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Synthetic Approach to 1,3-Polymethyl Function Based on Diastereoselective Conjugate Addition

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A new method for diastereo- and enantioselective preparation of 1,3-polymethyl functions was studied. The reaction of (1′*R*,2′*R*,5*R*)-(2*E*)-2′-hydroxycyclohexyl 5,9-dimethyl-2,8-decadienoate (6) with Me_2CuLi afforded a diastereomeric mixture of conjugate addition products ((3*R*,5*R*)-9 and (3*S*,5*R*)-9) in a ratio of 77 to 23.

Keywords diastereoselective conjugate addition; 1,3-polymethyl function; dimethylcopper lithium; enantioselective synthesis; (*R*,*R*)-cyclohexane-1,2-diol; double asymmetric induction

In the course of our studies[1] on diastereoselective conjugate addition of dialkylcopper lithium to α,β-unsaturated ester of (*R*,*R* or *S*,*S*)-cyclohexane-1,2-diol, we have developed a new method for enantio- and diastereoselective preparation of 1,3-polymethyl functions. 1,3-Polymethyl functions are commonly observed in the structures of antibiotic macrolides and insect pheromones,[2] so the method should be synthetically valuable. So far, Oppolzer *et al.*,[2b] Heathcock *et al.*,[3a] Yamamoto *et al.*[3b] and Marshall and Blough[3c] have independently reported their own methods. As shown in Chart 1, our method starts from diastereoselective conjugate addition of Me_2CuLi to a chiral α,β-unsaturated ester (A). The addition product (B) is converted to the second substrate (D) for conjugate addition *via* an aldehyde (C). By repeating this method, 1,3-polymethyl functions (E, F) may be constructed in optically active form.

The primary conjugate addition (A→B) has already been developed by us to afford addition products in a diastereomeric ratio of 10 to 1,[1a,c] in which the (*R*,*R*)-cyclohexane-1,2-diol moiety as a chiral auxiliary effected C_3-attack of the reagent from the *re*-face. For study of the second conjugate addition, enantiomerically pure substrates were needed. Substrates **5** and **6** were synthesized from commercially available (*R*)- and (*S*)-citronellals by means of the Horner–Emmons reaction with an optically active phosphonate (**3**). Compound **3** could be easily prepared by monobromoacetylation (69%) of (*R*,*R*)-cyclohexane-1,2-diol followed by Albusov reaction (86%) with triethyl phosphite (Chart 2). The second conjugate addition represents "double asymmetric induction". The effect of chirality at C_5 on the conjugate addition was estimated by the reaction of the methyl ester ((*dl*)-**4**) with Me_2CuLi, which afforded a mixture (72%) of *syn*-**7** and *anti*-**7** in a ratio of 65 to 35. This finding suggests that the C_5-methyl group results in predominant *syn*-addition. Reaction of the substrate **5** with Me_2CuLi afforded a mixture of (3*S*,5*S*)-**8** and (3*R*,5*S*)-**8** in a ratio of 55 to 45. Reaction of the other diastereomer **6** gave a mixture of (3*R*,5*R*)-**9** and (3*S*,5*R*)-**9** in a ratio of 77 to 23. These result (Table I) suggest that the (1*R*,2*R*)-2-hydroxycyclohexyl ester function predominantly effects C_3-attack of the reagent from the *re*-face, similarly to primary conjugate addition.[1a,c]

Relative stereochemistry of the 3,5-dimethyl function of **7**, **8** and **9** was determined as follows based on the ^{13}C-NMR spectra. An authentic sample of a 3 to 1 mixture of racemic *syn* and *anti* methyl 3,5-dimethyldecanoates ((*dl*)-**13**) was synthesized from a 3 to 1 mixture of *cis*- and *trans*-3,5-dimethylcyclohexanone (**10**) *via* four steps (i. Baeyer-Villiger oxidation, ii. solvolysis, iii. tosylation, iv. substitution) as shown in Chart 3. A diastereomeric mixture of conjugate addition products **7** was also converted to (*dl*)-**13** *via* three steps (i. ozonolysis, ii. Wittig

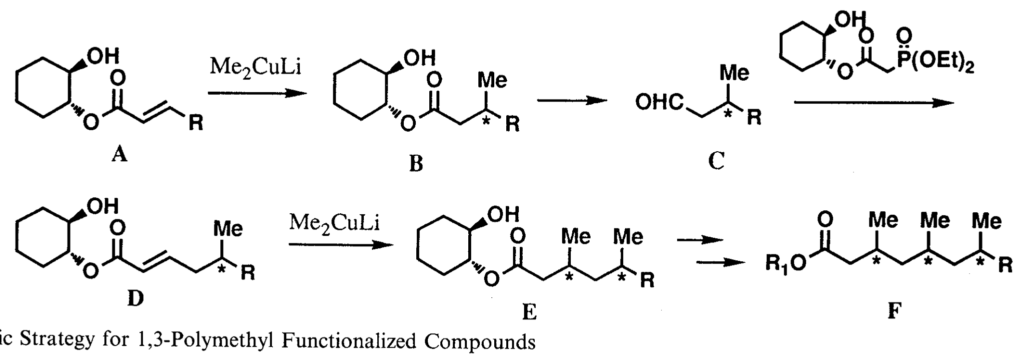


Chart 1. Synthetic Strategy for 1,3-Polymethyl Functionalized Compounds

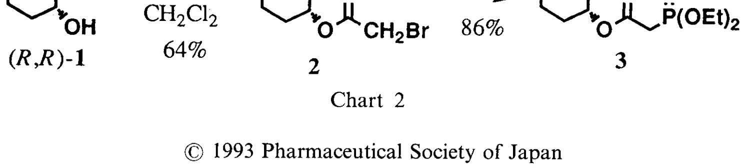
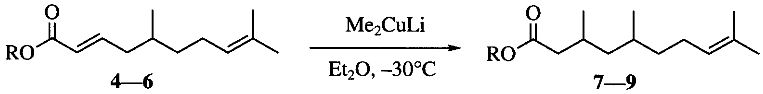
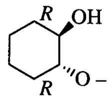
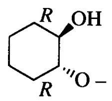


Chart 2

Table I. Diastereoselective Conjugate Addition



4—6 substrate → **7—9** product

Entry	Compd. No.	RO	Absolute config. at C5	Yields (%)	Compd. No.	3,5-*syn* : 3,5-*anti*
1	**4**	MeO	*RS*	72	**7**	(3*RS*,5*RS*) : (3*SR*,5*RS*) = 65 : 35
2	**5**		*S*	40	**8**	(3*S*,5*S*) : (3*R*,5*S*) = 55 : 45
3	**6**		*R*	42	**9**	(3*R*,5*R*) : (3*S*,5*R*) = 77 : 23

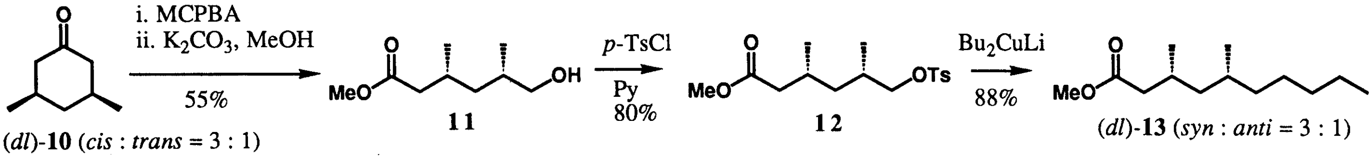


Chart 3

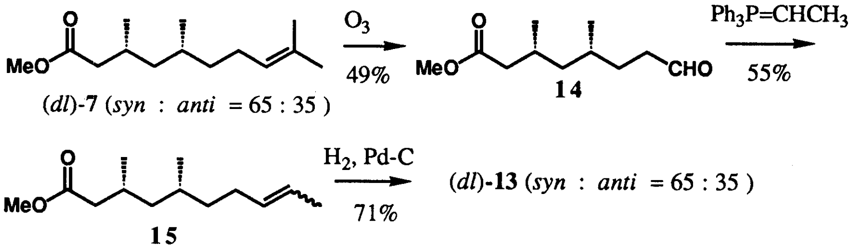


Chart 4

reaction, iii. hydrogenation) as shown in Chart 4. Comparison of the ^{13}C-NMR spectra of the products revealed that all the signals attributable to the major and the minor isomers were identical to each other. Typical differences of ^{13}C-NMR spectra of these diastereomers are as follows; *syn*-**13**: δ 20.4, 20.1 (3,5-Me); *anti*-**13**: δ 19.5, 19.4 (3,5-Me). Relative stereochemistry of **8** and **9** was determined by comparison of ^{13}C-NMR spectra after conversion to **7** by treatment with K_2CO_3/MeOH.

Experimental

Infrared (IR) spectra were measured on a JASCO A-202 spectrometer. ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were measured with a JEOL JNM-PX-100 or a JNM-GX 270 spectrophotometer. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Diethyl ether (Et_2O) and THF were dried and distilled from sodium-benzophenone ketyl under an Ar atmosphere prior to use. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used.

(1*R*,2*R*)-2-Bromoacetoxycyclohexanol (2) A mixed solution of (*R*,*R*)-cyclohexane-1,2-diol[1c] (**1**) (4.9 g, 4.2 mmol) and bromoacetyl chloride (7.5 g, 4.7 mmol) in CH_2Cl_2 (100 ml) was refluxed for 4 h. The reaction mixture was washed with brine and dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel. The fraction eluted with 25% AcOEt in hexane (v/v) yielded **2** (6.4 g, 64%) as a colorless solid. $[\alpha]_D^{19}$ −42.1° (c=1.85, $CHCl_3$). IR (Nujol): 3400, 1760, 1400, 1180, 1060 cm^{-1}. ^{1}N-NMR ($CDCl_3$) δ: 3.73 (1H, m, 1-H), 4.09(2H, s, CH_2Br), 4.62 (1H, m, 2-H). MS m/z: 236 (M^+), 219, 146, 128.

(1′*R*,2′*R*)-2′-Hydroxycyclohexyl Diethylphosphonoacetate (3) A solution of **2** (2.37 g, 10 mmol) in triethyl phosphite (15 ml) was heated at 100 °C for 10 h. After removal of excess triethyl phosphite *in vacuo*, the oily residue was purified by silica gel column chromatography. The fraction eluted with 10% hexane in AcOEt afforded **3** (2.35 g, 80%) as a colorless oil. $[\alpha]_D^{23}$ −49.9° (c=1.74, $CHCl_3$). IR (neat): 3450, 1740, 1450, 1270, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, m, $CH_3\times 2$), 2.87 (1H, dd, J=13.6, 18.1 Hz, 2-H), 3.09 (1H, dd, J=13.6, 20.3 Hz, 2-H), 3.55 (1H, m, 2′-H), 4.17 (4H, m, $OCH_2\times 2$), 4.63 (1H, m, 1′-H). MS m/z: 304 (M^+), 286.

Methyl (*RS*)-(*E*)-5,9-Dimethyl-2,8-decadienoate (4), (1′*R*,2′*R*,5*S*)- and (1′*R*,2′*R*,5*R*)-2′-Hydroxycyclohexyl (*E*)-5,9-Dimethyl-2,8-decadienoate (5 and 6) A solution of (*S*)-citronellal (500 mg, 3.25 mmol) in CH_3CN (2 ml) was added to a stirred mixture of LiCl (180 mg, 4.22 mmol), **3** (1.28 g, 4.22 mmol) and *N*,*N*-diisopropylethylamine (554 mg, 4.22 mmol) in CH_3CN (9 ml) at 0 °C under an Ar atmosphere. The whole was stirred for 6 h at room temperature. The reaction mixture was diluted with Et_2O (100 ml), then washed with brine and bried. After removal of the solvent *in vacuo*, the oily residue was submitted to column chromatography on silica gel. The fraction eluted with 10% AcOEt in hexane gave **5** (678 mg, 71%) as a colorless oil. $[\alpha]_D^{27}$ −26.6° (c=1.32, $CHCl_3$). IR (neat): 3420, 1710, 1650, 1440, 1270, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, J=6.6 Hz, 5-Me), 1.60, 1.68 (3H each, s, $=CMe_2$), 3.59 (1H, m, 2′-H), 4.63 (1H, m, 1′-H), 5.09 (1H, m, 8-H), 5.84 (1H, dt, J=15.5, 1.5 Hz, 2-H), 6.97 (1H, dt, J=15.5, 7.6 Hz, 3-H). MS m/z: 294 (M^+), 276, 238, 197, 179, 152. Compound **6** (506 mg, 75%) was obtained by the similar reaction of (*R*)-citronellal (350 mg, 2.27 mmol) with **3** (690 mg, 2.27 mmol) as a colorless oil. $[\alpha]_D^{25}$ −27.6° (c=1.08, $CHCl_3$). IR (neat): 3420, 1710, 1650, 1440, 1270, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, J=6.6 Hz, 5-Me), 1.60, 1.68 (3H, each, s, $=CMe_2$), 3.59 (1H, m, 2′-H), 4.63 (1H, m, 1′-H), 50.9 (1H, m, 8-H), 5.84 (1H, dt, J=15.5, 1.5 Hz, 2-H), 6.97 (1H, dt, $J=15.5$, 7.6 Hz, 3-H). MS m/z: 294 (M^+), 276, 238, 197, 179. Compound **4** (580 mg, 85%) was obtained by the similar reaction of (*dl*)-citronellal (500 mg, 3.25 mmol) with trimethyl phoshonoacetate (611 mg, 3.25 mmol) as a colorless oil. IR (neat): 1720, 1650, 1430, 1260, 1110, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, $J=6.6$ Hz, 5-Me), 1.60, 1.68 (3H each, s, $=CMe_2$), 3.73 (3H, s, OMe), 5.08 (1H, m, 8-H), 5.81 (1H, dt, $J=15.6$, 1.3 Hz, 2-H), 6.95 (1H, dt, $J=15.6$, 7.6 Hz, 3-H). MS m/z: 210 (M^+), 178, 136.

General Procedure for Conjugate Addition with Me_2CuLi Me_2CuLi was prepared by addition of MeLi (1.1 M in Et_2O, 6 mmol) to a suspension of $CuBr-Me_2S$ (3 mmol) in Et_2O (10 ml) at -30 °C, followed by stirring for 15 min. Substrate (0.6 mmol) in Et_2O (1 ml) was added to the above solution at -30 °C. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 ml) and diluted with Et_2O (20 ml). The mixture was stirred until the solid had been digested, when the aqueous layer turned a deep blue. The ethereal layer was separated, and the aqueous layer was extracted with Et_2O (20 ml × 2). The combined extracts were washed with brine and dried. After removal of the solvent *in vacuo*, the oily residue was purified by column chromatography on silica gel.

Entry 1. Reaction of **4** with Me_2CuLi: Product **7** was obtained in 72% yield as a diastereomeric mixture (*syn* : *anti* = 65 : 35). A colorless oil. IR (neat): 1740, 1640, 1250, 1130, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H × 2, m, 3, 5-Me), 1.60, 1.68 (3H each, s, $=CMe_2$), 3.66 (3H, s, OMe), 5.09 (1H, m, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 17.7 (q), 19.9 (19.2) (q), 20.4 (19.4) (q), 25.3 (25.5) (t), 25.7 (q), 27.9 (d), 29.7 (d), 41.5 (42.4) (t), 44.5 (44.2) (t), 51.3 (q), 124.9 (d), 131.1 (s), 173.8 (s). Chemical shifts in parentheses are those of the minor product. MS m/z: 226 (M^+), 195.

Entry 2. Reaction of **5** with Me_2CuLi: Product **8** was obtained in 40% yield as a diastereomeric mixture ((1′*R*,2′*R*,3*S*,5*S*)-**8** : (1′*R*, 2′*R*,3*R*,5*S*)-**8** = 55 : 45). A colorless oil. IR (neat): 3450, 1720, 1640, 1245, 1145, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H × 2, m, 3, 5-Me), 1.60, 1.68 (3H each, s, $=CMe_2$), 3.55 (1H, m, 2′-H), 5.09 (1H, m, 8-H). ^{13}C-NMR ($CDCl_3$): 17.7 (q), 20.0 (19.3) (q), 20.3 (19.4) (q), 23.8 (t), 25.5 (25.4) (t), 25.7 (q), 28.0 (d), 29.7 (d), 30.0 (30.1) (t), 33.0 (t), 36.7 (37.8) (t), 42.0 (42.9) (t), 44.6 (44.2) (t), 72.9 (72.8) (d), 78.0 (d), 124.9 (d), 131.1 (s), 173.7 (173.5) (s). Chemical shifts in parentheses are those of the minor product. MS m/z: 310 (M^+), 292, 195. A small amount of the major product was isolated in optically pure form. (1′*R*,2′*R*,3*S*,5*S*)-**8**: $[\alpha]_D^{24}$ $-13.8°$ ($c=2.14$, $CHCl_3$).

Entry 3. Reaction of **6** with Me_2CuLi: Product **9** was obtained in 42% yield as a diastereomeric mixture ((1′*R*,2′*R*,3*R*,5*R*)-**9** : (1′*R*,2′*R*,3*S*,5*R*)-**9** = 77 : 23). A colorless oil. IR (neat): 3450, 1720, 1640, 1245, 1145, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H × 2, m, 3,5-Me), 1.60, 1.68 (3H each, s, $=CMe_2$), 3.55 (1H, m, 2′-H), 5.09 (1H, m, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 17.7 (q), 20.0 (19.3) (q), 20.3 (19.4) (q), 23.8 (t), 23.9 (t), 25.4 (25.5) (t), 25.7 (q), 28.0 (d), 29.7 (d), 30.0 (30.1) (t), 33.0 (t), 36.8 (37.8) (t), 42.0 (42.9) (t), 44.6 (44.1) (t), 72.9 (d), 78.0 (d), 124.8 (d), 131.1 (s), 173.6 (173.5) (s). Chemical shifts in parentheses are those of the minor product. MS m/z: 310 (M^+), 292, 195. A small amount of the major product was isolated in optically pure form. (1′*R*,2′*R*,3*R*,5*R*)-**9**: $[\alpha]_D^{22}$ $-22.0°$ ($c=2.09$, $CHCl_3$).

Methyl 6-Hydroxy-3,5-dimethylhexanoate (11) *m*-Chloroperbenzoic acid (9.4 g, 43.7 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a solution of commercially available 3,5-dimethylcyclohexanone (3 to 1 mixture of *cis*- and *trans*-compounds) (5.0 g, 39.7 mmol) in CH_2Cl_2 (30 ml) at 0 °C, and the whole was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 (50 ml) and washed with 5% aqueous $NaHCO_3$ and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was dissolved in MeOH (20 ml). K_2CO_3 (6 g, 43.7 mmol) was added to the solution and the whole was stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O (40 ml) and the precipitate was filtered off. After removal of the solvent *in vacuo*, the oily residue was purified by silica gel column chromatography to give **11** (3.78 g, 55% from 3,5-dimethylcyclohexanone) as a colorless oil. A 3 to 1 mixture of *syn* and *anti*-diastereomers. IR (neat): 3410, 1730, 1240, 1100, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H × 2, m, 3,5-Me), 3.47 (2H, m, 6-H), 3.67 (3H, s, OMe). MS m/z: 175 ($M^+ + 1$), 156, 143, 112.

Methyl 3,5-Dimethyl-6-*p*-toluenesulfonyloxyhexanoate (12) *p*-Toluenesulfonyl chloride (817 mg, 4.31 mmol) was added to a stirred mixture of compound **11** (500 mg, 2.87 mmol), 4-(dimethylamino)pyridine (5 mg) and pyridine (5 ml) in CH_2Cl_2 (7 ml) at 0 °C. The whole was stirred at room temperature for 12 h. The reaction mixture was poured into brine (50 ml) and extracted with Et_2O (30 ml × 2). The combined extracts were washed successively with 10% aqueous HCl, 5% aqueous $NaHCO_3$ and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was chromatographed on silica gel. The fraction eluted with 10% AcOEt in hexane (v/v) afforded **12** (760 mg, 81%) as a colorless oil. IR (neat): 1740, 1600, 1360, 1100, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H × 2, m, 3,5-Me), 2.45 (3H, s, Ar-Me), 3.65 (3H, s, OMe), 3.85 (2H, m, 6-H), 7.28 (2H, d, $J=8.2$ Hz, Ar-H), 7.79 (2H, d, $J=8.2$ Hz, Ar-H). FDMS m/z: 328 (M^+).

Methyl 3,5-Dimethyldecanoate (13) Reaction of **12** (100 mg, 0.3 mmol) with Bu_2CuLi (1.5 mmol) was performed according to the general procedure of 1,4-addition but using BuLi instead of MeLi. Compound **13** (57 mg, 88%) was obtained as a colorless oil. A 3 to 1 mixture of *syn* and *anti*-diastereomers. IR (neat): 1740, 1240, 1130, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H × 3, m, 3,5-Me and 10-H), 2.20 (2H, m, 2-H), 3.66 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 20.1 (19.4) (q), 20.4 (19.5) (q), 22.7 (t), 26.5 (26.7) (t), 27.9 (d), 30.1 (d), 32.2 (t), 36.7 (37.7) (t), 41.6 (42.5) (t), 44.7 (44.5) (t), 51.3 (q), 173.8 (173.7) (s). Chemical shifts in parentheses are those of the minor product. MS m/z: 214 (M^+), 199, 183.

References and Notes

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