~2.10 (6H, m), 2.47 (1H, m, $CHCH_3$), 3.71 (1H, m, CHOD).

Desulfurization of cis 2-methyl-6,10-dithiaspiro[4.5]decan-1-ol (**3a–c**) *with metallic sodium.* Desulfurization of **3a–c** (1 g, 5 mmol) was carried out in the same manner as with the case of **3a–t** to give *cis*-alcohol **7-c**, bp 156~157°C (760 mmHg), 0.26 g (56%). EIMS *m/z*: 100 (M^+, 0), 56 (100), 43 (43), 41 (35). CIMS *m/z*: 118 $[(M+NH_4)^+$, 100], 101 $[(M+H)^+$, 17]. IR ν_{max}^{neat} cm^{-1}: 3300. ^1H NMR ($CDCl_3+D_2O$) δ: 0.94 (3H, d, J=7 Hz, CH_3), 1.11~2.00 (6H, m), 2.49 (1H, m, $CHCH_3$), 3.70 (1H, m, CHOD).

Reduction of 2-alkyl-2-methyl-6,10-dithiaspiro[4.5]decan-1-ones (**2b~2f**) *with lithium aluminum hydride.* A solution of each α-ketodithiane (**2b~2f**, 0.01 mol) in dry ether (5 ml) was added dropwise to a slurry of lithium aluminum hydride (0.38 g, 0.01 mol) in dry ether (30 ml) under cooling at 0°C, and the reaction mixture was refluxed for 2 hr. After the excess of lithium aluminum hydride had been decomposed with a 10% aqueous solution of sulfuric acid (10 ml) under cooling in an ice bath, the reaction mixture was saturated with NaCl and the ethereal layer was separated. The aqueous layer was extracted with ether. The ethereal solutions were combined, washed with brine and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was chromatographed over a silica gel column with a mixed solvent of hexane and ether (15 : 1 in v/v) to give the *gem*-dialkyldithiaspirodecanols (**3b~3f**), respectively.

2,2-Dimethyl-6,10-dithiaspiro[4.5]decan-1-ol (**3b**). Colorless viscous liquid (2.1 g, 96%). EIMS *m/z*: 218 (M^+, 40), 200 (16), 185 (33), 145 (100), 119 (24), 106 (31), 71 (17), 55 (10), 41 (39). CIMS *m/z*: 236 $[(M+NH_4)^+$, 100], 219 $[(M+H)^+$, 7], 201 $[(M+H-H_2O)^+$, 60]. IR ν_{max}^{neat} cm^{-1}: 3425. ^1H NMR ($CDCl_3+D_2O$) δ: 0.98 and 1.11 (6H, both s, *gem*-dimethyl), 1.41~2.25 (6H, m), 2.43~3.40 (4H, m), 3.80 (1H, s, CHOD).

2-Ethyl-2-methyl-6,10-dithiaspiro[4.5]decan-1-ol (**3c**). Colorless viscous liquid (2.2 g, 96%). EIMS *m/z*: 232 (M^+, 32), 203 (7), 185 (6), 145 (100), 119 (28), 106 (32), 71 (15), 55 (18), 41 (46). CIMS *m/z*: 250 $[(M+NH_4)^+$, 100], 233 $[(M+H)^+$, 10], 215 $[(M+H-H_2O)^+$, 62]. IR ν_{max}^{neat} cm^{-1}: 3425. ^1H NMR ($CDCl_3+D_2O$) δ: 0.88 (3H, m), 0.93 and 1.09 (3H, both s, CH_3), 1.23~2.23 (8H, m), 2.43~3.40 (4H, m), 3.87 (1H, s, CHOD).

2-n-Propyl-2-methyl-6,10-dithiaspiro[4.5]decan-1-ol (**3d**). Colorless viscous liquid (2.4 g, 97%). EIMS *m/z*: (M^+, 23), 203 (7), 228 (14), 185 (11), 145 (100), 119 (21), 106 (21), 71 (11), 55 (39), 41 (53). CIMS *m/z*: 264 $[(M+NH_4)^+$, 100], 247 $[(M+H)^+$, 5], 229 $[(M+H-H_2O)^+$, 85]. IR ν_{max}^{neat} cm^{-1}: 3420. ^1H NMR ($CDCl_3+D_2O$) δ: 0.91 (3H, m), 0.93 and 1.09 (3H, both s, CH_3), 1.21~2.18 (10H, m), 2.47~3.18 (4H, m), 3.83 and 3.85 (1H, both s, CHOD).

2-Benzyl-2-methyl-6,10-dithiaspiro[4.5]decan-1-ol (**3e**). Colorless viscous liquid (2.9 g, 97%). EIMS *m/z*: 294 (M^+, 39), 203 (21), 185 (13), 145 (100), 119 (25), 106 (43), 97 (45), 91 (61), 71 (11), 41 (36). CIMS *m/z*: 312 $[(M+NH_4)^+$, 100], 295 $[(M+H)^+$, 17], 277 $[(M+H-H_2O)^+$, 46]. IR ν_{max}^{neat} cm^{-1}: 3425, 760, 700. ^1H NMR ($CDCl_3+D_2O$): 0.91 and 1.03 (3H, both s, CH_3), 1.17~2.29 (8H, m), 2.67~3.05 (4H, m), 3.89 and 4.00 (1H, both s, CHOD), 7.09 (5H, s, C_6H_5).

2-Allyl-2-methyl-6,10-dithiaspiro[4.5]decan-1-ol (**3f**). Colorless viscous liquid (2.4 g, 98%). EIMS *m/z*: 244 (M^+, 59), 203 (12), 185 (7), 145 (100), 106 (64), 97 (40), 71 (24), 55 (25), 41 (81). CIMS *m/z*: 262 $[(M+NH_4)^+$, 100], 245 $[(M+H)^+$, 16], 227 $[(M+H-H_2O)^+$, 85]. IR ν_{max}^{neat} cm^{-1}: 3425, 1640, 910. ^1H NMR ($CDCl_3+D_2O$) δ: 0.98 and 1.12 (3H, both s, CH_3), 1.40~2.30 (8H, m), 2.45~3.20 (4H, m), 3.86 and 3.90 (1H, both s, CHOD), 4.77~5.20 (2H, m), 5.55~6.19 (1H, m).

Etherification of 2-alkyl-2-methyl-6,10-dithiaspiro[4.5]decan-1-ols (**3a–t~3f**). Each of **3a–t~3f** (0.01 mol) was mixed with ethyl 6-iodohexanoate (10.8 g, 0.04 mol) and the mixture was added dropwise to a mixed suspension of sodium hydride (50% mineral oil dispersion, 1.2 g, 0.025 mol) and 18-crown-6 (0.26 g, 0.001 mol) in dimethylformamide (130 ml) with constant stirring at room temperature in a nitrogen atmosphere. After stirring for 24~30 hr, additional sodium hydride (50% mineral oil dispersion, 0.96 g, 0.02 mol) and ethyl 6-iodohexanoate

(5.4 g, 0.02 mol) were supplied and stirring was further continued for about 24 hr at room temperature. When the alcohol had disappeared (checked by GLC), water (10 ml) was added to decompose the excess sodium hydride, and the reaction mixture was extracted with ether. The ethereal solutions were washed with water, dried over Na_2SO_4 and distilled off *in vacuo*. The residue was chromatographed over silica gel with a mixed solvent of petroleum ether and ethyl acetate (20:1 in v/v) to give the ethers, **4a–t**～**4f**, respectively.

Ethyl trans-7-oxa-7-(8-methyl-1,5-dithiaspiro[4.5]decan-7-yl)heptanoate (**4a–t**). Colorless viscous liquid (2.2 g, 64%). EIMS *m/z*: 346 (M^+, 35), 301 (5), 203 (9), 186 (100), 145 (92), 97 (56), 69 (80), 55 (58), 41 (74). CIMS *m/z*: 364 [$(M+NH_4)^+$, 17], 347 [$(M+H)^+$, 0], 187 (100). IR ν_{max}^{neat} cm^{-1}: 1735, 1160, 1095. ^1H NMR δ: 1.05 (3H, d, J=7 Hz, CH_3), 1.15～2.98 (19H, m), 1.23 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 3.57 (1H, d, J=7 Hz, $CHOCH_2$), 3.61 (2H, m), 4.07 (2H, q, J=7 Hz, $CO_2CH_2CH_3$). ^{13}C NMR δ: 14.33, 14.77, 24.88, 25.73, 28.19, 29.81, 30.04, 36.98, 39.98, 60.09, 72.73, 89.91, 173.66.

Ethyl 7-oxa-7-(8,8-dimethyl-1,5-dithiaspiro[4.5]decan-7-yl)heptanoate (**4b**). Colorless viscous liquid (2.4 g, 68%). EIMS *m/z*: 360 (M^+, 15), 310 (4), 200 (50), 185 (12), 145 (100), 97 (34), 69 (34), 55 (17), 41 (32). CIMS *m/z*: 378 [$(M+NH_4)^+$, 33], 361 [$(M+H)^+$, 0], 201 (100). IR ν_{max}^{neat} cm^{-1}: 1735, 1160, 1130. ^1H NMR δ: 1.01 and 1.05 (6H, both s, *gem*-dimethyl), 1.23 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.87～3.87 (20H, m), 3.14 (1H, s, $CHOCH_2$), 4.08 (2H, q, J=7 Hz, $CO_2CH_2CH_3$).

Ethyl 7-oxa-7-(8-ethyl-8-methyl-1,5-dithiaspiro[4.5]decan-7-yl)heptanoate (**4c**). Colorless viscous liquid (2.4 g, 65%). EIMS *m/z*: 374 (M^+, 8), 329 (2), 214 (33), 185 (10), 145 (100), 97 (19), 69 (28), 55 (19), 41 (26). CIMS *m/z*: 392 [$(M+NH_4)^+$, 9], 375 [$(M+H)^+$, 4], 215 (100). IR ν_{max}^{neat} cm^{-1}: 1735, 1160, 1130. ^1H NMR δ: 0.88 (3H, m, CH_2CH_3), 0.98 and 1.01 (3H, both s, CH_3), 1.23 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.23～3.65 (22H, m), 3.15 and 3.20 (1H, both s, $CHOCH_2$), 4.10 (2H, q, J=7 Hz, $CO_2CH_2CH_3$).

Ethyl 7-oxa-7-(8-n-propyl-8-methyl-1,5-dithiaspiro[4.5]decan-7-yl)heptanoate (**4d**). Colorless viscous liquid (2.4 g, 61%). EIMS *m/z*: 388 (M^+, 7), 343 (2), 228 (36), 185 (2), 145 (100), 97 (27), 69 (38), 55 (30), 41 (32). CIMS *m/z*: 406 [$(M+NH_4)^+$, 6], 389 [$(M+H)^+$, 3], 229 (100). IR ν_{max}^{neat} cm^{-1}: 1735, 1160, 1130. ^1H NMR δ: 0.91 [3H, m, $(CH_2)_2CH_3$], 0.98 and 1.01 (3H, both s, CH_3), 1.07～3.59 (24H, m), 1.22 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 3.13 and 3.15 (1H, both s, $CHOCH_2$), 4.05 (2H, q, J=7 Hz, $CO_2CH_2CH_3$).

Ethyl 7-oxa-7-(8-benzyl-8-methyl-1,5-dithiaspiro[4.5]decan-7-yl)heptanoate (**4e**). Colorless viscous liquid (3.1 g, 72%). EIMS *m/z*: 436 (M^+, 7), 276 (5), 185 (29), 145 (50), 97 (90), 69 (100), 55 (29), 41 (50). CIMS *m/z*: 456 [$(M+NH_4)^+$, 3], 437 [$(M+H)^+$, 0], 274 (100). IR ν_{max}^{neat} cm^{-1}: 1730, 1160, 1115, 760, 700. ^1H NMR δ: 0.99 (3H, s, CH_3), 1.22 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.29～3.55 (18H, m), 2.63 (2H, s, $CH_2C_6H_5$), 3.21 and 3.28 (1H, both s, $CHOCH_2$), 4.05 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 7.09 (5H, s, C_6H_5).

Ethyl 7-oxa-7-(8-allyl-8-methyl-1,5-dithiaspiro[4.5]decan-7-yl)heptanoate (**4f**). Colorless viscous liquid (2.8 g, 73%). EIMS *m/z*: 386 (M^+, 16), 341 (3), 226 (26), 185 (26), 145 (100), 132 (35), 97 (41), 69 (58), 55 (32), 41 (57). CIMS *m/z*: 404 [$(M+NH_4)^+$, 6], 387 [$(M+H)^+$, 0], 227 (100). IR ν_{max}^{neat} cm^{-1}: 1735, 1645, 1165, 1130. ^1H NMR δ: 1.01 and 1.03 (3H, both s, CH_3), 1.23 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.27～3.56 (22H, m), 3.20 (1H, s, $CHOCH_2$), 4.05 (2H, q, J=7 Hz, $CO_2CH_2CH_3$), 4.75～5.13 (2H, m), 5.42～6.02 (1H, m).

Oxidative hydrolysis of ethyl 7-oxa-7-(8-alkyl-8-methyl-1,5-dithiaspiro[4.5]decan-7-yl)heptanoates **4a–t**～**4f**. Each of the ethers **4a–t**～**4f** (1.5 mmol) was added to a solution of *N*-chlorosuccinimide (0.8 g, 6 mmol) and silver nitrate (1.15 g, 6.8 mmol) in a mixture of acetonitrile and water (4:1 in v/v), and the mixture was stirred for 2 hr. To the reaction mixture were added the saturated aqueous solutions of sodium sulfite (1 ml), sodium carbonate (1 ml) and sodium chloride (1 ml) in this order, and the mixture was filtered. The filtrate was extracted with ether, and the ethereal solution was worked up as usual to give the 7-oxacyclopentanones (**5a–t**～**5f**).

Ethyl trans-7-oxa-7-(2-methyl-5-oxocyclopentyl)heptanoate (**5a–t**). Colorless liquid (0.33 g, 85%), 2,4-DNP mp 278～278.5°C (dec.). EIMS *m/z*: 256 (M^+, 3), 211 (5), 159 (21), 143 (100), 115 (51), 97 (95), 69 (75), 55 (36), 41 (49). CIMS *m/z*: 274 [$(M+NH_4)^+$, 100], 257 [$(M+H)^+$, 9]. IR ν_{max}^{neat} cm^{-1}: 1750, 1735, 1165, 1095. ^1H NMR δ: 0.97 (3H, d, J=7 Hz, CH_3), 1.23 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.40～2.70 (13H, m), 3.34 (1H, m, $CHOCH_2$), 4.10 (2H, q, J=7 Hz, $CO_2CH_2CH_3$). ^{13}C NMR δ: 12.94, 14.33, 24.88, 25.73, 26.50, 29.42, 32.89, 33.66, 34.28, 60.17, 70.26, 84.36, 173.66, 215.50. High resolution EIMS *m/z*: 256.17223 (M^+, calcd. for $C_{14}H_{24}O_4$: 256.16732).

Ethyl 7-oxa-7-(2,2-dimethyl-5-oxocyclopentyl)heptanoate (**5b**). Colorless liquid (0.33 g, 82%), 2,4-DNP mp 245～246°C (dec.). EIMS *m/z*: 270 (M^+, 3), 225 (5), 159 (18), 143 (93), 115 (39), 97 (100), 69 (62), 55 (29), 41 (46). CIMS *m/z*: 288 [$(M+NH_4)^+$, 100], 271 [$(M+H)^+$, 5]. IR ν_{max}^{neat} cm^{-1}: 1750, 1735, 1165, 1105. ^1H NMR δ: 0.89 and 1.13 (6H, both s, *gem*-dimethyl), 1.23 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 1.39～2.47 (12H, m), 3.30 (1H, s, $CHOCH_2$), 3.25～3.97 (2H, m, OCH_2), 4.07 (2H, q, J=7 Hz, $CO_2CH_2CH_3$). High resolution EIMS *m/z*:

270.18796 (M^+, calcd. for $C_{15}H_{26}O_4$: 270.18296).

Ethyl 7-oxa-7-(2-ethyl-2-methyl-5-oxocyclopentyl)heptanoate (**5c**). Colorless liquid (0.35 g, 83%). EIMS *m/z*: 284 (M^+, 1), 238 (2), 159 (11), 143 (71), 123 (13), 97 (100), 69 (30), 55 (20), 41 (17). CIMS *m/z*: 302 [$(M+NH_4)^+$, 100], 285 [$(M+H)^+$, 28]. IR ν_{max}^{neat} cm^{-1}: 1745, 1730, 1160, 1100. ^1H NMR δ: 0.85 and 1.01 (3H, both s, CH_3), 0.86 (3H, m, CH_2CH_3), 1.21 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.30~2.45 (14H, m), 3.22 and 3.35 (1H, both s, $CHOCH_2$), 3.31~3.97 (2H, m, OCH_2), 4.04 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$). High resolution EIMS *m/z*: 284.19914 (M^+, calcd. for $C_{16}H_{28}O_4$: 284.19860).

Ethyl 7-oxa-7-(2-n-propyl-2-methyl-5-oxocyclopentyl)heptanoate (**5d**). Colorless liquid (0.37 g, 83%). EIMS *m/z*: 298 (M^+, 1), 253 (1), 159 (9), 143 (86), 115 (34), 97 (100), 69 (40), 55 (28), 41 (22). CIMS *m/z*: 316 [$(M+NH_4)^+$, 100], 299 [$(M+H)^+$, 35]. IR ν_{max}^{neat} cm^{-1}: 1750, 1740, 1170, 1110. ^1H NMR δ: 0.85 and 1.03 (3H, both s, CH_3), 0.89 [3H, m, $(CH_2)_2CH_3$], 1.21 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.15~2.43 (17H, m), 3.19 and 3.35 (1H, both s, $CHOCH_2$), 3.35~3.98 (2H, m, OCH_2), 4.05 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$). High resolution EIMS *m/z*: 298.22303 (M^+, calcd. for $C_{17}H_{30}O_4$: 298.21424).

Ethyl 7-oxa-7-(2-benzyl-2-methyl-5-oxocyclopentyl)heptanoate (**5e**). Colorless liquid (0.43 g, 82%). EIMS *m/z*: 346 (M^+, 0), 255 (5), 187 (4), 159 (9), 143 (72), 115 (31), 97 (100), 91 (60), 69 (63), 55 (45), 41 (46). CIMS *m/z*: 364 [$(M+NH_4)^+$, 100], 347 [$(M+H)^+$, 16]. IR ν_{max}^{neat} cm^{-1}: 1750, 1735, 1160, 1095, 750, 700. ^1H NMR δ: 0.90 and 0.99 (3H, both s, CH_3), 1.23 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.43~2.45 (12H, m), 2.71 (2H, s, $CH_2C_6H_5$), 3.23 and 3.35 (1H, both s, $CHOCH_2$), 3.27~3.98 (2H, m, OCH_2), 4.03 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 7.16 (5H, m, C_6H_5). High resolution EIMS *m/z*: 255.16688 ($M-CH_2C_6H_5$, calcd. for $C_{14}H_{23}O_4$: 255.15950).

Ethyl 7-oxa-7-(2-allyl-2-methyl-5-oxocyclopentyl)heptanoate (**5f**). Colorless liquid (0.37 g, 83%). EIMS *m/z*: 296 (M^+, 0), 255 (3), 209 (14), 159 (5), 145 (35), 115 (21), 97 (100), 69 (25), 55 (11), 41 (17). CIMS *m/z*: 314 [$(M+NH_4)^+$, 100], 297 [$(M+H)^+$, 25]. IR ν_{max}^{neat} cm^{-1}: 1750, 1740, 1645, 1165, 1105, 910. ^1H NMR δ: 0.89 and 1.07 (3H, both s, CH_3), 1.23 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.21~2.47 (14H, m), 3.27 and 3.42 (1H, both s, $CHOCH_2$), 3.23~3.97 (2H, m, OCH_2), 4.01 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 4.75~5.20 (2H, m), 5.40~6.15 (1H, m). High resolution EIMS *m/z*: 255.15962 ($M-CH_2CH=CH_2$, calcd. for $C_{14}H_{23}O_4$: 255.15950).

Desulfurization of **4a–t~4e** *with Raney-nickel.* Each of **4a–t~4e** (5 mmol) was refluxed in ethanol (20 ml) with a large excess of Raney-nickel (forty times in weight) for about 40 hr. The catalyst was filtered off through Celite and washed with hot ethanol. The combined filtrates were concentrated *in vacuo* to give the 7-oxa-cyclopentylheptanoates (**6a–t~6e**), respectively, which were chromatographed over silica gel with a mixture of hexane and ether (50 : 1 in v/v).

Ethyl trans-7-oxa-7-(2-methylcyclopentyl)heptanoate (**6a–t**). Colorless liquid (0.97 g, 80%). EIMS *m/z*: 242 (M^+, 0), 159 (52), 143 (54), 115 (84), 113 (82), 97 (84), 83 (42), 69 (100), 55 (12), 41 (67). CIMS *m/z*: 260 [$(M+NH_4)^+$, 60], 243 [$(M+H)^+$, 100]. IR ν_{max}^{neat} cm^{-1}: 1745, 1165, 1110. ^1H NMR δ: 0.93 (3H, d, $J=7$ Hz, CH_3), 1.23 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.21~1.97 (12H, m), 2.28 (2H, m, CH_2CO_2), 3.47 (3H, m), 4.09 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$). High resolution EIMS *m/z*: 83.09220 [$M-O(CH_2)_5CO_2CH_2CH_3$, calcd. for C_6H_{11}: 83.08602]; 159.10133 [$O(CH_2)_5CO_2CH_2CH_3$, calcd. for $C_8H_{15}O_3$: 159.10203].

Ethyl 7-oxa-7-(2,2-dimethylcyclopentyl)heptanoate (**6b**). Colorless liquid (1 g, 80%). EIMS *m/z*: 256 (M^+, 0), 160 (6), 159 (24), 143 (53), 115 (61), 97 (67), 96 (100), 81 (45), 69 (70), 55 (62), 44 (46). CIMS *m/z*: 274 [$(M+NH_4)^+$, 89], 257 [$(M+H)^+$, 100]. IR ν_{max}^{neat} cm^{-1}: 1740, 1160, 1125. ^1H NMR δ: 0.91 and 0.93 (6H, both s, *gem*-dimethyl), 1.23 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.23~2.00 (12H, m), 2.27 (2H, m, CH_2CO_2), 3.30 (3H, m), 4.07 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$). High resolution EIMS *m/z*: 96.09342 [$M-HO(CH_2)_5CO_2CH_2CH_3$, calcd. for C_7H_{12}: 96.09384]; 160.11437 [$HO(CH_2)_5CO_2CH_2CH_3$, calcd. for $C_8H_{16}O_3$: 160.10985].

Ethyl 7-oxa-7-(2-ethyl-2-methylcyclopentyl)heptanoate (**6c**). Colorless liquid (1.1 g, 82%). EIMS *m/z*: 270 (M^+, 0), 159 (26), 143 (45), 115 (56), 111 (20), 110 (89), 97 (62), 81 (31), 69 (100), 55 (66), 41 (52). CIMS *m/z*: 288 [$(M+NH_4)^+$, 27], 271 [$(M+H)^+$, 100]. IR ν_{max}^{neat} cm^{-1}: 1740, 1165, 1125. ^1H NMR δ: 0.82 (3H, m, CH_2CH_3), 0.83 and 0.85 (3H, both s, CH_3), 1.23 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.21~1.90 (14H, m), 2.25 (2H, m, CH_2CO_2), 3.33 (3H, m), 4.07 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$). High resolution EIMS *m/z*: 111.11838 [$M-O(CH_2)_5CO_2CH_2CH_3$, calcd. for C_8H_{15}: 111.11730]; 159.10334 [$O(CH_2)_5CO_2CH_2CH_3$, calcd. for $C_8H_{15}O_3$: 159.10203].

Ethyl 7-oxa-7-(2-n-propyl-2-methylcyclopentyl)heptanoate (**6d**). Colorless liquid (1.1 g, 80%). EIMS *m/z*: 284 (M^+, 0), 159 (22), 143 (42), 125 (12), 124 (81), 115 (58), 97 (60), 95 (78), 81 (33), 69 (100), 55 (63), 41 (57). CIMS *m/z*: 302 [$(M+NH_4)^+$, 45], 285 [$(M+H)^+$, 100]. IR ν_{max}^{neat} cm^{-1}: 1740, 1160, 1115. ^1H NMR δ: 0.83 and 0.86 (3H, both s, CH_3), 0.92 [3H, m, $(CH_2)_2CH_3$], 1.23 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.10~1.90 (16H, m), 2.28 (2H, m, CH_2CO_2), 3.32 (3H, m), 4.06 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$). High resolution EIMS *m/z*: 125.12814 [$M-O(CH_2)_5CO_2CH_2CH_3$, calcd. for C_9H_{17}:

125.13294]; 159.10190 [$O(CH_2)_5CO_2CH_2CH_3$, calcd. for $C_8H_{15}O_3$: 159.10203].

Ethyl 7-oxa-7-(2-benzyl-2-methylcyclopentyl)heptanoate (**6e**). Colorless liquid (1.4 g, 83%). EIMS *m/z*: 332 (M^+, 0), 240 (24), 172 (22), 160 (1), 159 (9), 143 (66), 115 (42), 97 (42), 91 (100), 81 (36), 69 (71), 55 (33), 41 (44). CIMS *m/z*: 350 [$(M+NH_4)^+$, 100], 333 [$(M+H)^+$, 64]. IR ν_{max}^{neat} cm^{-1}: 1735, 1160, 1110, 760, 700. ^1H NMR δ: 0.77 and 0.87 (3H, both s, CH_3), 1.22 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.33~1.97 (12H, m), 2.28 (2H, m, CH_2CO_2), 2.68 (2H, m, $CH_2C_6H_5$), 3.11 (3H, m), 4.07 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 7.10 (5H, s, C_6H_5). High resolution EIMS *m/z*: 172.12411 [$M-HO(CH_2)_5CO_2CH_2CH_3$, calcd. for $C_{13}H_{16}$: 172.12512]; 160.10669 [$HO(CH_2)_5CO_2CH_2CH_3$, calcd. for $C_8H_{16}O_3$: 160.10985].

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