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Stereopentads Derived from a Sequence of Mukaiyama Aldolization and Free Radical Reduction on α-Methyl-β-alkoxy Aldehydes: A General Strategy for Efficient Polypropionate Synthesis

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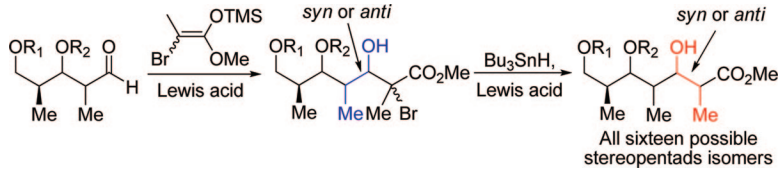

In a stereodivergent manner, all 16 diastereomeric stereopentads **7**−**22** were synthesized starting with α-methyl-β-alkoxy aldehydes **25** and **27**. We designed an approach based on a sequence of a Mukaiyama aldolization with enoxysilane **24** followed by a hydrogen transfer reaction. Recent advancements concerning these reactions are described, and novel key intermediates are characterized in the aldol step. The synthesis of C(1)−C(11) fragment **60** of zincophorin, which contains a synthetically challenging stereopentad unit, is described attesting the usefulness of our strategy.

Introduction

For more than a century, isolated natural products of the polyketide family have attracted the interest of the scientific community. The biological properties of representative compounds (see Figure 1) of this class, as well as their structural complexity, have justified research in synthetic organic chemistry but also in biochemistry, genetics, and pharmacology.[1] Polypropionate motifs (stereotriads, stereotetrads, stereopentads, etc.), consisting of a repeating sequence of stereogenic centers bearing methyl and hydroxyl functionalities, are common components of these polyketide natural products. Synthesizing these contiguous stereogenic centers is challenging, considering the number of possible stereoisomers, thus the need for stereocontrolled approaches.

As illustrated in Figure 2, the methyl−hydroxyl−methyl array having three stereogenic centers was defined as stereotriad[2] (diastereoisomers **3**−**6**) subunits while adding another propionate unit leads to stereopentads. Sixteen stereoisomers (**7**−**22**) are thus possible if one starts with a substrate possessing a unique stereogenic center.

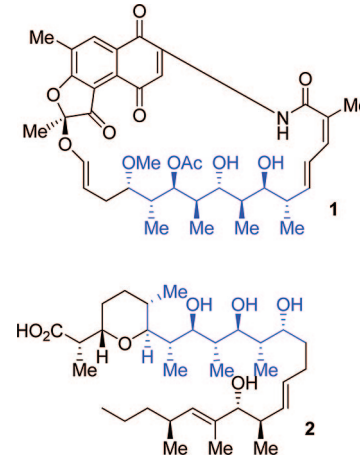

FIGURE 1. Structure of rifamicyn (**1**) and zincophorin (**2**).

In the past, the most common strategies for the synthesis of these stereotriads involved a carbon−carbon bond forming aldol reaction (titanium,[3] tin,[3] and boron enolates[3,4]). Just as important are methodologies based on additions of crotylboranes,[5] crotylboronates,[6] crotylsilanes,[7] allenyl stannane,[8] and allyltitanates[9]

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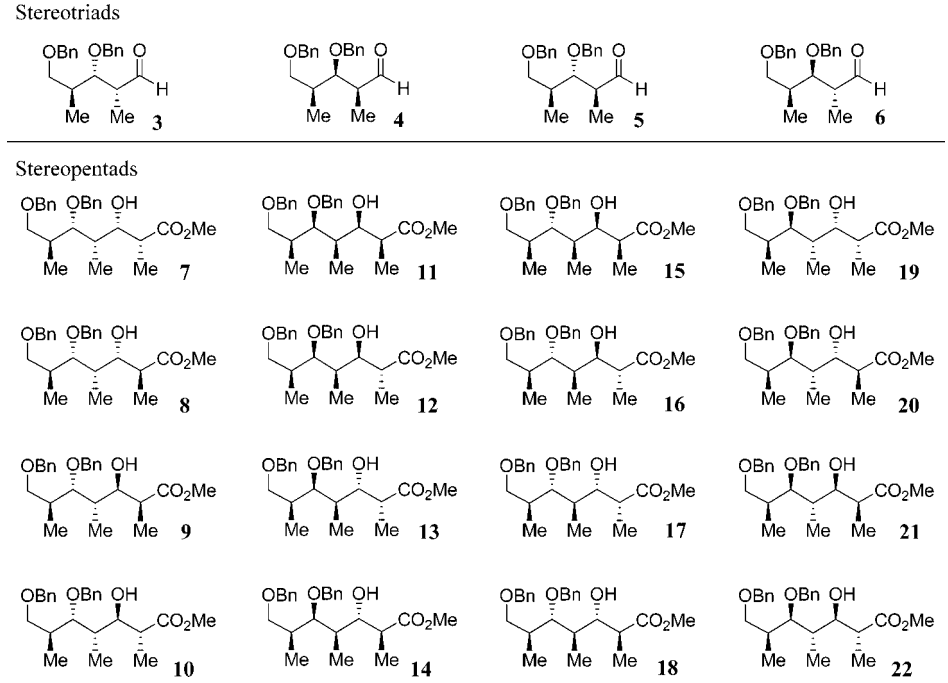

FIGURE 2. Stereotriads and the corresponding polypropionate stereopentads.

to aldehydes, which showed a high level of stereoselectivity, advancing significantly our collective capacity of creating stereogenic centers in acyclic molecules. They have been used successfully for the assembly of the four stereotriads. Other approaches based on the stereoselective transformations of cyclic and acyclic precursors produced these molecules, as well as higher analogues, attesting to the challenges and opportunities that the synthesis of polypropionate motifs and the related natural products provides.[10]

Yet, no single strategy has been reported leading directly to all 16 stereopentad diastereoisomers. Many of the approaches listed before used chiral reagents and took advantage of double asymmetric induction. Not surprisingly, mismatched scenarios were at times noticed. For instance, the addition of the well-known crotylboronate and the crotylborane on stereotriad aldehydes led to the 2,3-*anti*-3,4-*anti* polypropionate stereopentads with poor stereoselectivity.[5,6,11] To overcome this problem, Roush elegantly took advantage of the silicon hypervalence using crotyltrifluorosilanes for the elaboration of α,*β*-*anti*-polypropionate stereopentads from 2,3-*anti*-*β*-hydroxy aldehydes.[12] Unfortunately, aldehydes having a 2,3-*syn* relationship led to less impressive results. As for Marshall, he proposed a compelling strategy based on the reactions of chiral allenylzinc reagents with the propionate stereotriads previously obtained through the methodology developed in his group.[13] Only the α,*β*-*anti* stereopentad isomers can be obtained via this route. Six out of the eight possible polypropionate were constructed selectively, poor diastereoselectivity being noted with 2,3-*anti*-aldehydes and (*M*)-allenylzinc. Paterson also proposed a systematic approach to stereopentads that combines three steps: an aldol addition with enol borinates, a hydroxyl-directed ketone reduction, followed by a hydroboration of the terminal alkene.[4]

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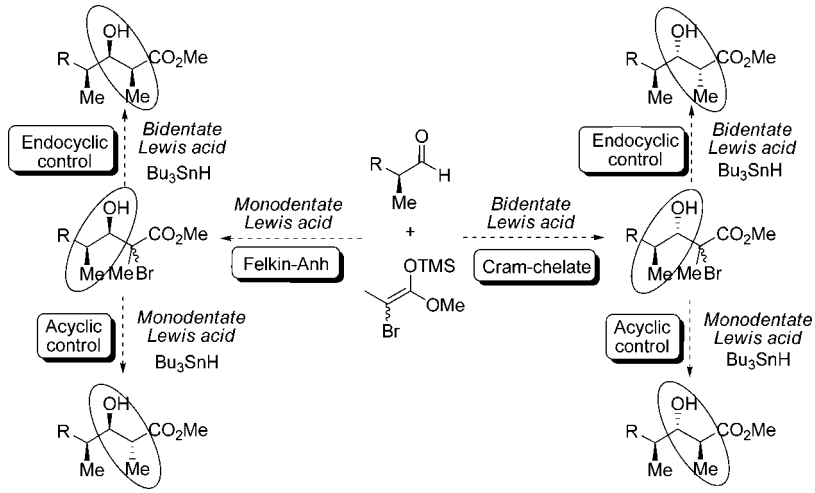


FIGURE 3. Mukaiyama and free radical hydrogen transfer approach to polypropionate construction.

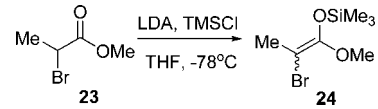
Twelve out of the 16 isomers were obtained directly.[14] All of the above-mentioned approaches provided important conceptual advancements to the field while pointing out the difficulties of creating stereogenic centers on acyclic molecules which possess a complex stereochemical environment.

Our group designed a conceptually different strategy in which no mismatched scenarios should be observed.[15] Central to our strategy is a substrate control approach involving the two reactions depicted in Figure 3. The first one, an aldol-like Mukaiyama reaction, involves a mixture of *E* and *Z* tetrasubstituted enoxysilanes bearing a bromide atom and an aldehyde in the presence of a Lewis acid. In this first step, we are only concerned about forming the carbon−carbon bond and creating the stereogenic center at C(3). Their 3,4-relative stereochemistry would be determined by the nature of the Lewis acid used and the transition states thus favored, as illustrated in Figure 3. The use of monodentate Lewis acid would lead to 3,4-*syn* isomers while bidentate Lewis acid to 3,4-*anti* isomers.

The second set of reactions used in this sequence involves the creation of a carbon-centered free radical at C(2), followed by a hydrogen transfer reaction. Prior to our studies, free radical intermediates were never seriously considered in the synthesis of acyclic complex molecules. Over the years, we found that Lewis acids are crucial in controlling the *anti*[16] and *syn*[17] relative stereochemistry between C(3) and the newly created C(2) stereogenic center. We observed that the presence of a heteroatom on the secondary carbon C(3) and of an ester at C(1) was critical for the diastereoselectivity.[16a]

Herein, we report the full details of our studies aiming at an iterative sequence using aldehydes derived from stereotriads **3**−**6**

SCHEME 1



(Scheme 1) for the synthesis of polypropionate stereopentads **7**−**22**.[18] Our investigation addresses the fundamental stereochemical issues originating from α,β-substituent effects in Mukaiyama aldol reactions and radical reductions. Interestingly, the success of the aldolization step is highly dependent on the stoichiometry and the nature of the Lewis acid used, especially under chelated control conditions. An application of our new strategy is outlined in the elaboration of the C(1)−C(11) fragment of zincophorin (Figure 1).

Results and Discussion

Development of the Mukaiyama Reaction. The enoxysilane **24** used in the aldol Mukaiyama has three important characteristics. First, it contains a bromide−carbon bond which, in the aldol product, will serve as a source of the carbon-centered free radical for the second step of our sequence. Second, the enoxysilane is tetrasubstituted and thus sterically congested. This will provide a significant advantage in the synthesis of stereopentads, whereas the 1,2-induction will be the stereocontrolling factor in the aldol step (vide infra).[19] Finally, it is important to note that a mixture of *E*- and *Z*-enoxysilanes is used, the stereochemistry at C(2) in the aldol product being irrelevant for the second step of our sequence. The enoxysilanes can be readily synthesized starting from the commercially available 2-bromopropionate **23** by using a standard enolization procedure (Scheme 1). The reaction can be performed on a significant scale (>250 mmol), and the enoxysilane **24**, present in a 4:1 *E*:*Z* selectivity, is stable for months when stored at −20 °C under inert atmosphere.

As illustrated in Scheme 2, the aldehydes **3**, **4**, **5**, **6**, **30**, and **34** were prepared from their corresponding ester precursors using

(14) The others were constructed by switching the terminal hydroxy group of isomers previously obtained. See ref 4.

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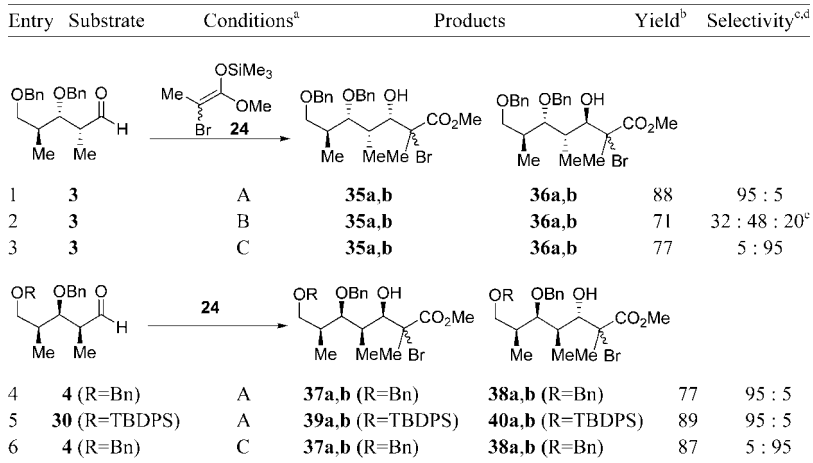
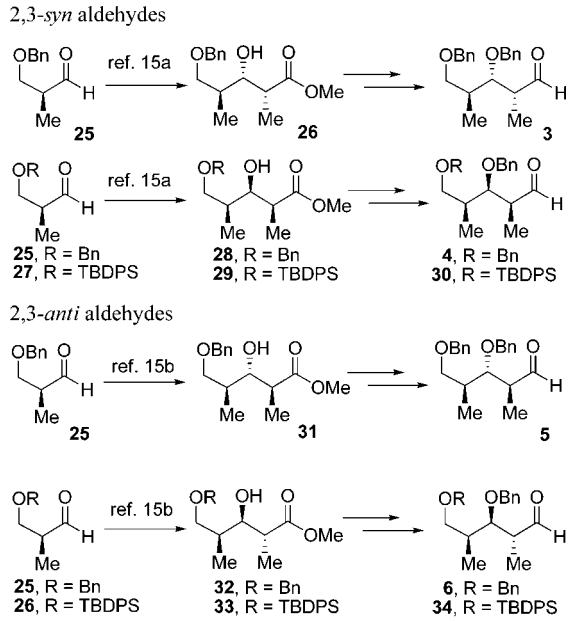
TABLE 1. Mukaiyama Aldolization with 2,3-*syn* Aldehydes 3, 4, and 30



Entry	Substrate	Conditions[a]	Products		Yield[b]	Selectivity[c,d]
1	**3**	A	**35a,b**	**36a,b**	88	95 : 5
2	**3**	B	**35a,b**	**36a,b**	71	32 : 48 : 20[e]
3	**3**	C	**35a,b**	**36a,b**	77	5 : 95
4	**4** (R=Bn)	A	**37a,b** (R=Bn)	**38a,b** (R=Bn)	77	95 : 5
5	**30** (R=TBDPS)	A	**39a,b** (R=TBDPS)	**40a,b** (R=TBDPS)	89	95 : 5
6	**4** (R=Bn)	C	**37a,b** (R=Bn)	**38a,b** (R=Bn)	87	5 : 95

[a] **Conditions A**: Reactions were conducted with 2.0 equiv of enoxysilane **24** followed by 1.2 equiv. $BF_3 \cdot OEt_2$ in CH_2Cl_2 (0.1 M) at −78 °C for 2 h, unless noted otherwise. **Conditions B**: Aldehydes were precomplexed with 1.1 equiv of $TiCl_3(OiPr)$ followed by the addition of 2.0 equiv of enoxysilane **24** in CH_2Cl_2 (0.1 M) at −78 °C for 2 h, unless noted otherwise. **Conditions C**: Aldehydes were precomplexed with 2.5 equiv of $TiCl_3(OiPr)$ followed by the addition of 2.0 equiv of enoxysilane **24** in CH_2Cl_2 (0.1 M) at −78 °C for 2 h, unless noted otherwise. [b] Isolated yields. [c] Product ratios were determined by ^1H analysis (400 or 500 MHz) of the crude reaction mixture. [d] In all cases, products were separable by chromatographic methods. [e] 20% of undesired 3,4-*syn* isomer was observed.

SCHEME 2



a sequence of protection and reduction/oxidation.[20] These esters were obtained using our approach to the propionate stereotriads as described before and used in our synthesis of the stereopentads.[15a,b]

The first group of aldehydes **3**, **4**, and **30** share a 2,3-*syn* relative stereochemistry. Opposing 1,2- and 1,3-stereoinductions are therefore possible when nucleophiles are added on such aldehydes when activated by monodentate Lewis acid. However, a high 3,4-*syn* diastereoselectivity was observed when $BF_3 \cdot OEt_2$ was added to these aldehydes followed with a mixture of enoxysilane **24** (Table 1, entries 1, 4, and 5). This is consistent with the predominance of 1,2-induction when sterically encumbered enoxysilane reagents are used.[19]

We were more concerned about the reactions involving those aldehydes activated by bidentate Lewis acids. The substituents at C(2) and C(3) being gauche to each other in these complexes, the energy necessary for their formation should therefore be increased. Many attempts to construct the Cram-chelated Mukaiyama aldol products using bidentate Lewis acids such as $TiCl_4$, $MgBr_2 \cdot OEt_2$, Et_2BOTf, $SnCl_4$, Me_2AlCl, etc. led to disappointing results. Interestingly, as we focused on lowering the titanium Lewis acidity, the use of $TiCl_3(OiPr)$ provided our first positive result, the aldol products **36** being obtained in good yield, albeit with modest Cram-chelate selectivity (Table 1, entry 2). Even more interesting was our observation that this drawback could be overcome by increasing the stoichiometry of the Lewis acid, as indicated by the impressive 3,4-*anti* stereoselectivity favoring compounds **36** when 2.5 equiv of $TiCl_3(OiPr)$ is used (entry 3). Similar results are obtained with aldehyde **4** (entry 6). The importance of the stoichiometry of the Lewis acid on the reaction outcome will be further discussed (vide infra).

The aldehydes **5**, **6**, and **34** having a 2,3-*anti* relative stereochemistry were then reacted with our enoxysilane **24**. As seen in Table 2, an excellent diastereoselectivity was noted when $BF_3 \cdot OEt_2$ was used as the Lewis acid, a 3,4-*syn* relative stereochemistry being induced (entries 1, 3, and 4). Interestingly, under Cram-chelated conditions, opposing 1,2- and 1,3-inductions are possible in these cases, both substituents being on the opposite face of the chelate intermediate. Fortunately, as seen in entry 5, an excellent ratio favoring the 3,4-*anti* products was noted using an excess of $TiCl_3(O$*i*-Pr) and aldehyde **6**.

Surprisingly, the Mukaiyama reaction of 2,3-*anti*-3,4-*anti* aldehyde **5** in presence of an excess of $TiCl_3(OiPr)$ was selective but much less efficient. The reaction time is longer, and the presence of α,β-unsaturated aldehyde was noted. Fortunately, in this case, the use of 1.1 equiv of $TiCl_4$ was very efficient, the major 3,4-*anti* products being obtained in good yield (entry 2). One should note that, under these conditions (1.1 equiv of $TiCl_4$), only degradation of the substrates was noted with aldehydes **3**, **4**, and **6**. As seen in Table 1 (entry 5) and Table 2 (entry 4), a silyloxyether can be used as the protecting group

(20) The crude β-benzyl aldehydes so prepared were very clean by ^1H NMR analysis and were used directly in the Mukaiyama reactions without chromatographic purification to avoid racemization. For all detailed procedures, see Supporting Information.

TABLE 2. Mukaiyama Aldolization with 2,3-*anti* Aldehydes 5, 6, and 34

Entry	Substrate	Conditions[a]	Products		Yield[b]	Selectivity[c,d]
1	**5**	A	**41a,b**	**42a,b**	84	95 : 5
2	**5**	B	**41a,b**	**42a,b**	77	5 : 95
3	**6** (R=Bn)	A	**43a,b** (R=Bn)	**44a,b** (R=Bn)	94	95 : 5
4	**34** (R=TBDPS)	A	**45a,b** (R=TBDPS)	**46a,b** (R=TBDPS)	92	95 : 5
5	**6** (R=Bn)	C	**43a,b** (R=Bn)	**44a,b** (R=Bn)	72	5 : 95

[a] **Conditions A**: Reactions were conducted with 2.0 equiv of enoxysilane **24** followed by 1.2 equiv of BF_3OEt_2 in CH_2Cl_2 (0.1 M) at −78 °C for 2 h, unless noted otherwise. **Conditions B**: Aldehydes were precomplexed with 1.1 equiv of $TiCl_4$ followed by the addition of 2.0 equiv of enoxysilane **24** in CH_2Cl_2 (0.1 M) at −78 °C for 2 h, unless noted otherwise. **Conditions C**: Aldehydes were precomplexed with 2.5 equiv of $TiCl_3(OiPr)$ followed by the addition of 2.0 equiv of enoxysilane **24** in CH_2Cl_2 (0.1 M) at −78 °C for 2 h, unless noted otherwise. [b] Isolated yields. [c] Product ratios were determined by ^1H analysis (400 or 500 MHz) of the crude reaction mixture. [d] In all cases, products were separable by chromatographic methods.

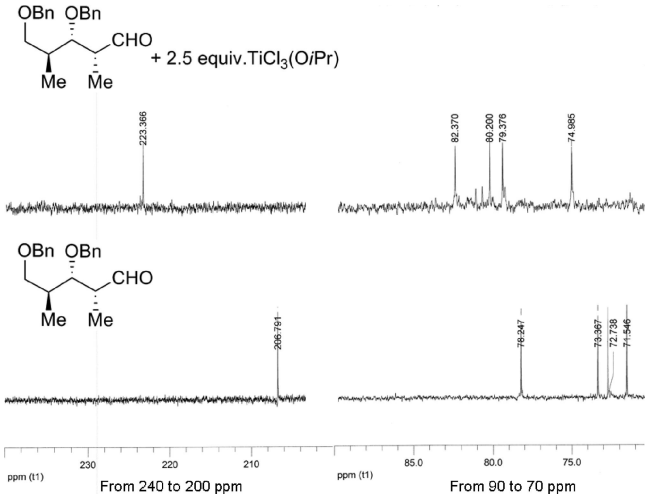


FIGURE 4. ^{13}C NMR spectra of aldehyde **3** with 0.0 and 2.5 equiv of $TiCl_3(OiPr)$ recorded at −20 °C.

of the primary alcohol in the $BF_3 \cdot OEt_2$ protocol (conditions A). Unfortunately, this protecting group in **30** and **34** is not compatible with the titanium-based Lewis acids. From the four stereotriads depicted in Figure 2, we have thus successfully synthesized, with high diastereoselectivities, the eight pairs of desired tertiary bromides.

NMR Studies of the Chelation-Controlled Mukaiyama Reaction. The peculiarity of the conditions necessary to achieve the aldolization in presence of $TiCl_3(OiPr)$ led us to seek more information on the nature of the intermediates implicated. Low-temperature ^{13}C NMR studies with 2,3-*syn*-3,4-*anti* aldehyde **3** were performed to better understand the impact of the stoichiometry of $TiCl_3(OiPr)$ (see Figure 4). Since no difference in the diastereomeric ratio is observed at −20 °C, the study was performed in CD_2Cl_2 at this temperature as the spectra were better defined.

The bottom spectrum in Figure 4 illustrates the ^{13}C NMR of the free aldehyde **3** in CD_2Cl_2 at the same concentration as the reaction studied. The spectrum of aldehyde **3** with 1.1 equiv of $TiCl_3(OiPr)$ was relatively complex, and no single discernible chemical entity could be identified: a mixture of different complexes and free aldehyde seemed to be present. Most importantly, no significant shift of the carbonyl signal was observed.

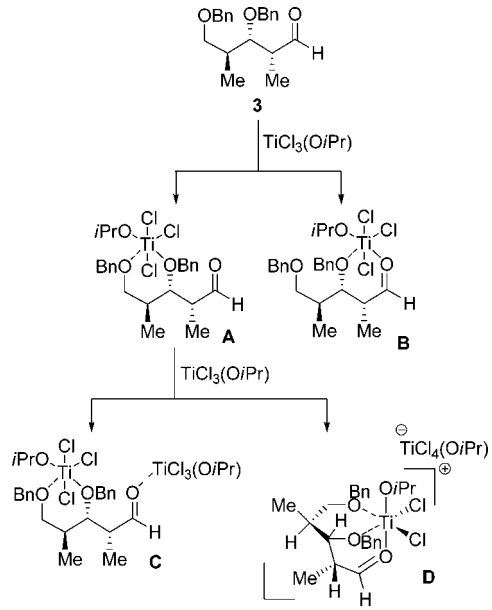
The spectrum corresponding to aldehyde **3** in presence of 2.5 equiv of $TiCl_3(OiPr)$ is shown (Figure 4). A striking 18 ppm downfield shift of the carbonyl is now noticed. Particularly interesting are the shifts of the carbon bearing OBn groups. The carbon C(3) bearing the secondary benzyloxy substituent now lies 5 ppm downfield. As for the carbon bearing the primary benzyloxy group, the interpretation is more difficult since the signal is in close proximity to benzylic carbons. However, since all these signals have been shifted downfield, one could conclude that all the oxygens of aldehyde **3** are involved in the complex when 2.5 equiv of $TiCl_3(OiPr)$ is used.

Our results indicated that, with 1 equiv of $TiCl_3(OiPr)$, a mixture of complexes are noted in solution. The activated aldehyde (monodentate, bidentate, or dimeric complexes) is present at a concentration below the sensitivity threshold of the NMR spectrometer. The diastereoselectivity observed is poor, suggesting that the Cram-chelate pathway sought after is not predominant and that monodentate activation (Felkin−Anh) is competitive. With 2.5 equiv of $TiCl_3(OiPr)$, the situation changes as the oxygen of the benzylethers at C(3) and C(5) seemed to be involved as the aldehyde.

Gau's studies on titanium complexes are instructive on the nature of the possible intermediates involved in our reactions.[21] He noted the prevalence of complexes having six ligands on the titanium center. He suggested, as well, that the binding ability of various chemical entities to titanium was such as *i*-PrO- > Cl- > THF > Et_2O > PhCHO > RCO_2Me. The following scenario is therefore suggested and depicted in Scheme 3. With 1 equiv, many complexes are in equilibrium. One could then suggest that complex **A** be significantly populated, both oxygens of the benzylethers being ligands to the titanium center. However, this is a nonreactive intermediate, the carbonyl being unactivated by the Lewis acid. Since the

(21) Gau, H.-M.; Lee, C.-S.; Lin, C.-C.; Jiang, M.-K.; Ho, Y.-C.; Kuo, C.-N. *J. Am. Chem. Soc.* **1996**, *118*, 2936.

SCHEME 3



ratio of aldol products is low, reactive complexes respectively leading to *syn* and *anti* have to be implicated. Complex **B** leading to the 3,4-*anti* product could obviously play a role. Similarly, complexes such as **C** derived from **A** with another equivalent of Lewis acid could lead to the 3,4-*syn* product. However, with an excess of $TiCl_3(OiPr)$, the thermodynamically preferred complex could involve both benzyloxy and the carbonyl. In order to accommodate three new ligands, a chloride has to be displaced, creating a cationic species stabilized by its counteranion as the *ate* complex **D**, thus the need for more than 2 equiv of Lewis acid.[22] Once the rigid three-points chelate is formed, 1,2-induction dictates the stereochemical outcome of the reaction, and because of the steric importance of the enoxysilane **24**, the 3,4-*anti* product is obtained.

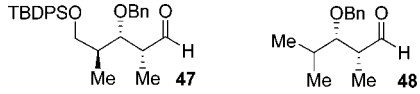


FIGURE 5. Structures of aldehydes **47** and **48**.

To support these observations, we noted that the remarkable shift of the aldehyde carbon was also observed (15 ppm) when the complex was prepared from 1.0 equiv of $TiCl_3(OiPr)$ followed by addition of 1.0 equiv of sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate (NaBARF). This salt is known to be easily solvated.[23] The BARF anion could thus act as the counteranion of the *ate* complex and sodium chloride be formed.[24] The relevance of the three-points chelation intermediate is also supported by the poor efficiency of the Mukaiyama aldol reactions with aldehydes **47** and **48** (Figure 5) in presence of an excess of $TiCl_3(OiPr)$. The bulky silyl protecting group of aldehyde **47** should prevent the chelation on this oxygen. In the case of aldehyde **48**, the oxygen at C(5) is absent. In both cases, the formation of the tridentate intermediate is therefore not possible. One will note that the desired 3,4-*anti* adducts could not be isolated, the elimination product of the starting material being observed as the major product in both reactions. In conclusion, an excess of $TiCl_3(OiPr)$ in presence of bisbenzyloxy aldehydes led to a three- points chelate as an *ate* complex in which the carbonyl was activated and where 1,2-induction dominated.

Development of the Radical Reduction. We have developed a strategy to control the stereochemical outcome of the second step of our sequence: the hydrogen transfer reaction. Once again, Lewis acids have a important role. Crucial to the success of these reactions is the presence of ester, amide, or ketone α to the secondary radicals.[16] The delocalization of the radicals in these functionalities induces the planarity of these tetrasubstituted "enol-like" radicals. The presence of a heteroatom on the stereogenic center adjacent to the delocalized radicals was shown to be important to control the diastereoselectivities sought after. Using a mixture of C(2)-diastereomeric Mukaiyama adducts, a 2,3-*syn* or 2,3-*anti* relative stereochemistry could be established in the reduced product, depending on the choice of Lewis acid in the hydrogen transfer reaction.

First, in the presence of aluminum-based Lewis acid, a 2,3-*syn* relative stereochemistry could be induced using the hydrogen transfer reaction by taking advantage of the endocyclic effect (Scheme 4).[17] In this case, the Lewis acid first reacts with the free hydroxyl group and a ligand is exchanged. Subsequently, a cyclic complex is created involving the carbonyl of the ester which will imbed the free radical center in a ring for the next step. This leads to the lower energy transition state **A** depicted in Scheme 4 with an attack from the top face by the trialkyltin hydride giving the 2,3-*syn* motif. One would note that a free hydroxyl group at C(3) could, through hydrogen bonding with the oxygen of the carbonyl, allow such reaction pathway in the absence of Lewis acid, albeit with low ratio.

A 2,3-*anti* relative stereochemistry in the stereopentad could also be obtained using the hydrogen transfer reaction. The *anti* diastereoselectivity depends, in this case, on the lowest energy transition state depicted in **B** (Scheme 5), whereas minimization of allylic 1,3-strain and intramolecular dipole−dipole are achieved.[16a,b] As stated before, when β-hydroxy esters are used, one has to be concerned by the existence of a competing pathway leading to the 2,3-*syn* product. Hydrogen bonding between the C(3) hydroxyl and the carbonyl needs to be eliminated in order to maximize the *anti* diastereoselectivity. Obviously, the introduction of a protecting group on the oxygen at C(3) could achieve such goal with the downside of adding steps to our process. We have discovered that Bu_2BOTf was an optimal solution to this problem.[15,25] Indeed, this Lewis acid reacts with the hydroxyl at C(3) to generate the dialkyl borinate in situ in the presence of a base, such as DIEA. The resulting product does not need to be isolated prior to the hydrogen transfer reaction, and the borinate can be released easily in the subsequent workup of the reaction. One should note that the borinate does not activate intramolecularly the carbonyl as demonstrated by the selective formation of the 2,3-*anti* product when one uses this Lewis acid. An additional property justified even more the use of the borinate. Indeed, we have noted that poor *anti* diastereoselectivity was observed when $R_2 = H$, a

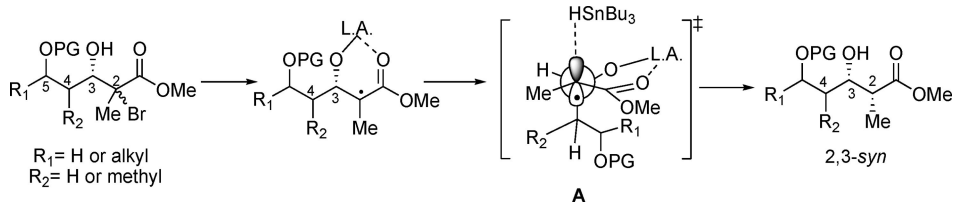
(22) This intermediate is not necessarily the reactive specie since the Curtin−Hammett principle can be evoked. However, many stereoselective nucleophilic additions with $TiCl_4$ and $SnCl_4$ have been explained by models supported by NMR spectroscopy. See: Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136, and references therein.

(23) Krossing, I.; Raabe, I. *Angew. Chem., Int. Ed.* **2004**, *43*, 2066.

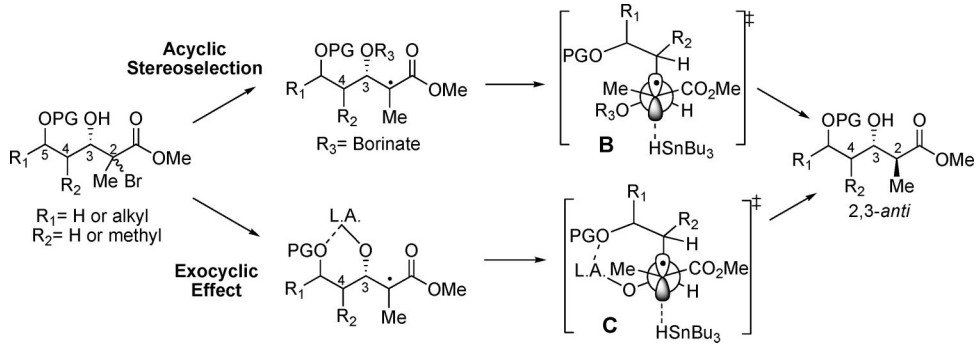
(24) Also used to support the formation of an "*ate*" complex with Me_2AlCl in Diels−Alder reactions. See: Castellino, S.; Wesley, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

(25) Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* **2001**, *3*, 1391.

SCHEME 4



SCHEME 5



scenario not faced in the context of this study. These ratios could be increased by taking advantage of the exocyclic effect (Scheme 5, transition state **C**).[16c,d] In this case, a ring (permanent or temporary) is created by linking together the hydroxyls at C(3) and C(5). We showed that boron-based Lewis acids could generate such temporary rings by chelating preferentially the C(3) and C(5) hydroxyl groups, even in the presence of the carbonyl at C(1).[25] As suggested in transition state **C**, an optimized orientation of the substituents at C(4) leads to increase energy differences between the *syn* and *anti* transition states, favoring the 2,3-*anti* product. However, we think it is very unlikely that such bidentate complexes would be formed in the compounds studied herein because of steric effects, especially in the case of the stereopentads. As stated before, the formation of the borinate was nevertheless important to prevent the endocyclic effect induced by a free hydroxyl.

Having the 4,5-s*yn* aldol adducts **35**−**39** in hand, we evaluated the free radical reductions of these substrates using Et_3B/O_2 as radical initiator. The 2,3-*syn* products were obtained when $AlMe_3$ was first precomplexed with the α-bromo-*β*-hydroxyesters prior to the hydrogen transfer reaction (Table 3, entries 1, 3, 5, 7, and 9). Regardless of the substrate relative stereochemistry, reductions under the endocyclic effect (Scheme 4) were highly efficient and 2,3-*syn* diastereoselective.

Boron-based Lewis acids were then evaluated, and impressive results were also obtained. As illustrated in entries 2, 4, 6, 8, and 10, very high 2,3-*anti* selectivity (>20:1) was observed, suggesting that the acyclic stereocontrol (Scheme 5, transition state **B**) was efficient in those cases.

Results of the stereoselective hydrogen transfer of the 4,5-*anti* bromoesters **41**−**45** are summarized in Table 4. Again, as with the 4,5-*syn* α-bromoesters, reactions were very selective when $AlMe_3$ was added prior to the reducing agent, the endocyclic pathway being at the origin of the 2,3-*syn* selectivity (Table 4, entries 1, 3, 5, 7, and 9).

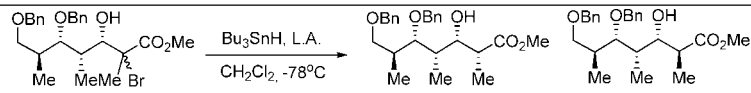
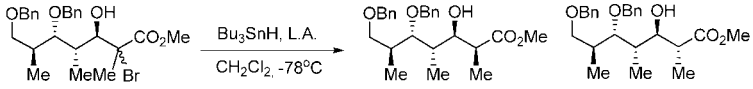
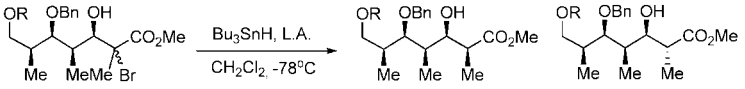
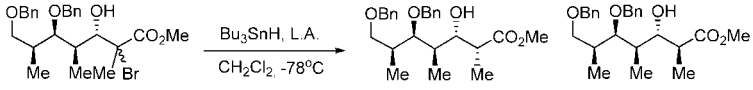
Having 12 out of the 16 stereopentads in hand, we then turned our attention to the 2,3-*anti* series using our boron-based Lewis acid strategy. One will note that the "arduously accessible"[8a] *all-anti* stereopentad **18** was obtained with excellent stereocontrol from the corresponding bromides **42a**,**b** (entry 4). For **41** and **44**, excellent selectivities were also observed (entries 6 and 8). An extremely surprising result was noted for the 3,4-*syn*-4,5-*anti*-5,6-*syn* tertiary bromides **43** and **45**. Indeed, having 15 out of 16 diastereoisomers in hand, we were astonished to find that the *anti* conditions led to a disappointing 1:1 ratio between the C(2) and C(3) in the reduced products. As noted before, simply changing the stereochemistry at C(5), as in **41**, gave an excellent diastereoselectivity. We are presently investigating the factors at the origin of the lack of stereoselectivity noted for this particular polypropionate motif. One hypothesis suggests that the folding of the chain in **43** and **45** is such that it interferes with the reagent trajectory (Bu_3SnH) from the bottom face of the radical, raising the energy of transition state **B**. Such putative conformational bias could be alleviated by introducing other torsional strains in this substrate. Linking the heteroatom at C(3) and C(5) through an acetonide was therefore considered. Another reason to do so streams from our previous studies on the exocyclic effect[17b] which suggested that the presence of a six-membered cycle adjacent to the carbon-centered radical (Scheme 5, path B) improved significantly the 2,3-*anti* ratios in such reactions. The bromides **53** and **54** were therefore prepared, and the hydrogen transfer reaction was then realized without Bu_2BOTf (Table 5). We were extremely pleased with the high diastereoselectivity noted favoring the desired 2,3-*anti* polypropionates **55** and **57**. *In conclusion, we achieve our goal to design a general and divergent strategy for the synthesis of the 16 stereopentads.*

Proof of Stereostructures. The proof of structures for all the polypropionate was realized by converting the stereopentads into their corresponding cyclic lactones for NMR and X-ray studies to confirm the substitution pattern.[26] An example of which is illustrated in Scheme 6. The *all-anti* stereopentad **18** was transformed into lactone **59** via a hydrogenolysis process. X-ray analysis confirmed the all-*anti* substitution pattern of molecule **18**.

Synthesis of the C(1)−C(11) Fragment of Zincophorin. Zincophorin[27] is a natural product that has attracted the attention of many groups because of its antibiotic profile and its

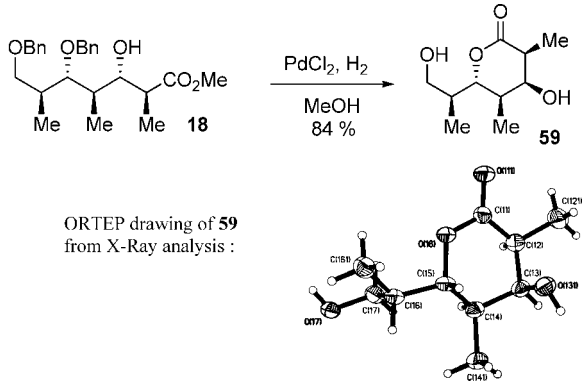
(26) See Supporting Information.

TABLE 3. Stereoselective Hydrogen Transfer Reactions with 4,5-*syn*-α-Bromoesters

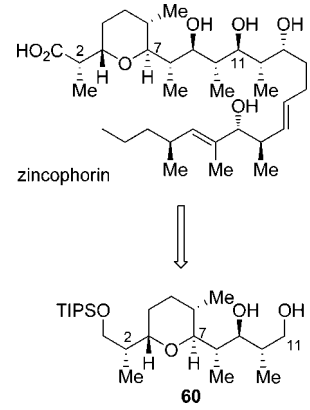
Entry	Substrate	Conditions[a]	Products	Yield[b]	Selectivity[c,d]
					
1	**35a**,**b**	A	**7**	**8** 84	95 : 5
2	**35a**,**b**	B	**7**	**8** 90	5 : 95
					
3	**36a**,**b**	A	**9**	**10** 83	95 : 5
4	**36a**,**b**	B	**9**	**10** 89	5 : 95
					
5	**37a**,**b** (R=Bn)	A	**11** (R=Bn)	**12** (R=Bn) 84	95 : 5
6	**37a**,**b** (R=Bn)	B	**11** (R=Bn)	**12** (R=Bn) 82	5 : 95
7	**39a**,**b** (R=TBDPS)	A	**49** (R=TBDPS)	**50** (R=TBDPS) 77	95 : 5
8	**39a**,**b** (R=TBDPS)	B	**49** (R=TBDPS)	**50** (R=TBDPS) 71	5 : 95
					
9	**38a**,**b**	A	**13**	**14** 81	95 : 5
10	**38a**,**b**	B	**13**	**14** 83	5 : 95

[a] **Conditions A**: Substrates (0.1 M) were pretreated with $AlMe_3$ for 45 min followed by Bu_3SnH (1.5 equiv) in CH_2Cl_2 at −78 °C. Addition of air and Et_3B (0.2 equiv) every 30 min was done until the reaction was complete by TLC. **Conditions B**: Substrates (0.1 M) were pretreated with iPr_2NEt (1.5 equiv) and Bu_2BOTf followed by Bu_3SnH (1.5 equiv) in CH_2Cl_2 at −78 °C. Addition of air and Et_3B (0.2 equiv) every 30 min was done until the reaction was complete by TLC. [b] Isolated yields. [c] Product ratios were determined by ^1H analysis (400 or 500 MHz) of the crude reaction mixture. [d] In all cases, products were separable by chromatographic methods.

SCHEME 6



SCHEME 7

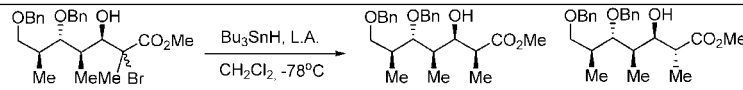
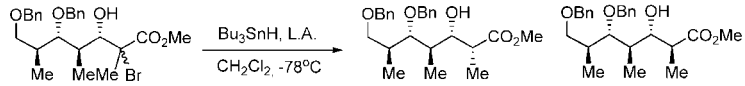
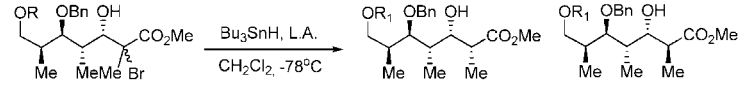
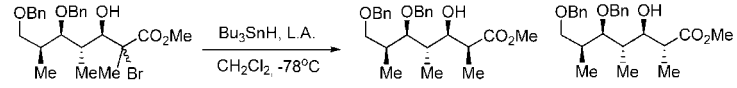


mechanism of action.[12,13,28] As seen in Scheme 7, Miyashita et al. has recently synthesized the C(1)−C(11) fragment **60** of zincophorin.[28d] The molecule **60** could be targeted starting from polypropionate stereopentad **16** which was synthesized in its enantiomerically pure version from Roche ester.

As depicted in Scheme 8, the stereopentad **16** was protected with a TES group and then transformed into alcohol **61**. Swern oxidation furnished the aldehyde which was treated under Horner−Emmons−Wadsworth conditions, thereby providing the α,β-unsaturated ester **62**. Chemoselective reduction of the double bond was realized in the presence of pyridine. The ester obtained was reduced and treated under the Swern conditions, leading to the formation of aldehyde **63**. Addition of $BiBr_3$ followed by the silyl enol ether **24** furnished the desired 3,7-*anti*-tetrahydropyrans **64a**,**b** with good yield (79%) in a 1:1 ratio at C(2).[29] These radical precursors were used as a mixture and

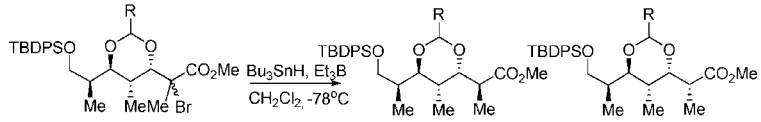
(27) Grafe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot.* **1984**, *37*, 836.

TABLE 4. Stereoselective Hydrogen Transfer Reactions with 4,5-*anti*-α-Bromoesters

Entry	Substrate	Conditions[a]	Products		Yield[b]	Selectivity[c,d]
						
1	**41a**,**b**	A	**15**	**16**	76	95 : 5
2	**41a**,**b**	B	**15**	**16**	85	5 : 95
						
3	**42a**,**b**	A	**17**	**18**	77	95 : 5
4	**42a**,**b**	B	**17**	**18**	70	5 : 95
						
5	**43a**,**b** (R=Bn)	A	**19** (R=Bn)	**20** (R=Bn)	81	95 : 5
6	**43a**,**b** (R=Bn)	B	**19** (R=Bn)	**20** (R=Bn)	84[e]	1 : 1
7	**45a**,**b** (R=TBDPS)	A	**51** (R=TBDPS)	**52** (R=TBDPS)	74	95 : 5
8	**45a**,**b** (R=TBDPS)	B	**51** (R=TBDPS)	**52** (R=TBDPS)	77[e]	1 : 1
						
9	**44a**,**b**	A	**21**	**22**	78	95 : 5
10	**44a**,**b**	B	**21**	**22**	79	5 : 95

[a] **Conditions A**: Substrates (0.1 M) were pretreated with $AlMe_3$ for 45 min followed by Bu_3SnH (1.5 equiv) in CH_2Cl_2 at −78 °C. Addition of air and Et_3B (0.2 equiv) every 30 min was done until the reaction was complete by TLC. **Conditions B**: Substrates (0.1 M) were pretreated with iPr_2NEt (1.5 equiv) and Bu_2BOTf followed by Bu_3SnH (1.5 equiv) in CH_2Cl_2 at −78 °C. Addition of air and Et_3B (0.2 equiv) every 30 min was done until the reaction was complete by TLC. [b] Isolated yields. [c] Product ratios were determined by ^1H NMR analysis (400 or 500 MHz) of the crude reaction mixture. [d] In all cases, products were separable by chromatographic methods. [e] Combined yields.

TABLE 5. Stereoselective Hydrogen Transfer Reactions

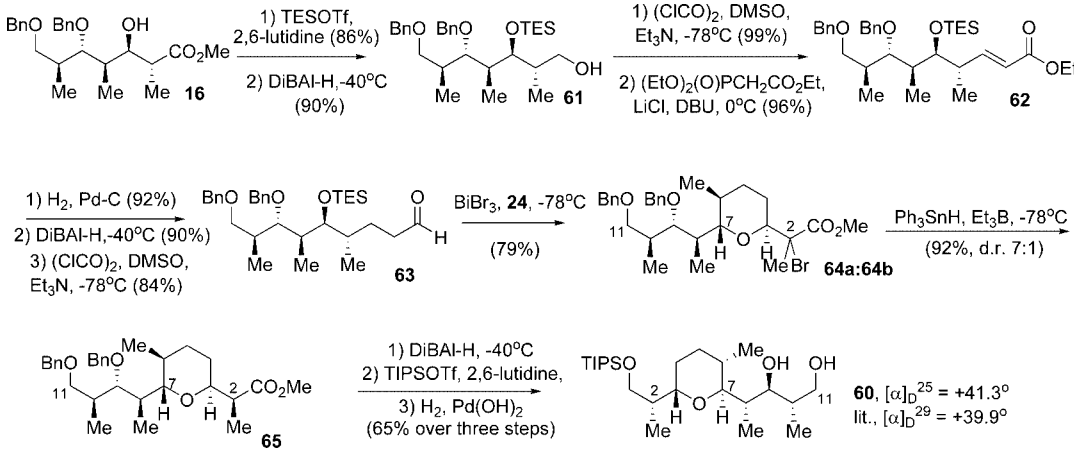
Entry	Substrate	Products		Yield[a]	Selectivity[b]
					
1	**53a,b** (R=H)	**55** (R=H)	**56** (R=H)	81	95 : 5
2	**54a,b** (R=PMB)	**57** (R=PMB)	**58** (R=PMB)	66	95 : 5

[a] Isolated yields. [b] Product ratios were determined by ^1H NMR analysis (500 MHz) of the crude reaction mixture.

were subjected to a radical reduction under the classical exocyclic effect in the presence of Ph_3SnH/Et_3B. This afforded **65** as a diastereomeric mixture (88:12) in a combined yield of 92% that was further separated by flash chromatography. Completion of the C(1)−C(11) fragment of zincophorin was done by reducing the ester, protecting the resulting hydroxyl with a TIPS, followed by removal of the benzyloxy groups to provide **60**, the structure of which being confirmed by comparison to the spectroscopic data reported in the total synthesis of Miyashita.

(28) (a) Song, Z.; Hsung, R. P.; Lu, T.; Lohse, A. G. *J. Org. Chem.* **2007**, *72*, 9722. (b) Song, Z.; Hsung, R. P. *Org. Lett.* **2007**, *9*, 2199. (c) Cossy, J.; Meyer, C.; Defosseux, M.; Blanchard, N. *Pure Appl. Chem.* **2005**, *77*, 1131. (d) Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4341. (e) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626. (f) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *Org. Lett.* **2003**, *5*, 4037. (g) Cossy, J.; Blanchard, N.; Defosseux, M.; Meyer, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2144. (h) Guindon, Y.; Murtagh, L.; Caron, V.; Landry, S. R.; Jung, G.; Bencheqroun, M.; Faucher, A.-M.; Guérin, B. *J. Org. Chem.* **2001**, *66*, 5427. (i) Booysen, J. F.; Holzapfel, C. W. *Synth. Commun.* **1995**, *25*, 1473. (j) Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103. (k) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.

SCHEME 8



Conclusion

In this report, we have described the first direct synthesis of all diastereomeric stereopentads. This integrated strategy could be a valuable tool for the determination of stereochemistry of unassigned structures of natural products, for the synthesis of a polyketide library, and for the study of unnatural analogues of important polyketides, which are all active areas of research.[10,30] Our stereodivergent synthesis starts from readily available materials which can be easily synthesized in both enantiomerically pure forms. Of crucial importance was the discovery of the efficiency of $TiCl_3(OiPr)$ in Mukaiyama aldolization to form a three-points-chelated intermediate. Central to our approach was the usefulness of the free-radical-based reductions developed by our group. Finally, a first application of this strategy was demonstrated with the stereoselective synthesis of a C(1)−C(11) building block for the construction of zincophorin.

Experimental Section[31]

General Procedure for the Mukaiyama Reaction−Felkin−Anh. (3*S*,4*S*,5*R*,6*S*)-Methyl-5,7-bis(benzyloxy)-2-bromo-3-hydroxy-2,4,6-trimethylheptanoate (43a,b). To a cold (−78 °C) solution of aldehyde **6** (1 equiv) in dry CH_2Cl_2 (0.1 M) was added bromoenoxysilane **24** (1.3 equiv). The mixture was stirred for 1 min at −78 °C then BF_3•OEt (1.5 equiv) was added slowly. The resulting solution was stirred for 2 h until the aldehyde was completely consumed, as determined by TLC. A saturated aqueous solution of NH_4Cl was poured into the reaction mixture. After the aqueous layer was extracted with ether, the organic layer was successively washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel using 20% EtOAc/hexane to give the desired compounds **43a**,**b** (yield = 94%). A 3:1 mixture of 2,3-*syn*:2,3-*anti* was observed on the basis of NMR data. **Diastereoisomer A:** Colorless oil, R_f = 0.29 (hexanes/EtOAc, 85:15); IR (neat) ν_{max} = 3529, 3062, 2949, 1735, 1453, 1268; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 10H), 4.57 (s, 2H), 4.48 (s, 2H), 4.34 (d, J = 4.4 Hz, 1H), 3.69 (s, 3H), 3.58 (dd, J = 4.0, 7.0 Hz, 1H), 3.45 (dd, J = 7.6, 9.0 Hz, 1H), 3.37 (dd, J = 5.6, 9.0 Hz, 1H), 2.90 (d, J = 4.4 Hz, 1H), 2.17−2.09 (m, 1H), 1.92−1.86 (m, 1H), 1.89 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 138.9, 138.6, 129.4, 129.4, 129.25, 129.20, 129.1, 129.07, 128.99, 128.94, 128.8, 128.64, 128.56, 128.22, 128.18, 128.02, 127.96, 127.87, 127.84, 127.78, 127.6, 127.5, 127.4, 83.0, 75.4, 74.1, 73.5, 73.3, 68.1, 53.4, 37.3, 35.8, 25.0, 24.9, 11.6, 11.5, 11.4; MS (ESI) m/z 493 (MH^+, 95), 475 (100), 369 (28), 277 (65); HRMS calcd for $C_{25}H_{34}BrO_5$ (MH^+) 493.1590, found 493.1598 (1.7 ppm). **Diastereoisomer B:** Colorless oil, R_f = 0.17 (hexanes/EtOAc, 85:15); IR (neat) ν_{max} = 3529, 3062, 2949, 1735, 1453, 1267; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 10H), 4.62 (d, J = 11.0 Hz, 1), 4.58 (d, J = 10.9 Hz, 1H), 4.49 (s, 2H), 4.43 (d, J = 5.8 Hz, 1H), 3.77 (s, 3H), 3.61 (dd, J = 5.8, 5.8 Hz, 1H), 3.50 (m, 2H), 2.90 (d, J = 5.8 Hz, 1H), 2.27−2.19 (m, 1H), 2.18−2.12 (m, 1H), 1.88 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.2, 138.8, 138.7, 128.65, 128.61, 128.1, 128.0, 127.9, 127.8, 83.8, 75.6, 75.0, 73.34, 73.31, 63.8, 53.5, 36.1, 24.6, 12.2, 11.8; MS (ESI) m/z 493 (MH^+, 100), 475 (90), 369 (28), 277 (55); HRMS calcd for $C_{25}H_{34}BrO_5$ (MH^+) 493.1590, found 493.1590 (0.1 ppm).

General Procedure for the Mukaiyama Reaction−Cram-Chelate. (3*R*,4*S*,5*R*,6*S*)-Methyl-5,7-bis(benzyloxy)-2-bromo-3-hydroxy-2,4,6-trimethylheptanoate (44a,b). To a cold (−78 °C) solution of the appropriate aldehyde **6** (1 equiv) in dry CH_2Cl_2 (0.1 M) was added slowly a freshly prepared solution of $TiCl_3(OiPr)$[32] (0.8 M in dry CH_2Cl_2), and the mixture was stirred for 15 min at −78 °C. Then, the bromoenoxysilane **24** (1.3 equiv) was added, and the resulting solution was stirred at −78 °C until the aldehyde was completely consumed, as determined by TLC. A saturated aqueous solution of NH_4Cl was poured into the reaction mixture. After the aqueous layer was extracted with ether, the organic layer was successively washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel using 15% EtOAc/hexanes to give the desired compounds **44a**,**b** (yield = 72%). A 3:1 mixture of 2,3-diastereoisomers was observed on the basis of NMR data. **Diastereoisomer A:** Colorless oil, R_f = 0.25 (hexanes/EtOAc, 85:15); IR (neat) ν_{max} = 3455, 2949, 1737, 1452, 1259; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 10H), 4.65 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.23 (d, J = 9.1 Hz, 1H), 3.93 (br s, 1H), 3.82 (dd, J = 3.0, 6.0 Hz, 1H), 3.79 (s, 3H), 3.37 (d, J = 3.4 Hz, 2H), 2.16−2.09 (m, 1H), 2.06−1.99 (m, 1H), 1.87 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.77 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 138.3, 138.1, 128.7, 128.4, 128.3, 127.8, 127.7, 127.6, 82.0, 75.8, 73.8, 73.5, 73.1, 67.2, 52.9, 39.5, 35.4, 21.2, 12.6, 11.9; MS (ESI) m/z 493 (MH^+, 100), 475 (21), 345 (90), 323 (60); HRMS calcd for $C_{25}H_{34}BrO_5$ (MH^+) 493.1590, found 493.1583 (−1.2 ppm). **Diastereoisomer B:** Colorless oil, R_f = 0.18 (hexanes/EtOAc, 85:15); IR (neat) ν_{max} = 3437, 3030, 2933, 1743, 1453, 1256; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 10H), 4.64 (d, J = 11.4 Hz, 1), 4.54 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.45 (d,

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J = 11.9 Hz, 1H), 4.28 (d, J = 4.2 Hz, 1H), 4.01 (dd, J = 4.1, 8.4 Hz, 1H), 3.79−3.72 (m, 1H), 3.74 (s, 3H), 3.41−3.33 (m, 2H), 2.20−2.12 (m, 2H), 1.91 (s, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 138.4, 138.1, 128.7, 128.6, 128.1, 128.0, 127.9, 83.1, 74.3, 73.8, 73.4, 53.4, 40.7, 36.1, 26.4, 14.7, 11.9; MS (ESI) *m/z* 493 (MH^+, 100), 345 (55); HRMS calcd for $C_{25}H_{34}BrO_5$ (MH^+) 493.1590, found 493.1596 (1.3 ppm).

General Procedure for Radical Reduction under Chelation-Control—The Endocyclic Effect. (2*S*,3*R*,4*S*,5*R*,6*S*)-Methyl-5,7-bis(benzyloxy)-3-hydroxy-2,4,6-trimethylheptanoate (21). To a stirred solution of the α-bromoesters **44a**,**b** (1 equiv) in dry CH_2Cl_2 (0.1 M) at −78 °C was added $AlMe_3$ (2.0 M in toluene, 3.0 equiv). The mixture was stirred for 1 h at the same temperature before adding Bu_3SnH (1.8 equiv) and Et_3B (0.2 equiv of a 1.0 M solution in hexane). The resulting solution was stirred at −78 °C, and 0.2 equiv of Et_3B then air were added each 30 min until the reaction was judged complete by TLC (around 3 h). 1,4-Dinitrobenzene (0.2 equiv) was then added to the solution, and the mixture was stirred for an additional 15 min at −78 °C. A saturated aqueous solution of NH_4Cl was carefully poured into the reaction mixture. After the aqueous layer was extracted with ether, the organic layer was successively washed with saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in ether (0.5 M) and mixed vigorously for 2 h with KF/Celite[33] (0.75 g/mmol of substrate) to eliminate tin residues. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 25% EtOAc/hexanes to give the desired compound **21** (yield = 78%). The ratio of 2,3-*syn*:2,3-*anti* was found to be >20:1 on the basis of NMR data: Colorless oil, R_f = 0.17 (hexanes/EtOAc, 80:20); IR (neat) ν_{max} = 3476, 3029, 2973, 1735, 1455; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 10H), 4.65 (d, J = 11.4 Hz, 1H), 4.50 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.04 (td, J = 2.6, 9.4 Hz, 1H), 3.88 (br s, 1H), 3.77 (dd, J = 2.4, 7.0 Hz, 1H), 3.71 (s, 3H), 3.37 (dd, J = 1.6, 6.3 Hz, 1H), 3.36 (s, 1H), 2.64 (qd, J = 3.7, 6.7 Hz, 1H), 2.17−2.11 (m, 1H), 1.97−1.88 (m, 1H), 1.14 (d, J = 7.1 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 138.5, 138.3, 128.7, 128.6, 128.0, 127.9, 83.0, 74.6, 74.3, 73.8, 73.3, 52.0, 42.3, 38.7, 35.9, 13.7, 11.7, 8.9; MS (ESI) *m/z* 415.1 (MH^+, 100), 307.1 (25), 181.0 (50); HRMS calcd for $C_{25}H_{35}O_5$ (MH^+) 415.2484, found 415.2479 (1.3 ppm).

General Procedure for Radical Reduction Acyclic Effect. (2*R*,3*RS*,4*S*,5*R*,6*S*)-Methyl-5,7-bis(benzyloxy)-3-hydroxy-2,4,6-trimethylheptanoate (22). To a stirred solution of the α-bromoesters **44a**,**b** (1 equiv) in dry CH_2Cl_2 (0.1 M) at −78 °C were added *i*Pr_2NEt and Bu_2BOTf. The mixture was stirred for 1 h at the same temperature before adding Bu_3SnH (1.5 equiv) and Et_3B (0.2 equiv of a 1.0 M solution in hexane). The resulting solution was stirred at −78 °C, and 0.2 equiv of Et_3B then air were added each 30 min until the reaction was judged complete by TLC (around 3 h). 1,4-Dinitrobenzene (0.2 equiv) was then added to the solution, and the mixture was stirred for an additional 15 min at −78 °C. A saturated aqueous solution of NH_4Cl was poured into the reaction mixture. After the aqueous layer was extracted with ether, the organic layer was successively washed with saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. To recover the resultant free alcohol, addition of H_2O_2 (30%, 1.5 mL/mmol of starting material in 5 mL of MeOH) in the reaction mixture was necessary. After the resultant solution was stirred for 2 h at 0 °C, organic solvents were then evaporated. The reaction mixture was quenched with brine and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was dissolved in ether (0.5 M) and mixed vigorously for 2 h with KF/Celite (0.75 g/mmol of substrate) to eliminate tin residues. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 25% EtOAc/hexanes to give the desired compound **22** (yield = 79%). The ratio of 2,3-*anti*:2,3-*syn* was found to be >20:1 on the basis of NMR data: Colorless oil, R_f = 0.15 (hexanes/EtOAc, 80:20); IR (neat) ν_{max} = 3498, 3030, 2972, 1737, 1455; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 10H), 4.63 (d, J = 11.0 Hz, 1H), 4.59 (d, J = 11.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.09 (dd, J = 4.3, 9.7 Hz, 1H), 3.70 (s, 3H), 3.67 (t, J = 5.6 Hz), 3.45 (dd, J = 6.4, 9.2 Hz, 1H), 3.38 (dd, J = 5.4, 9.2 Hz, 1H), 3.25 (d, J = 2.8 Hz, 1H), 2.58 (qd, J = 7.1, 9.7 Hz, 1H), 2.22−2.12 (m, 1H), 1.85−1.78 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 138.6, 128.6, 128.0, 127.9, 84.3, 75.9, 73.3, 73.3, 72.6, 52.0, 43.9, 36.6, 36.1, 14.0, 12.9, 10.5; MS (ESI) *m/z* 437 (M + Na, 100), 415 (MH^+, 88), 397 (60); HRMS calcd for $C_{25}H_{35}O_5$ (MH^+) 415.2484, found 415.2493 (2.0 ppm).

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Supporting Information Available: Experimental procedures and characterization data for compounds **5**, **6**, **15**−**22**, **28**, **31**−**34**, **41**−**45**, **47**, **49**−**51**, **53**−**59**, and **60**−**65**; determination of relative configuration for compounds **15**−**22**; experimental procedure for ^{13}C NMR spectra of compound **3** at low temperature with $TiCl_3$(O*i*Pr); CIF data for compound **59**. This material is available free of charge via the Internet at http://pubs.acs.org.

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