

# Carbanion vs. Carbon Radical in Tandem 1,4-Addition to Two Connected Units of Acrylate or Methacrylate

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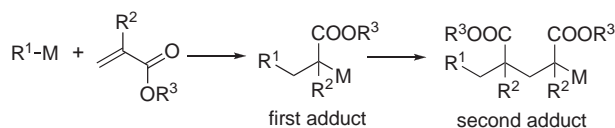
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Two units of acrylate or methacrylate were connected with 2,4-pentanediol. Michael addition of organometallic compounds to this substrate failed to cause the intended intramolecular Michael addition of the generated enolate, but the addition of carbon radical induced the internal addition to give cyclic compounds in yields up to 79%.

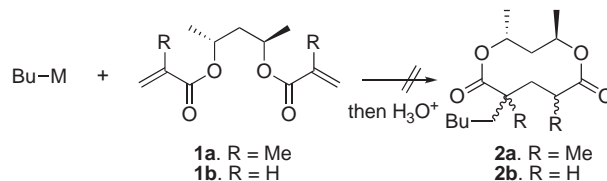
Addition of an olefinic molecule is an often employed reaction for C–C bond formation, but it becomes difficult to perform selectively if one wishes to add two, but not three or more, olefin-units sequentially, because the first adduct and the second adduct could have similar reactivity to the olefin. In fact, addition of a Grignard reagent to acrylate analogues gives a tandem adduct with two units in yields up to 97% after quenching with water (Scheme 1).<sup>1</sup> The yields are high when the acrylate has a bulky  $\alpha$ -substituent, but are low as 21–58% with methacrylate ( $R^2 = \text{Me}$ ), and no such example has been reported for unsubstituted acrylate ( $R^2 = \text{H}$ ) to our knowledge.

A simple idea to realize the tandem addition irrespective of the olefin structure is connection of the two units of the olefin. The connector must be flexible enough to allow intramolecular addition, but, at the same time, should keep the reaction sites in some restricted space to perform effective intramolecular addition. Here, an acrylate or methacrylate that is connected with 2,4-pentanediol could not undergo tandem Michael addition with alkylmetals, but the radical version of substrates gave 69 and 79%, respectively, of the tandem adduct.

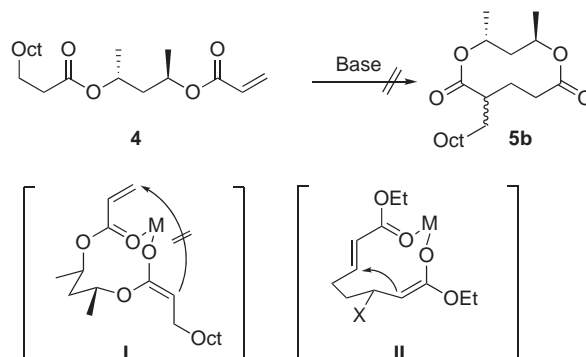
Two substrates, methacrylate ester **1a**<sup>2</sup> and acrylate ester **1b** of (2*R*,4*R*)-2,4-pentanediol were prepared by reacting it with the corresponding acid chloride (82 and 63%, respectively, after sufficient purification). The reaction of butyl anion with **1a** was studied under varied conditions: butyllithium or butylmagnesium bromide as a source of carbanion, in the presence of a copper(I) reagent, such as CuBr·SMe<sub>2</sub>, CuCN, CuI·PBu<sub>3</sub>, or CuI/BF<sub>3</sub>, in THF or ether, at –78 °C, or higher temperature, –50 °C or rt, prior to the aqueous quenching (Scheme 2). In spite of the expected effectiveness of the intramolecular addition,<sup>3</sup> **2a** was not detected in the reaction mixtures. The main



Scheme 1. Tandem Michael addition with alkylmetal.



Scheme 2. Intramolecular tandem Michael addition.



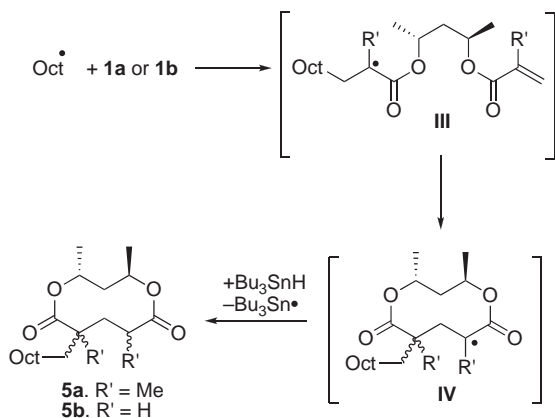
Scheme 3. Simple intramolecular Michael addition.

component except unreacted **1a** was the double intermolecular Michael adduct **3** with two butyl groups. Similar approaches also failed to obtain **2b** with acrylate **1b**.

Inefficient intramolecular addition was also found in a simpler reaction system with **4**. When **4** was treated with LDA in THF or THF/TMEDA, the intramolecular adduct **5b** was not obtained, but polymeric products were obtained after quenching with water (Scheme 3). Treatment of **4** with *t*-BuOK in *t*-BuOH or THF only resulted in partial hydrolysis after aqueous workup. The poor reactivity is not readily understood, because ten-membered ring formation in **1a** or **1b** should not generate notable strain. However, if coordination of a counter cation of the enolate to the intramolecular carbonyl of the unsaturated ester is considered, the reaction sites for the Michael addition are forced to be far away from each other, and do not seem to be accessible, as shown **I**. This situation is in contrast to the intermediate when the two unsaturated esters are connected at the olefinic ends, e.g., intermediate **II** is fixed to a proper conformation to perform intramolecular addition by coordination to the metal.<sup>4</sup>

The unwanted arrangement, shown as **I**, does not exist in the corresponding radical version, and actually, the radical reaction involving **1a** has previously been found to yield effectively the cyclized product.<sup>2</sup> That is, photolysis of thiophenol with **1a** (3 molar amounts) gave ten-membered ring products (PhS or H adduct) in 94% of the total yield based on the amount of thiophenol. Hence, the alkyl radical addition to **1a** or **1b** was expected to be followed by the cyclization.<sup>5</sup>

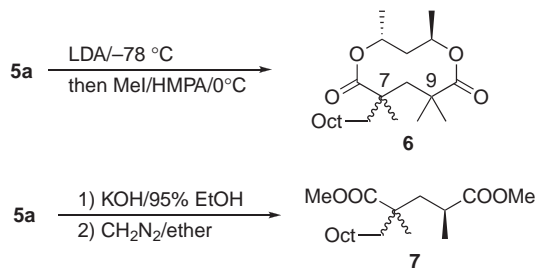
A mixture of octyl bromide (25 mmol dm<sup>–3</sup>), Bu<sub>3</sub>SnH

Scheme 4. Radical tandem 1,4-addition with **1a** and **1b**.

(equimolar amount) and **1a** (equimolar amount) in benzene was heated to reflux in the presence of AIBN (0.1 molar amount). After consumption of **1a**, cyclic product **5a** was isolated in 34% yield (Scheme 4). The remainder was insoluble in ether and was a mixture of polymeric compounds of **1a**, containing a tributyltin group. The reaction must start with generation of octyl radical by the abstraction of bromine atom with tributyltin radical. The octyl radical adds to one of the olefins of **1a** to generate radical **III**, and intramolecular addition gives the second radical **IV**, which is converted to **5a**, when the radical reaction is terminated by trapping with the hydrogen abstracted from tributyltin hydride. Mechanistic difference with the reaction with thiophenol is that the generation process of **III** is not reversible and hydride abstraction with the carbon radicals from  $\text{Bu}_3\text{SnH}$  is much slower than that from  $\text{PhSH}$ .<sup>6</sup> In addition, the reaction temperature and molar amounts of **1a** are also different.

The yield of **5a** was increased to 39% when octyl iodide was reacted at room temperature with a catalytic amount of  $\text{Bu}_3\text{SnCl}$  (0.1 molar amount) in the presence of  $\text{NaBH}_4$  (1.5 molar amounts) and **1a** (equimolar amount) initiated by irradiation with a high-pressure mercury lamp through a Pyrex filter.<sup>7</sup> The yield was further improved to 69% by the use of two molar amounts of **1a**. Under these mild conditions, polymerization of **1a** was minimized, and 41% (0.8 molar amount) of **1a** was recovered. Similarly, by using of **1b** (5 molar amounts), **5b** was obtained in 79% yield after column chromatography. The high yields indicate that the reaction of  $\text{Bu}_3\text{SnH}$  with the octyl radical and radical **III** are sufficiently suppressed, whereas that to **IV** still occurs. Thus, balance of the reactivities of the radical intermediates predominates the product yield. As a matter of fact, the yield reduced to 0–31% for the addition of **1a** to a benzylic or arene carbon.<sup>8</sup>

Two stereoisomers were detected for both **5a** and **5b** in equal amounts (by  $^1\text{H NMR}$ ), even though **5a** has four possible stereoisomers. After  $\alpha$ -methylation of the isomeric mixture of **5a** at C9, obtained **6** was still a mixture of the isomers in the same ratio (59% yield), and thus, C7 of **5a** was determined to be racemic (Scheme 5). Solvolysis to remove the chiral auxiliary resulted in **7** (74%) also in a 1:1 isomeric mixture, indicating that relative stereochemistry of C9 against C7 is different between the two isomers of **5a**, and C9 must be stereochemically uniform. Thus, in the reactions of **1a** and **1b**, the

Scheme 5. Conversions of **5a**.

chirality at C7 generated in the cyclization step is uncontrolled, but the termination step to generate the chirality at C9 of **5a** is fully controlled. The stereochemistry of C9 was not determined, but it is thought to be *S* by the previously reported results with thiyl radical.<sup>2</sup> When the reaction of **1b** to give **5b** was performed at  $-50^\circ\text{C}$ , stereo-uncontrolled cyclization was slightly suppressed, resulting in a ratio of 54:46.

In the present paper, tandem 1,4-addition with two units of acrylate or methacrylate was demonstrated. The results show once again that the radical reaction is superior to the anionic version.<sup>9</sup> The reaction could be a carbon-chain extension method for simple iodo compounds.

## Experimental

All reactions were carried out under a dry nitrogen atmosphere. Photochemical reactions were performed with a high-pressure mercury lamp (350 W) made by Eiko-sha, Japan. MPLC was carried out using an FMI pump ( $10\text{ mL min}^{-1}$ ) and a Lobar column (MERCK Si-60 type B).

**Preparation of 1a.** To a solution of (2*R*,4*R*)-2,4-pentanediol (10.0 g) and triethylamine (66.1 mL, 5.0 molar amounts) in dichloromethane (100 mL) was added methacryloyl chloride (23.4 mL, 2.5 mol) in 10 min at  $0^\circ\text{C}$ , and after stirring for 2 h at rt, water was added. Extraction and purification by using a silica-gel column (elution with 10% ethyl acetate in hexane) gave **1a** as a colorless oil (18.9 g, 82% yield). Alternatively, **1a** was obtained from methacrylic acid and DCC in the presence of 4-dimethylaminopyridine (82% yield).

**Preparation of 1b.** To a solution of (2*R*,4*R*)-2,4-pentanediol (1.95 g) and triethylamine (7.8 mL, 3.0 molar amounts) in dichloromethane (20 mL) was added acryloyl chloride (4.6 mL, 3.0 molar amounts) at  $0^\circ\text{C}$  in 10 min. After 7 h, the mixture was poured into water, extracted, and separated by column chromatography on silica gel (elution with 10% ethyl acetate in hexane) to give **1b** as a colorless oil (2.51 g, 63% yield).

**Reaction of 1a with a Carbanion,  $\text{BuLi/CuCN}$ .** A butyllithium solution ( $1.6\text{ mol dm}^{-3}$  in hexane, 1.0 mL, 4 molar amounts) was added to a suspension of copper(I) cyanide (75.2 mg, 2 molar amounts) in ether (1 mL) in 10 min at  $-78^\circ\text{C}$ . The mixture was warmed up to  $0^\circ\text{C}$  for 1 h, and then cooled again to  $-78^\circ\text{C}$ . A solution of **1a** (100 mg) in ether (0.5 mL) was added in 5 min, and the mixture was warmed up to  $-50^\circ\text{C}$  for 30 min and then allowed to stand for 3 h at the same temperature. The mixture was extracted, dried, and separated on a silica-gel column (elution with 50% ethyl acetate in hexane) and then MPLC (elution with 6% ethyl acetate in hexane) to give **3** as a colorless oil (41.6 mg, 31%).

**Preparation of 4.** A mixture of (2*R*,4*R*)-2,4-pentanediol (2.00 g), undecanoic acid (3.90 g, 1.1 molar amounts) 4-dimethylamino-

pyridine (235 mg) in dichloromethane (200 mL) was cooled with an ice-water bath, and a solution of DCC (4.35 g, 1.1 molar amounts) in dichloromethane (50 mL) was added in 1 h. After 11 h, the acid (258 mg, 0.1 molar amount) and DCC (396 mg, 0.1 molar amount) were added. The mixture was stirred for an additional 4 h, filtered through a Celite pad, concentrated, and separated on a silica-gel column (elution with 20% ethyl acetate in hexane) to give a mono-ester as a colorless oil (4.83 g, 92% yield). To a solution of the mono-ester (2.0 g), triethylamine (1.2 mL, 1.2 molar amounts) in dichloromethane (100 mL), acryloyl chloride (0.7 mL, 1.2 molar amounts) was added at 0 °C in 10 min, and after 4 h, triethylamine (0.5 mL, 0.5 molar amount) and acryloyl chloride (0.3 mL, 0.5 molar amount) were further added. After 1.5 h the mixture was extracted, dried over sodium sulfate, and separated on a silica-gel column (elution with 10% ethyl acetate in hexane) to give 1.3 g of **4** as a colorless oil (54% yield).

**Enolate Formation from 4.** Ester **4** (100 mg) was treated with LDA (1.2 molar amounts) in ether (5 mL) at –78 °C. After 2 h, the mixture was extracted with ether, dried over sodium sulfate, and concentrated. The obtained mixture contained mostly polymeric compounds in addition to unreacted **4**. Use of lithium hexamethyldisilazane in THF at 0 °C, or potassium *t*-butoxide in *t*-butyl alcohol or in THF at rt did not afford **5b**.

**Reaction of 1a with OctBr/Bu<sub>3</sub>SnH/AIBN.** A solution of **1a** (150 mg), octyl bromide (132 mg, 1.1 molar amounts), tributyltin hydride (198 mg, 1.1 molar amounts), and AIBN (9.8 mg) in benzene (30 mL) was heated at reflux for 25 h. After concentration, the mixture was purified by MPLC (elution with 6% ethyl acetate in hexane) to give 74.3 mg of a diastereomeric mixture of **5a** as a colorless oil (34% yield).

**Reaction of 1a with OctI/Bu<sub>3</sub>SnCl/NaBH<sub>4</sub> under Photolysis.** A solution of octyl iodide (240 mg), **1a** (480 mg, 2 molar amounts), sodium borohydride (55.6 mg, 1.5 molar amounts), and tributyltin chloride (27 µL, 0.1 molar amount) in ethanol (300 mL) was placed in a Pyrex photo-reactor. Nitrogen gas was passed through the solution and stirring during photolysis with a high-pressure mercury lamp at rt. Photolysis was maintained for 32 h, and then the mixture was purified by MPLC (6% ethyl acetate in hexane) to give **5a** (195 mg) and **1a** (ca. 200 mg). The yield of **5a** based on octyl iodide was 69%.

**Reaction of 1b with OctI/Bu<sub>3</sub>SnCl/NaBH<sub>4</sub> under Photolysis.** A mixture of octyl iodide (40.0 mg), **1b** (170 mg, 5 molar amounts), and sodium borohydride (8.9 mg, 1.5 molar amounts) in ethanol (50 mL) was placed in a Pyrex tube (100 mL), and de-aerated with nitrogen gas. Tributyltin chloride (4.3 µL, 0.1 molar amount) was added to the tube, and the tube was irradiated with a high-pressure mercury lamp for 4 h while bubbling with nitrogen. After removal of the solvent under vacuum, the mixture was purified on a short column (silica gel, elution with 30% ethyl acetate in hexane) and then MPLC (elution with 4.5% ethyl acetate in hexane) to give 41.5 mg of **5b** as a colorless oil (79% based on octyl iodide). The isomers of **5b** were partly separated.

**Methylation of 5a with LDA/Mel to Give 6.** A solution of LDA was prepared by mixing diisopropylamine (0.12 mL) and butyllithium (1.56 mol dm<sup>–3</sup>, 0.54 mL) in THF (5 mL) at –78 °C. To this solution, HMPA (0.12 mL) was added at the same

temperature, followed by dropwise addition of a solution of **5a** (30.0 mg) in THF (1 mL). After 1.5 h, the mixture was warmed to –15 °C, and methyl iodide (52 µL) was added to this mixture. The mixture was allowed to stand for 21 h at 0 °C. The mixture was extracted, dried over magnesium sulfate, and purified by MPLC (elution with 6% ethyl acetate in hexane) to give 18.5 mg of **6** as a colorless oil (59% yield as a diastereomer mixture).

**Conversion of 5a to 7.** A solution of **5a** (27 mg) in 95% ethanol (3 mL) containing 3% potassium hydroxide was heated at reflux for 10 h. After cooling, the mixture was concentrated to one half, neutralized with hydrochloric acid (2 mol dm<sup>–3</sup>), and extracted with ether. The extract was dried and concentrated to one tenth. To this solution, a solution of diazomethane was added. After concentration, the mixture was purified by MPLC (elution with 10–20% ethyl acetate in hexane) to give 17.8 mg of **7** as a colorless oil (74% yield).

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### Supporting Information

Reaction conditions for Scheme 2, and spectral data for all new compounds. This material is available free of charge on the web at <http://www.csj.jp/journals/bcsj/>.

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