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Radical Reaction of the Dimethacrylic Ester of (2*R*,4*R*)-2,4-Pentanediol. Addition-Cyclization-Termination Process of High Yield under Rigorous Stereocontrol of the Termination Step

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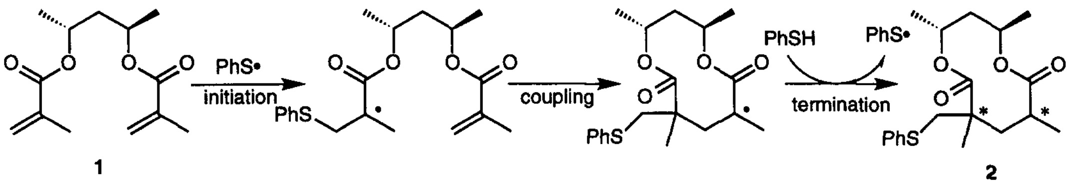
Abstract: Photolysis of the dimethacrylic ester of (2*R*,4*R*)-2,4-pentanediol in the presence of thiophenol resulted in intramolecular C-C bond formation and, after desulfurization, diastereomerically pure (4*S*)-2,2,4-trimethylglutarate ester was obtained in 93.6% for two steps.

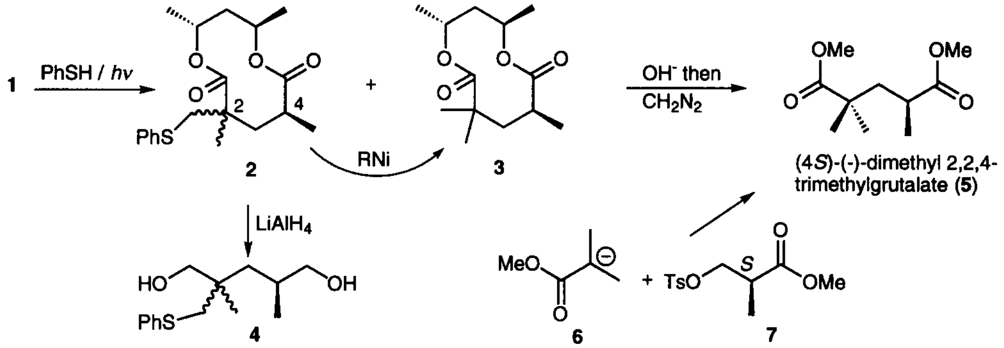
Radical polymerization of vinyl compounds affords oligomers of relatively low molecular weight in average, if the monomer concentration is low and amount of the chain-transfer agent is large. Under these conditions, we assumed that if two vinyl groups were linked by a chiral diol, the chiral "dimer type" product is obtained predominantly under the control of the stereochemistries. When methacrylate is used as a vinyl group, the expected product is considered to be a good C-8 synthon having chiral centers on a five-carbon chain. As the chiral diol, we employed optically active 2,4-pentanediol (PD) of a C_2-symmetric simple 1,3-diol. Thiophenol was used as a chain-transfer agent and also as an initiator under photo irradiation.[1] The reaction pathway consisted of the following tandem reactions as shown in Scheme 1: 1) intermolecular benzenethio radical addition (initiation), 2) intramolecular coupling step producing a chiral centre, 3) chain-transfer by thiophenol (termination) making the second chiral centre.

In this communication, we report that the dimer type products **2** were produced from **1** in high yield under the full stereocontrol of the second chiral centre.



Scheme 1

The substrate **1** was prepared from optically pure (2*R*,4*R*)-PD and methacryloyl chloride in 82.0% yield. Photolysis of **1** in benzene (9.9 mM) in the presence of thiophenol (3.3 mM) afforded **2** and a hydrodimer type product **3**. By chromatographic purification, one of the diastereomers of **2** was isolated in 31.0% yield (based on thiophenol), but the other diastereomer of **2** could not be separated from **1** and its polymer. To evaluate the yield of **2**, the reaction mixture was converted to diol **4** by lithium aluminum hydride. The diastereomer ratio of **4** was 57 to 43, and the minor one was identical with **4** from the isolated diastereomer of **2**. Thus, **2** of a diastereomeric mixture was produced in high yield (72.1% by calculation). The hydrodimer type product **3** was isolated as a diastereomerically pure form from the radical reaction mixture in 16.5% yield and no diastereomer was detected in the mixture. The fact indicated that the radical termination step in the production of **3** was fully controlled by the chiralities on the PD moiety. It is also suggested that the termination step producing **2** is controlled by the PD moiety producing high stereochemical purity at the 4-position, if the termination step is not affected by the stereochemistry at the 2-position. As a matter of fact, Raney nickel reduction of the reaction mixture gave only **3** without any detectable amount of its diastereomer. Overall yield of **3** in two steps based on thiophenol reached 93.6%.[2] Optically active dimethyl 2,2,4-trimetylgrutalate (**5**) was obtained from **3** by hydrolysis and treatment with diazomethane (44.3% yield for two steps, $[\alpha]_D = -43.5$). Absolute configuration of (-)-**5** was determined to be 4*S* by the chemical correlation, in which substitution of (2*S*)-**7** by lithium anion **6** to afforded levorotatory **5**.[3]



Scheme 2

The excellent yield of the "dimer type" products is noteworthy because the intramolecular addition step is the entropically unfavorable ten-membered ring cyclization. Since the anion version of the reaction of **1** did not result in the intramolecular coupling,[4,5] the present study constructing a ten-membered ring was succeeded only by using the nature of the radical reaction. Although stereocontrol of the intramolecular addition step was poor, the termination step of the radicals of the ten-membered ring compounds was highly diastereo-differentiating.[6] The detailed study to analyze the stereocontrol factors will be reported elsewhere.

REFERENCES AND NOTES

1. For review, see, Stacy, F. W.; Harris, Jr., J. F., *Organic reactions Vol. 13* (1963) John Wiley, New York, Ed. by Adams, R., pp. 150–376.
2. The two-steps yields under the other conditions were as follows; with 3.3 mM of **1** and 3.3 mM of thiophenol, 20.7%; with 1.1 mM of **1** and 1.1 mM of thiophenol, 42.2%; with 3.3 mM of **1** and 9.9 mM of thiophenol, 35.6% based on **1**.
3. Optically purity of **5** obtained by this method was low ($[\alpha]_D = -8.5$) because of the side processes of β-elimination of **7** and following Michael addition of **6** to the resulting methyl methacrylate.
4. When **1** was treated with various butyl cuprates, the intramolecular C–C bond was not formed at all, but only the Michael adduct of two butyl groups was obtained in 7–31% yield. The reactions of **1** with lithium diethylamide or allyltrimethylsilane/$TiCl_4$ also did not result in the intramolecular cyclization.
5. Addition of lithium amide to the α,β-unsaturated dioic esters resulted in a tandem reaction consisting of Michael addition of amide and subsequent intramolecular addition of the resulting ester anion when the produced ring size was five or six. This reaction could not be applied for the substrate to construct a seven-membered ring. Uyehara, T.; Shida, N.; Yamamoto, Y., *J. Chem. Soc., Chem. Commun.*, **1986**, 113–114. See also, Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T., *J. Am. Chem. Soc.*, **1989**, *111*, 4533–4535.
6. Curran, D. P.; Porter, N. D.; Giese, B., Stereochemistry of Radical Reaction, VHC, Weinheim (1996) pp. 116–146.

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