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A straightforward strategy toward the construction of polypropionate frameworks, based on a sequence of diastereoselective Lewis acid-mediated aldol reaction and diastereoselective radical debromination reaction

Syun-ichi Kiyooka,[a,b,*] Mineyuki Shiinoki,[b] Kumi Nakata[b] and Fumitaka Goto[c]

[a]*Institute of Fundamental Research for Organic Chemistry, Kyushu University, Higashi-ku, Fukuoka 812-8581, Japan*
[b]*Department of Chemistry, Kochi University, Akebono-cho, Kochi 780-8520, Japan*
[c]*Cellular Technology Institute, Otsuka Pharmaceutical Co., Ltd, Kawauchi-cho, Tokushima 771-0130, Japan*

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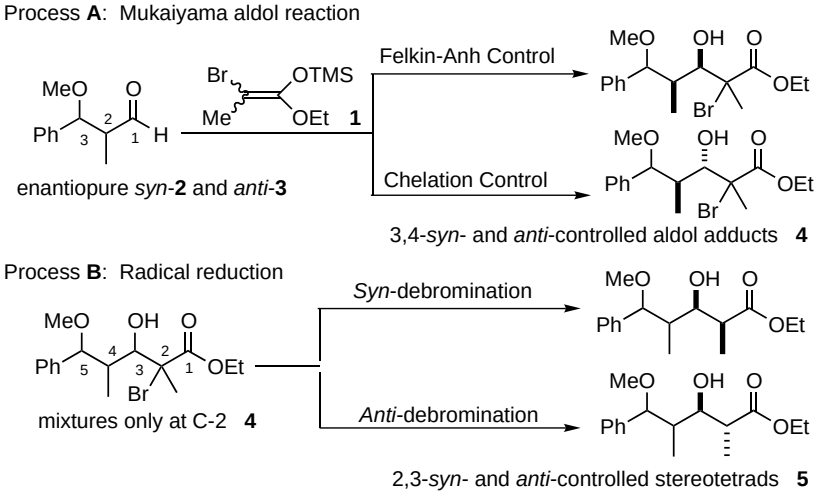
Abstract—An approach joining highly diastereoselective Mukaiyama aldol reaction (process **A**) to the following radical debromination reaction (process **B**) provides a reliable way to the stereoselective divergent synthesis of polypropionate frameworks. A practical and reliable synthesis of the complete set of propionate stereotetrads from enantiopure *syn*- and *anti*-2-methyl-3-methoxy-3-phenylpropanals was achieved by using the straightforward strategy.

More straightforward approaches to the diastereoselective construction of polypropionates possessing units with alternative hydroxyl and methyl groups are being awaited for the versatile synthesis of biologically active polyketide natural products. We have recently succeeded in a highly enantioselective, divergent synthesis of *syn*- and *anti*-propionates, which was accomplished in a sequential procedure of a chiral oxazaborolidinone-promoted enantioselective aldol reaction with silylketene acetal **1** and a radical debromination reaction.[1,2] The approach joining the highly enantioselective aldol reaction[3] to the highly diastereoselective radical reaction[4] persuaded us to develop a reliable way to the stereoselective divergent synthesis of polypropionate



Scheme 1.

* Corresponding author.

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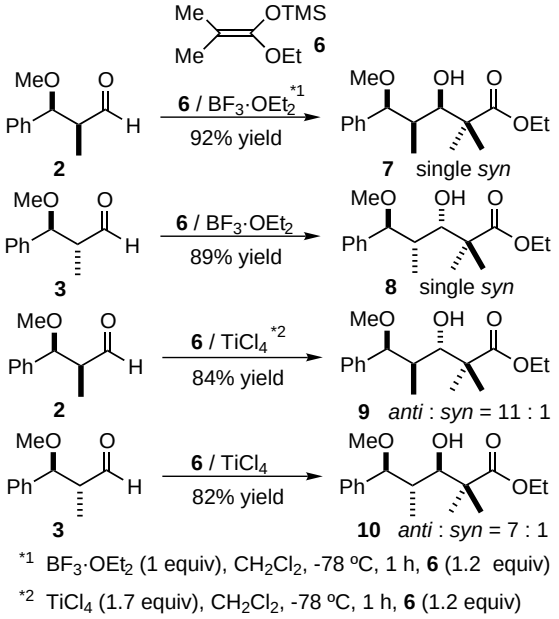
frameworks by combining a highly diastereoselective Mukaiyama aldol reaction to the following radical procedure.[5] Although iteration of the aldol reactions was believed to be difficult and unavailable for polypropionate construction,[6] the linear approach, if possible, might bring about a practical shortening of the synthetic approach to various types of polypropionate frameworks.[7] We disclose herein a practical and reliable synthesis of the complete set of propionate stereotetrads from enantiopure *syn*- and *anti*-2-methyl-3-methoxy-3-phenylpropanal, **2** and **3**,[8] by using a straightforward strategy with a sequence of process **A**, in which diastereoselective Mukaiyama aldol reactions are expected to divergently give 3,4-*syn*- and *anti*-aldol adducts **4**, and process **B**, in which diastereoselective debromination reactions are requested to divergently lead 2,3-*syn*- and *anti*-stereotetrads **5**, as shown in Scheme 1.

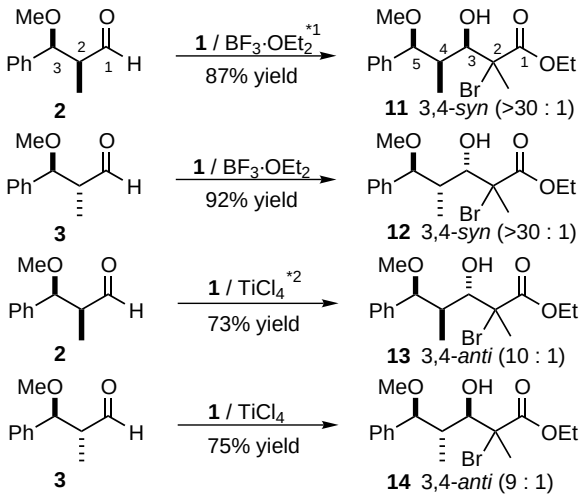
Excellent *syn*-diastereoselection (Felkin–Anh control) has been recognized in the $BF_3{\cdot}OEt_2$-mediated aldol reaction of α-methyl-β-siloxy aldehydes with a silylketene acetal from ethyl propionate.[9] A complementary access is, however, needed to clarify the iterative *syn*- and *anti*-stereoselection necessary for the diastereoselective polypropionate construction because such systematic studies have been restricted to the case of aldehydes bearing only an α- or a β-stereocenter.[10] Typical bidentate Lewis acids, e.g. $TiCl_4$ and $SnCl_4$, were known to undergo chelation-controlled addition reactions in the case of the above aldehydes.[11] However, such Lewis acids were reported to exhibit little to no chelating capability in the aldol reaction of α-methyl-β-benzyloxy aldehydes bearing a β-substituent with enolsilanes.[12] Then, the *syn*- and *anti*-diastereoselections in Mukaiyama aldol reaction of **2** and **3** were investigated by using a model nucleophile **6**. *Felkin–Anh control with $BF_3{\cdot}OEt_2$*: Excellent *syn* diastereoselection was observed in the $BF_3{\cdot}OEt_2$-mediated reaction of both **2** and **3**, with **6** to give essentially single aldol adducts, **7** and **8**, respectively, without incurring any interference from the relative configuration at C-2 and C-3 and the β-protecting group of the aldehydes (Scheme 2). The *syn* adducts might be afforded via the Felkin–Anh controlled addition modes where the major factor responsible for the high *syn* selection is attributable to the potential differences in the steric bulkiness between the methyl group and the residual group, involving the methoxy substituent, at C-2 of the aldehydes. *Chelation control with $TiCl_4$*: In spite of the indefinite prediction of $TiCl_4$ chelation control on α-methyl-β-protected-oxy aldehydes as described above,[12] the $TiCl_4$-mediated reaction of *syn* aldehyde **2** with **6** resulted in fairly good *anti* selection (11:1) to give **9** in 84% yield (Scheme 2). Such *anti* selection (6:1) has been reported only in a similar $TiCl_4$ reaction system with *syn*-3-benzyloxy-2-methyl-4-TBDMsilyloxybutanal and **6**, related to an epothilone A synthesis.[13] There are noteworthy reaction conditions under which the TMS-trapped *syn*-selective adducts, probably obtained through a catalytic reaction mode, were found when a sufficient amount of $TiCl_4$ was not used. When we used $SnCl_4$ under similar reaction conditions, very high *syn*-selection (30:1) was found which exhibits loss of the chelating ability of the Lewis acid. In the case of *anti* aldehyde **3**, if the chelation with $TiCl_4$ would be possible, the *anti* selectivity could be supposed to be considerably diminished because the desired approach of the silyl nucleophile under the chelation control should be prevented by the β-methoxy substituent, oppositely directed relative to α-methyl in the chelated conformer. Unexpectedly, the $TiCl_4$-mediated reaction led to remarkably good *anti* selection (7:1) to give **10**. These results suggest that the chelation controls are surely possible in the $TiCl_4$-mediated reaction of both *syn*- and *anti*-aldehydes, **2** and **3**.[14]



Scheme 2.

With respect to process A, the Mukaiyama aldol reaction of the silylketene acetal **1** under consideration was examined by using $BF_3{\cdot}OEt_2$ and $TiCl_4$. As expected above, the $BF_3{\cdot}OEt_2$-mediated addition reaction of silylketene acetal **1** to diastereomeric aldehydes, **2** and **3**, resulted in excellent 3,4-*syn*-selection to give Felkin–Anh controlled products, **11** and **12**, respectively, without any selection at C-2, as shown in Scheme 3. Thus, the complete *syn*-selection was confirmed to be reproducible at least in this reaction system, although a relatively different contribution of the resident β-stereocenter has been reported for the Felkin–Anh control diastereoselectivity in the non-chelate-controlled addition reaction of similar aldehydes with enolsilanes.[9a] On the other hand, in spite of the predicted drawbacks on less chelation ability of $TiCl_4$ to the aldehyde type in question, the $TiCl_4$-mediated addition reaction of aldehydes, **2** and **3**, with **1** was also found to lead to fairly good 3,4-*anti* selection to give the desired chelate-controlled adducts, **13** and **14**, respectively, without any selection at C-2.

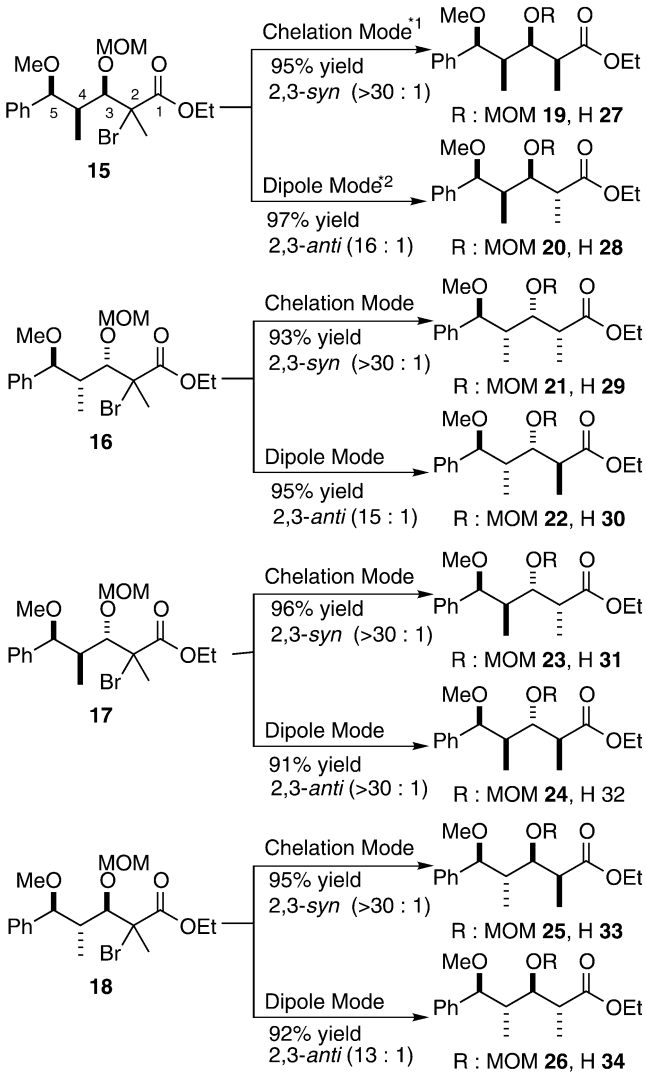
Next, for process **B** in elongating the polypropionate chains an appropriate choice of the β-hydroxy protect-



Scheme 3.

ing group of **4** is strictly required in line with the stereochemical demands for the following both debromination procedures directed to *syn*- and *anti*-selections. Surveying a number of protection groups suitable for the following diastereoselective debromination reactions, we selected a methoxymethyl (MOM) protection group, which can be smoothly introduced and deprotected under mild conditions, as an effective protection group available for highly diastereoselective debrominations to the desired eight stereotetrads **5**. The major aldol adducts, **11**–**14**, were treated with dimethoxymethane and P_2O_5 to give the corresponding MOM-protected esters, **15**–**18**, which consist of isomers (almost 1:1) at C-2. In the debromination processes, the MOM protection group allowed excellent and very high diastereoselection in both routes to 2,3-*syn*-isomer via chelation control and 2,3-*anti*-isomer via dipole control, as shown in Scheme 4.[15] The stereocenter at C-2 of the bromides, **15**–**18**, does not contribute to the stereochemical outcome in the radical debromination process because the diastereoselection is achieved at the sp^2 carbon center of the radical species generated by Et_3B. The 2,3-*syn*-selection might be attributable to the effective chelation of $MgBr_2$ to the ethoxycarbonyl and the MOM moiety while the 2,3-*anti*-selection is presumably enhanced by the induced dipole–dipole repulsion between the ethoxycarbonyl and the MOM moiety.[1,4] After deprotection of the MOM group, followed by simple column chromatography, the expected eight stereotetrads, **27**–**34**, were obtained in enantiopure state in good yields.

In conclusion, a sequence of a highly diastereoselective aldol reaction (process **A**) and the following highly diastereoselective radical reaction (process **B**) has opened up a very versatile, iterative approach toward the divergent construction of polypropionate chains with practically acceptable selectivity in good overall yield. The straightforward strategy can tailor the desired configuration in question during the synthesis



Scheme 4.

of a class of polyketide natural products. In process **A**, a reliable discrete way to the reverse diastereoselection could be achieved by the selection of classical Lewis acids, $BF_3{\cdot}OEt_2$ and $TiCl_4$. In process **B** the MOM protection group effectively affected both debromination reactions so as to more predominantly allow an alternative diastereoselection. This methodology using iterative aldol reactions is being developed in the stereoselective construction of (+)-discodermolide.

Acknowledgements

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14. The relative stereochemistries of the intermediates and the final stereotetrads were determined by the NOE experiments of their cyclic derivatives. Full details of the stereochemistry determination will be published in due course.
15. The MOM protection bearing two oxygens presumably prevents the participation of the methoxy group at C-5 under the conditions of chelation control, while the two oxygens enhances the transient dipole moment under the conditions of dipole control.