JOC Article

Regulated-Stereoselective Construction of Thirteen Stereogenic Centers Necessary for the Frame of (+)-Discodermolide, Based on Iterative Lewis Acid-Promoted Aldol Reactions

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The segments C_1-C_{13} and $C_{15}-C_{21}$ containing the 13 stereogenic centers required for the frame of (+)-discodermolide were synthesized in good to excellent enantio- and diastereoselectivities from a common racemic aldehyde, derived from 2-methyl-1,3-propanediol. The enantioselective aldol reactions of the racemic aldehyde with a silylketene acetal, derived from ethyl 2-bromopropionate, in the presence of chiral oxazaborolidinones, prepared in situ with *N*-*p*-toluenesulfonyl-(*R*)- and -(*S*)-valine and BH_3·THF, proceeded under kinetic control to give the stereotriads with a high degree of enantioselectivity. Enantioselective (chiral borane) and diastereoselective (BF_3·OEt_2 and $TiCl_4$) aldol reactions with the silylketene acetal, coupled with diastereoselective radical debrominations (Bu_3SnH, Et_3B, with or without $MgBr_2$), were used iteratively. This aldol reaction strategy for the construction of the polypropionate frame dramatically shortened the steps needed for the construction of the final segments.

Introduction

(+)-Discodermolide, a polypropionate-derived natural product, is known to be a potent microtubule-stabilizing agent, which retains activity against Taxol-resistant cancer.[1] While the compound is highly desirabe for use as an anticancer agent, immunosuppression,[1a] and cytotoxicity,[1b] it must be chemically synthesized, due to the scarcity of the natural product. In addition, a unique polyketide structure containing 13 stereogenic centers represents an attractive target for synthetic chemists. Since the determination of the absolute configuration of (+)-discodermolide by Schreiber,[2a,b] numerous efforts directed at its total synthesis have been made.[2,3] The highly stereoselective construction of the complex frame continues to be a challenging and attractive target for synthetic chemists. However, an approach to this problem based on Lewis acid-mediated aldol reactions has not been reported, probably because no reliable methodology has been established for diastereoselectively constructing *syn*- and *anti*-propionates in sequence. A more straightforward approach would be desirable for the versatile synthesis of such biologically active polyketide natural products. We recently succeeded in a highly enantioselective, divergent synthesis of *syn*- and *anti*-propionates, accomplished in a sequential procedure,[4] of a chiral oxazaborolidinone-promoted enantioselective aldol reaction with a silylketene acetal,[5] having a bromine at the α position, using a radical debromination reaction.[6] The approach has the potential for realizing a reliable procedure for the stereoselective divergent synthesis for the construction of polypropionate frames by combining highly diastereoselective Mukaiyama aldol reactions with the radical procedure.[7,8] Although it has been previously thought that iteration of aldol reactions is difficult and unavailable for use in polypropionate construction,[9] we confirmed the linear approach, as shown in Figure 1, which leads to the practical shortening of the number of

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steps involved in the synthesis of various types of polypropionate frames. As a result, we were able to use the aldol reaction strategy in the divergent construction of a variety of polypropionate frames. This unique approach permits the introduction of all 13 stereocenters of (+)-discodermolide by means of iterative Lewis acid-mediated aldol reactions accompanied by a radical reduction with a high degree of stereoselection. The strategy involved is described herein.

Results and Discussion

Retrosynthetic Analysis. With respect to an acyclic form related to (+)-discodermolide, our retrosynthetic analysis dissected the target molecule at both sides of C-14, thus generating segments **A** and **B** which contain the necessary 13 stereogenic centers (Scheme 1). A two-carbon unit at C-14 can be incorporated into segment **B** as a (*Z*)-vinyl iodide by known methods,[2e,f,10] prior to the developed palladium(0)-*cross*-coupling reaction between C-13 and C-14. Here segments **A** and **B** are the actual targets. The fragments are similar, as depicted by the squares in Scheme 1, which are bound in a series of stereotriads.[11] Smith effectively utilized a stereotriad as a precursor in the total synthesis of (+)-discodermolide.[2f] If an easier synthetic access to the enantiopure equivalents of the stereotriads were developed, it would directly permit a systematic approach to the synthesis of a natural product containing a variety of polypropionate units. In practice, a series of *chiral* stereotriads could be prepared from our chiral oxazaborolidinone-promoted aldol reaction of *racemic* aldehydes.[7] When the equivalent segments, **A** and **B**, are simply derived from the corresponding stereotriads, a versatile total synthesis of (+)-discodermolide could be achieved. The $C_{15}-C_{21}$ segment **A** could be prepared via two aldol reactions (providing two *syn*-propionates) at the positions indicated by the two slanted lines while the C_1-C_{13} segment **B**, having eight stereogenic centers, is shown by four slanted lines indicating suitable positions for bond formation by four sequential aldol reactions (providing one acetate, two *anti*-propionates, and one *syn*-propionate). Thus, a quite simple retrosynthetic route to (+)-discodermolide could

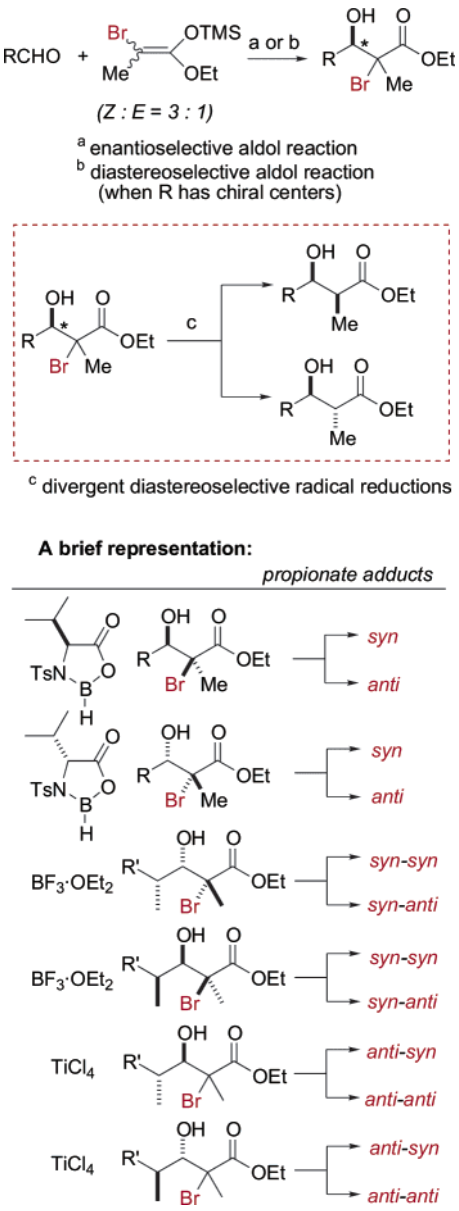

FIGURE 1. Enantioselective or diastereoselective approach to propionate units.

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(8) A similar approach with selenides has been reported but it was limited to the α-methyl-*β*-protected-oxy aldehydes, not bearing the other substituent at the *β* position, which is essential for a model of aldehydes toward the construction of polypropionate frameworks: (a) Guindon, Y.; Houde, K.; Prévost, M.; Cardinal-David, B.; Landry, S. R.; Daoust, B.; Bencheqroun, M.; Guérin, B. *J. Am. Chem. Soc.* **2001**, *123*, 8496−8501. (b) Guindon, Y.; Prévost, M.; Mochirian, P.; Guérin, B. *Org. Lett.* **2002**, *4*, 1019−1022.

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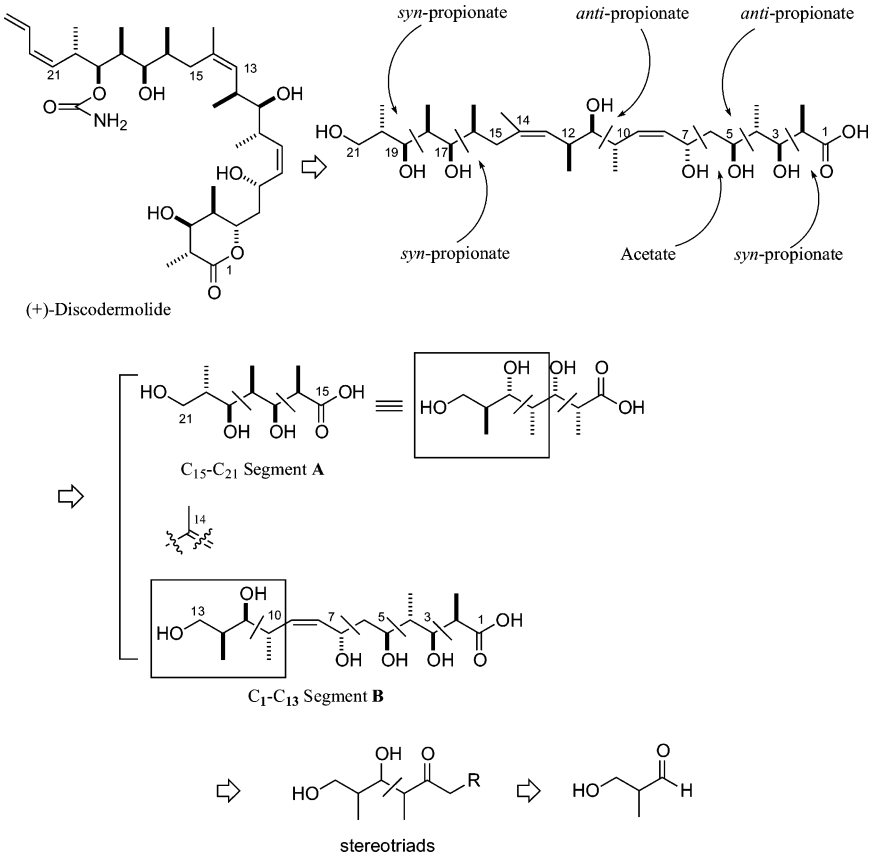
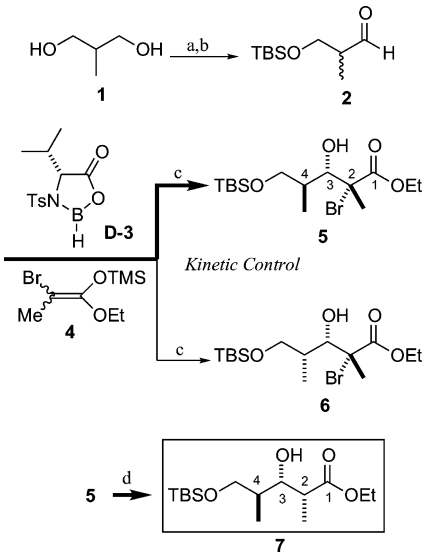
SCHEME 1. A Retrosynthesis Based on Iterative Lewis Acid-Promoted Aldol Reactions



be developed, where the use of enantioselective and diastereoselective aldol reactions is a prerequisite for successful performance.

Enantioselective Synthesis of Starting Stereotriads. A versatile asymmetric approach, starting from the achiral diol **1** via the racemic aldehyde **2** to give the enantiopure stereotriad **7** of segment **A**, which has the same stereochemistry with different functionality as Smith's stereotriad,[2f] and the enantiopure unit **16**, equivalent to the left-hand part of the segment **B**, is described as follows. The enantioselective synthesis of versatile stereotriads was designed in the form of a sequence of chiral oxazaborolidinone-promoted asymmetric aldol reactions of racemic aldehyde **2**, derived from the readily available achiral diol **1**,[12] with silylketene acetal **4**,[13] followed by a radical debromination reaction.[4] The reaction sequences are shown in Scheme 2. After the monoprotection of **1** with TBSCl and NaH, a Swern oxidation gave **2** in good yield. In the presence of a stoichiometric amount of chiral borane **D-3**, prepared in situ by stirring *N*-*p*-toluenesulfonyl-(*R*)-valine (D-TsVal) and BH_3·THF in CH_2Cl_2 at 0 °C, the aldol reaction of **2** with **4** was carried out at −78 °C for 3 h. The reaction proceeded smoothly to give a mixture of aldol adducts in 85% yield. The mixture consisted of a nearly 1:1 ratio of 2,3-*syn*-3,4-*anti* **5** and 2,3-*syn*-3,4-*syn* **6** with a small amount of isomers at C-2. The 2,3-syn selection is known[14] to be characteristic of the chiral oxazaborolidinone-promoted aldol reaction with **4** but the selection is unnecessary for the diastereoselection of debromination at C-2 because the stereocenter is reformed via a radical. The most impor-

SCHEME 2[a]



[a] Reaction conditions: (a) TBSCl, NaH, THF, rt, 15 h (88%). (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, Et_3N, 0 °C (82%). (c) Chiral oxazaborolidinone-promoted aldol reaction of **2** with **4** in the presence of a stoichiometric amount of **D-3** in CH_2Cl_2 at −78 °C for 3 h gave a 1:1 mixture of enantiopure **5** and **6** in 82% yield and then by using flash column chromatography **5** was easily separated. (d) Bu_3SnH, Et_3B, $MgBr_2$·OEt_2, 0 °C, 3 h: chelation-controlled debromination resulted in good 2,3-syn selection, 10:1 (80%).

(12) 2-Methyl-1,3-propanediol was purchased from Aldrich.

(13) The silylketene acetal **4** (*Z*:*E* = 3:1), which accompanies the corresponding C-silyl ester, by trapping the lithium enolate with TMSOTf.

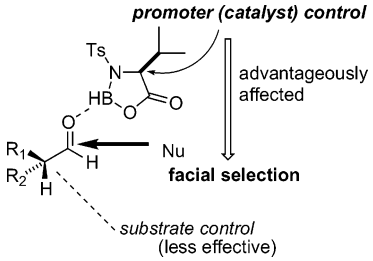
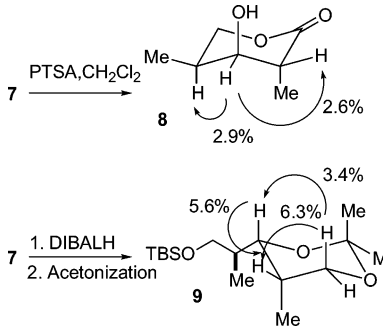


FIGURE 2. Promoter (catalyst) control.

SCHEME 3[a]



[a] Arrows indicate NOE's interactions.

tant aspect of this step is the almost complete selection in the creation of the stereogenic center at C-3 of **5** and **6** (>98% ee, determined by chiral HPLC), which is kinetically controlled only by the stereocenter of promoter **D-3** without any influence by the existing α-chirality of aldehyde **2**, that is, the so-called "catalyst (promoter) control in acyclic stereoselection", as shown in Figure 2.[15] The desired bromo aldol adduct, **5**, was easily separated by silica gel flash column chromatography. When a solution of **5** in CH_2Cl_2 was exposed to Bu_3SnH (5 equiv) and Et_3B (1 equiv) in the presence of $MgBr_2{\cdot}OEt_2$ (7 equiv) at 0 °C for 3 h, a smooth debromination reaction took place to give 2,3-*syn*-3,4-*anti* **7** (stereotriad) in 80% yield. The stereochemistry of **7** was confirmed by *J* values and NOE measurements of cyclic **8** and **9**, derived from **7**, as indicated in Scheme 3. The preferential syn selection of a 10:1 ratio can be rationally explained by the chelation control assisted by magnesium where R merely plays the role of a bulky substituent, not as a chirality-affecting component, as shown in Figure 3.[16]

The preparation of the C_1-C_{13} segment **B** also started with the chiral oxazaborolidinone (**L-3**)-promoted asymmetric aldol reaction of the same racemic aldehyde, **2**, with the silylketene acetal, **4**, in a manner similar to that described above. The satisfactory asymmetric induction guaranteed an *R* configuration at C-3 controlled by **L-3** in the resulting stereotriads, **11** and **12**. Conversion of the necessary aldol adduct, **11**, to cyclic compound **13** was required because **13** might be prone to allow a high 2,3-anti diastereoselection through the so-called "*exo*-cyclic

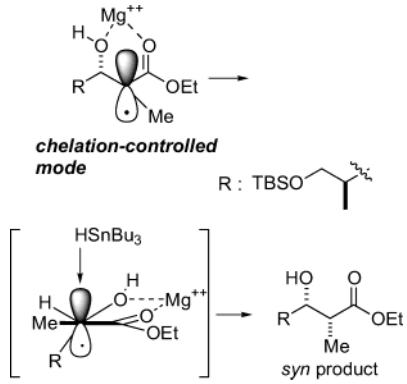


FIGURE 3. A transition state to *syn*-propionate.

effect"[17] in the subsequent debromination process. However, during the acidic deprotection of **11**, it, unfortunately, underwent cyclization to the corresponding δ-valerolactone, **14**.[18] We, therefore, selected an alternative route to the 2,3-*anti*-3,4-*syn* stereotriad, **16,** by conversion from 2,3-*syn*-3,4-*anti* **7**, having a reverse stereochemical array relative to **16**, where **7** and **16** are correlated to the C_2 symmetry on C-3. Reversing the stereochemistry of **7** to that of **16** was anticipated by replacing the functional groups at both terminals of **7**. Actually, the desired stereotriad, **16**, was obtained after the following five-step reaction sequence: TBS protection, DIBALH reduction to the corresponding alcohol, TBDPS protection, selective deprotection of the primary TBS group, and a Swern oxidation in good overall yield (Scheme 4). Thus, the first three stereogenic centers in segment **B** could be eventually introduced from the same starting compound as was used for segment **A**. However, a more direct route to the stereotriad, **16**, would be desirable. A resistant protection group against acidic conditions in the place of the TBS group of **11** for the terminal hydroxy function is needed so as to prevent the δ-lactonization. A TBDPS protecting group was chosen to realize the desired route. The aldol reaction of the TBDPS protected aldehyde **18** with **4** in the presence of L-**3** resulted in almost complete kinetic resolution to give a mixture of the expected aldols, **19** and **20**. The desired **19** was easily separated by silica gel flash column chromatography. Since we have recently improved a process for obtaining a high anti selection in radical debrominations without assistance by the *exo*-cyclic effect,[7] the cyclization of **19** to the corresponding acetonide was not attempted at this stage. The anti selection of the debromination (Bu_3SnH/Et_3B/toluene) can be reliably achieved with the corresponding MOM-protected compounds in good selectivity (~10:1). The aldol **19** was then protected with a MOM group to give **21** in good yield. The MOM-protected **21** underwent the

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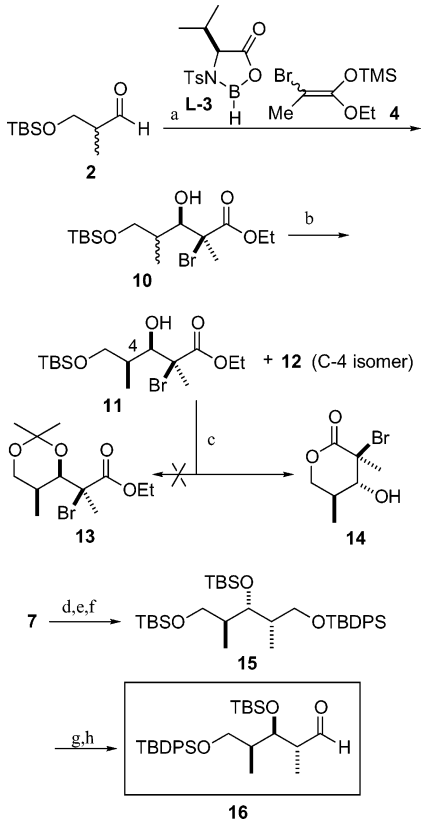
(18) A complete selection in the radical debromination of a series of δ-valerolactones, like **14**, was observed to lead an unexpected route to acyclic skeltons: Kiyooka, S.-i.; Li, Y.-N.; Shahid, K. A.; Okazaki, M.; Shuto, Y. *Tetrahedron Lett.* **2001**, *42*, 7299−7301.

SCHEME 4[a]

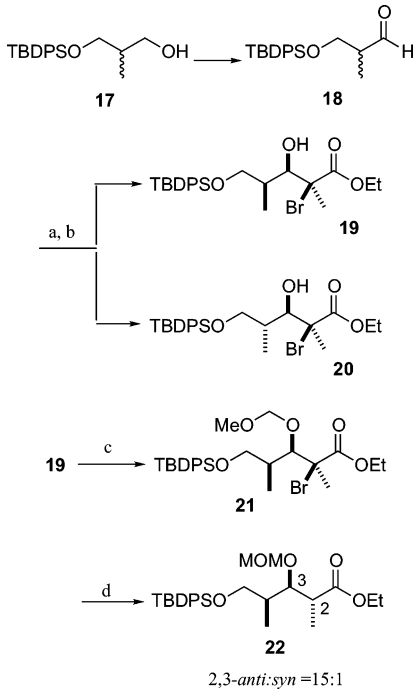


[a] Reaction conditions: (a) L-TsValine, BH_3·THF, **4**, −78 °C, 10 h (80%). (b) Silica gel column chromatography. (c) PTSA, MeOH, rt, 1 h (95%). (d) TBSOTf, 2,6-lutidine, rt, 1 h (87%). (e) DIBALH, CH_2Cl_2, −78 °C, 3 h (80%). (f) TBDPSCl, imidazole, CH_2Cl_2, rt, 1 h (92%). (g) PTSA, MeOH, rt, 20 h (90%). (h) Swern oxidation (87%).

debromination by treatment with Bu_3SnH and Et_3B in toluene at −78 °C to give 2,3-*anti*-3,4-*syn* **22** with a high anti selectivity (15:1), which is adequate for **16** (Scheme 5). The β-methoxymethyl moiety presumably assists the dipole mode in the debromination process, since it is enhanced by an additional oxygen atom, and furthermore the β-R substituent merely functions as a bulky group, as indicated in Figure 4. The conversion of **22** to **16** was performed as follows: $TiCl_4$ treatment of **22** led to the facile deprotection of the MOM group without affecting the TBDPS function to give **23**, followed by TBS protection (**24**), DIBALH reduction (**25**), and a Swern oxidation under standard conditions to give **16** in good overall yield, as shown in Scheme 6. As a result of examining the two routes to **16**, the number of steps is nearly the same.

Synthesis of Segment A.[19] The synthesis of **31** as a synthetic equivalent to segment **A** is shown in Scheme 7. Alcohol **7** was protected by treatment with PMBCO(=NH)CCl_3 and TfOH to give the corresponding *p*-methoxybenzyl ether, **26**, in 67% yield. DIBALH reduction of **26** gave aldehyde **27** directly in 86% yield with a small amount of over-reduction product **28**, which was recycled to **27** via a Swern oxidation. The BF_3·OEt_2-mediated diastereoselective aldol reaction (CH_2Cl_2, −78 °C, 1 h) of **27** with **4** resulted in the highly 3,4-syn

SCHEME 5[a]



[a] Reaction conditions: (a) Chiral oxazaborolidinone-promoted aldol reaction, **L-3**, **4** (75%). (b) Separation (SiO_2). (c) Methylal, P_2O_5 (92%). (d) Bu_3SnH, Et_3B, toluene, −78 °C (89%).

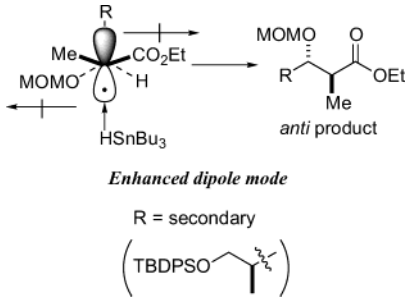


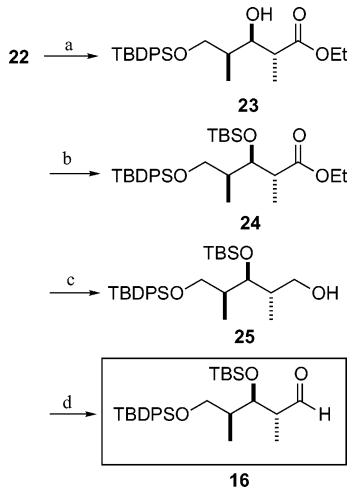
FIGURE 4. More effective assistance with methoxymethyl moiety.

selective formation of 2,3-*syn*-3,4-*syn* aldol adduct **29** in 65% yield along with a high selection at C-2.[14] This 3,4-syn selection (~98% de), assisted by BF_3, is known[20] to be reliable, which can be rationally interpreted by using a Felkin-Anh model without any influence of the residual stereocenters at the β and γ positions of the substrate aldehyde, as shown in Figure 5. The stereochemistry of **29** was determined by *J* values and NOE measurements of cyclic **32**, derived from **29** by treatment with DDQ, as shown in Scheme 8. The subsequent debromination reaction (Bu_3SnH, Et_3B, CH_2Cl_2) in the presence of $MgBr_2$·OEt_2 at −78 °C for 3 h gave the desired 2,3-*syn*-3,4-*syn*-4,5-*syn*-5,6-*anti* compound, **30**, in 81% yield (2,3-syn selectivity = 7:1). Even in the presence of a nonprotected β-OH group, the chelation-controlled syn product was obtained as the major product, as previously shown in Figure 3. The stereochemistry of **30** was determined by *J* values and NOE measurements of cyclic **33**, derived

(19) Shahid, K. A.; Li, Y.-N.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S.-i. *Tetrahedron Lett.* **2002**, *43*, 6373−6376.

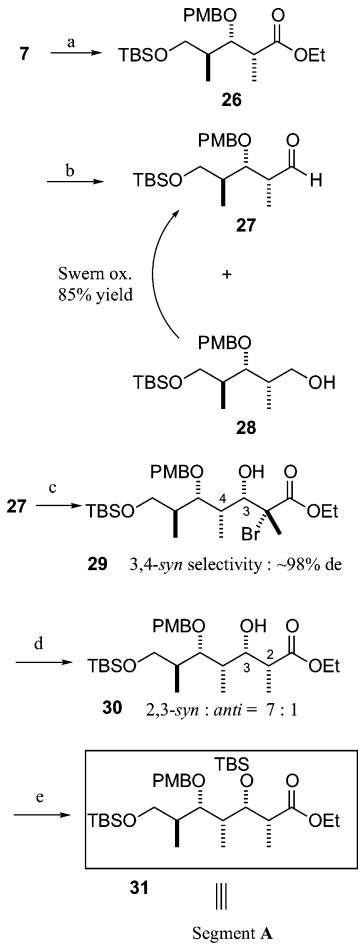
(20) Kiyooka, S.-i.; Shahid, K. A.; Murai, K.; Li, Y.-N.; Okazaki, M.; Shuto, Y. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2343−2349.

SCHEME 6[a]



[a] Reaction conditions: (a) $TiCl_4$, CH_2Cl_2 (89%). (b) TBSOTf, 2,6-lutidine (93%). (c) DIBALH (89%). (d) Swern oxidation (87%).

SCHEME 7[a]



[a] Reaction conditions: (a) $PMBCO(=NH)CCl_3$, TfOH, Et_2O, rt, 15 h (67%). (b) DIBALH, CH_2Cl_2, −78 °C, 3 h (86%). (c) $BF_3{\cdot}OEt_2$, **4**, CH_2Cl_2, −78 °C, 1 h (65%). (d) Bu_3SnH, Et_3B, CH_2Cl_2, $MgBr_2{\cdot}OEt_2$, −78 °C, 3 h (81%). (e) TBSOTf, 2,6-lutidine (95%).

from **30** by treatment with LAH, followed by acetonization, as shown in Scheme 8. This diastereoselective sequence, using the Mukaiyama aldol reaction, followed by debromination is an effective approach to the reliable

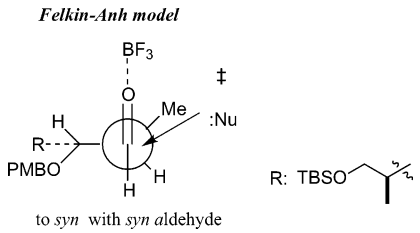
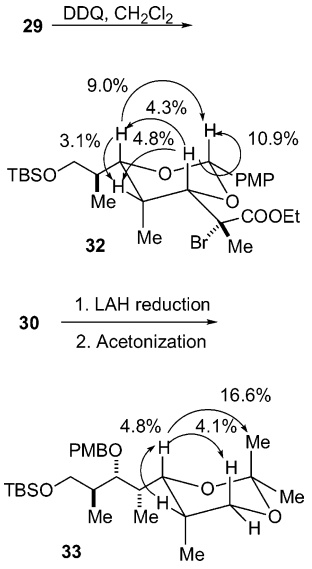


FIGURE 5. 1,2-Syn predominance enhanced by $BF_3{\cdot}OEt_2$.

SCHEME 8 [a]



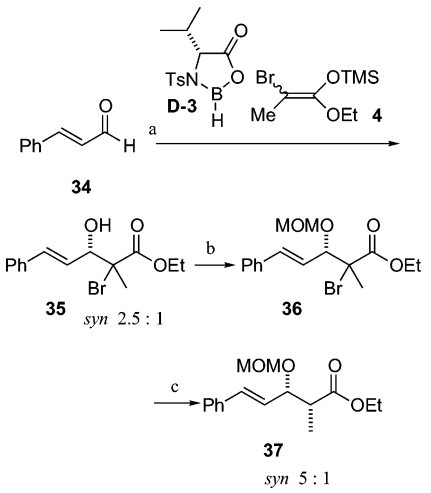
[a] Arrows indicate NOE's interactions.

construction of *syn*-polypropionate frames. A similar approach also has been reported by other workers.[21] The protection of alcohol **30** was carried out without incidents to give TBS ether **31**, a synthetic equivalent of segment **A**, in 95% yield. Thus, a versatile and systematic asymmetric approach was developed for the preparation of segment **A** for the synthesis of (+)-discodermolide, based on the chiral oxazaborolidinone-promoted asymmetric aldol reaction of racemic aldehyde **2** with **4** with respect to catalyst (promoter) control and the following diastereoselective BF_3-mediated aldol reaction. The above results suggest that the sequence of enantioselective and/or diastereoselective aldol reactions with silylketene acetal **4**, coupled with diastereoselective debromination reactions, provides a practical and useful method for the stereoselective syntheses of a series of polypropionates.

Construction of the Stereogenic Centers at C-7. On our sequential strategy of an aldol reaction followed by debromination, there is an uncertainty as to whether it works well or not in the case involving a double bond, e.g., α-bromo-*γ*,*δ*-unsaturated esters, because the double bond could capture radicals formed in the radical debromination process. A sequential reaction was tested with use of *trans*-cinnamaldehyde. The debromination reaction

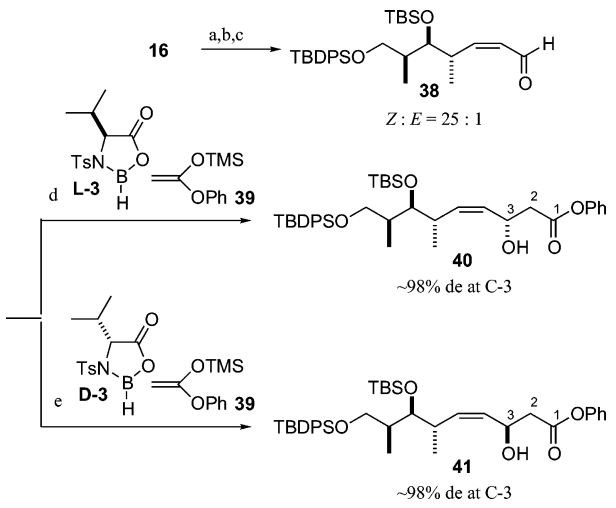
(21) In a more simple system, the diastereoselective synthesis of 2,3-*anti*-3,4-*anti* and 2,3-*anti*-3,4-*syn* propionates has recently been reported by using a tandem sequence of Mukaiyama aldol reaction of α-methyl-*β*-protected-oxypropanal with a selenoenoxysilane and the following hydrogen transfer reaction: Guindon, Y.; Prévost, M.; Mochirian, P.; Guérin, B. *Org. Lett.* **2002**, *4*, 1019−1022.

SCHEME 9[a]



[a] Reaction conditions: (a) D-Ts-Valine, **4**, BH_3·THF, −78 °C, 3 h (78%). (b) $CH_2(OCH_3)_2$, $CHCl_3$, P_2O_5, rt, 2 h (96%). (c) $MgBr_2$·OEt_2, Bu_3SnH, Et_3B, CH_2Cl_2, −78 °C, 3 h (89%).

SCHEME 10[a]



[a] Reaction conditions: (a) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, 18-crown-6, KHMDS, THF, −78 °C, 15 h (95%). (b) DIBALH, CH_2Cl_2, −78 °C, 3 h (90%). (c) Swern oxidation (86%). (d) L-TsValine, BH_3·THF, **39**, −78 °C, 16 h (86%). [e] D-TsValine, BH_3·THF, **39**, −78 °C, 16 h (83%).

with the MOM-protected intermediate **36** proceeded to give the corresponding propionate aldol **37**, with no damage of the double bond, in 87% yield with syn predominance (5:1), as shown in Scheme 9. This result allowed us to construct the stereogenic center at C-7 of segment **B** using the following strategy. The aldehyde **16** was converted into the corresponding *Z*-enoate in 95% yield (*Z*:*E* = 25:1), using the Still procedure of the Horner−Wadsworth−Emmons reaction with $(CF_3CH_2O)_2$-$POCH_2COOCH_3$; when $(CH_3)_2POCH_2COOCH_3$ was used under similar conditions, the *E* isomer was formed predominantly (10:1).[22] After DIBALH reduction of the *Z*-enoate, followed by a Swern oxidation to the *Z*-enal **38**, **38** was subjected to the aldol reaction with use of silyl nucleophile **39**, related to an acetate equivalent, to create the next chiral center. At this stage, the chiral oxazaborolidinoine-promoted asymmetric aldol reaction played an extraordinary role in creating the expected chiral center at C-7 of segment **B**. When we used **L-3**, the expected alcohol, **40**, having a 3,6-syn relationship, was obtained with almost complete selection, while **D-3** led to the corresponding epimeric adduct, **41**, having a 3,6-anti relationship, with the same level of selection (Scheme 10). The configuration created at C-3 in these aldol adducts likely arose from the stereocenter of the promoters used in a superior manner of catalyst (promoter) control on facial selection, that is, the existing chiral centers of the starting aldehyde **38** had no effect at all on the stereochemical outcome. The approach of silyl nucleophile **39** to the carbonyl group from the opposite side of the isopropyl moiety of the chiral borane was allowed, thus stabilizing each transition state, **A** and **B**, as depicted in Figure 6 (along with Figure 2).[23] *This is an outstanding example of catalyst (promoter) control.*

Synthesis of Segment B. [24] An ideal construction of the stereogenic centers at C-4 and C-5 of segment **B** would be to create an anti configuration through an *exo*-cyclic effect via the use of a six-membered cyclic compound available for the 1,3-dihydroxy system. For the construction of the necessary cyclic moiety, a useful protection group for the hydroxy function at C-3 of **40** was deemed to be a *p*-methoxybenzyl (PMB) moiety because it would be expected to undergo an advantageous cyclization by DDQ oxidation.[25] The hydroxy group of **40** was protected by treatment with methoxybenzyl-2,2,2-trichloroacetimidate ($PMBCO(NH)CCl_3$)/cat. TfOH to give **42** in 88% yield. The ester function was converted to the corresponding aldehyde function via alcohol **43** by means of a couple reactions of DIBALH reduction (74% yield), followed by a Swern oxidation (88% yield) to afford **44**. The following aldol reaction of **44** with **4** in the presence of **D-3** proceeded in fairly good yield with excellent 98% de, in which other isomers were not found. The oxidative cyclization of **45** with DDQ gave the corresponding *p*-methoxybenzylidene acetal, in which the newly formed stereocenter bearing a PMP group in the ring was determined to be epimeric, followed by debromination with Bu_3SnH/Et_3B to give the final cyclic product, **46** (Scheme 11). The debrominated **46** was a mixture in a ratio of 1:∼1, which presumably corresponds to 2,3-anti compounds, but their structure determinations were not feasible because the isomers could not be separated. An attempt was then made to convert the *p*-methoxybenzylidene group of **46** into the corresponding isopropylidene group. Deprotection of the PMB group of **45** was easily achieved by treatment with DDQ in the presence of 4 Å molecular sieves, followed by acetonization with dimethoxymethane and CSA to give acetal **47** in 73% yield. The debromination of **47** under *exo*-cyclic conditions resulted in excellent anti diastereoselection (>98% de) to afford **48** in 89% yield (Scheme 12).

(22) Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405−4408.

(23) In the boron-mediated aldol reactions of similar γ-chiral (*Z*)-enals, competition between reagent control and substrate control has been observed (ref 3j).

(24) (a) Shahid, K. A.; Mursheda, J.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S.-i. *Tetrahedron Lett*. **2002**, *43*, 6377−6381. (b) Shahid, K. A.; Mursheda, J.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S.-i. *Tetrahedron Lett*. **2003**, *44*, 1519−1520.

(25) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 885−888.

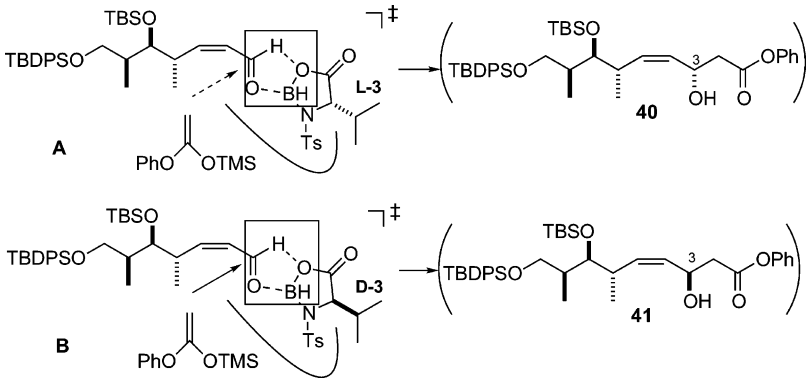
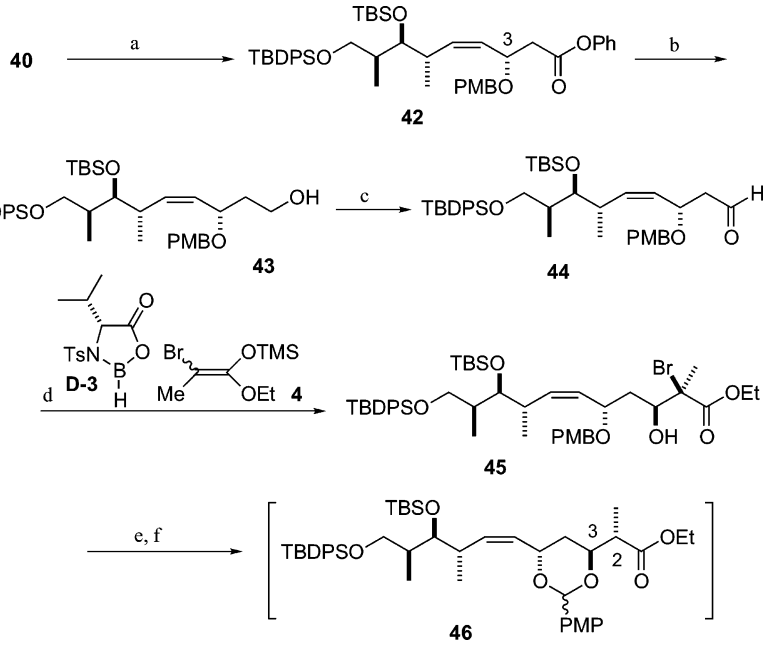


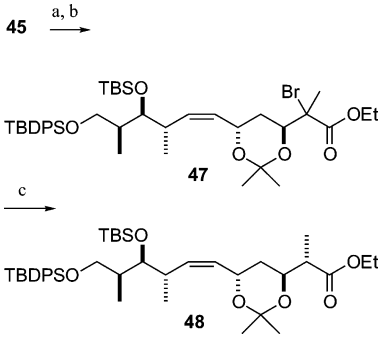
FIGURE 6. Catalyst (promoter) control on facial selection.

SCHEME 11[a]



[a] Reaction conditions: (a) $PMBCO(NH)CCl_3$, cat. TfOH, rt (88%). (b) DIBALH, −78 °C, 2 h (74%). (c) Swern oxidation (88%). (d) Chiral oxazaborolidinone-promoted aldol reaction (89%). (e) DDQ (78%). (f) Bu_3SnH, Et_3B (86%).

SCHEME 12[a]



[a] Reaction conditions: (a) DDQ, MS 4 Å, 0 °C, 5 h (81%). (b) $CH_2(OCH_3)_2$, CSA (73%). (c) Bn_3SnH, Et_3B, toluene (89%).

With regard to construction of the 3,4-*anti*-3,5-*syn* diol system of segment **B**, the most useful reaction was expected to be the highly diastereoselective $TiCl_4$-promoted Mukaiyama aldol reaction with a silyl nucleophile **4**, which was designed to proceed through a chelation pathway. An interesting anti selection (6:1) has been reported in a similar $TiCl_4$ reaction system with *syn*-3-benzyloxy-2-methyl-4-TBDMsilyloxy-butanal, related to an epothilone **A** synthesis.[26] Contrary to this result, a report has appeared that even $TiCl_4$ did not exert the expected chelation control in the reaction of β-protected-oxy aldehydes, having substituents at the α- and β-positions.[27] Taking this into account, model experiments were then conducted in more detail of $TiCl_4$-promoted aldol reactions, using similar aldehydes with a variety of silyl nucleophiles, as shown in Figure 7. A remarkable result was obtained in which $TiCl_4$ clearly accelerated the chelation-controlled aldol reaction in question, inducing moderate to good anti selection, regardless of the stereochemistry at the β position bearing an alkoxy group.[7] On the basis of this reconfirmation, the $TiCl_4$-promoted aldol reaction of **49**, derived from **48**, with **4** was carried out. However, the expected product was not obtained

(26) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575−2578.
(27) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

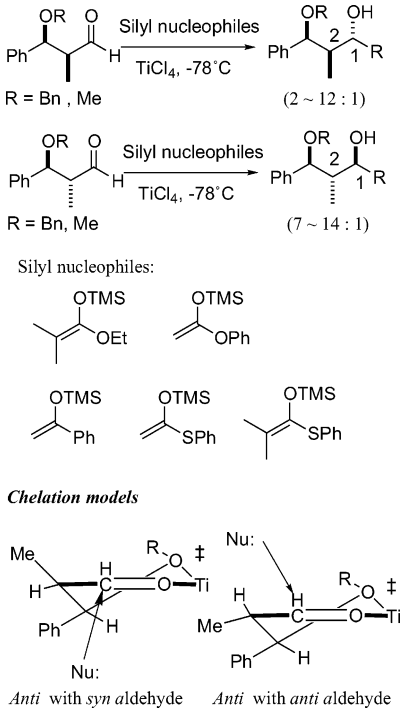
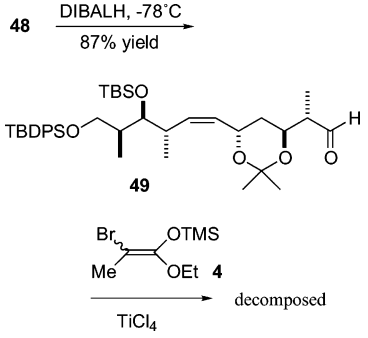


FIGURE 7. 1,2-Anti predominance enhanced by $TiCl_4$.

SCHEME 13

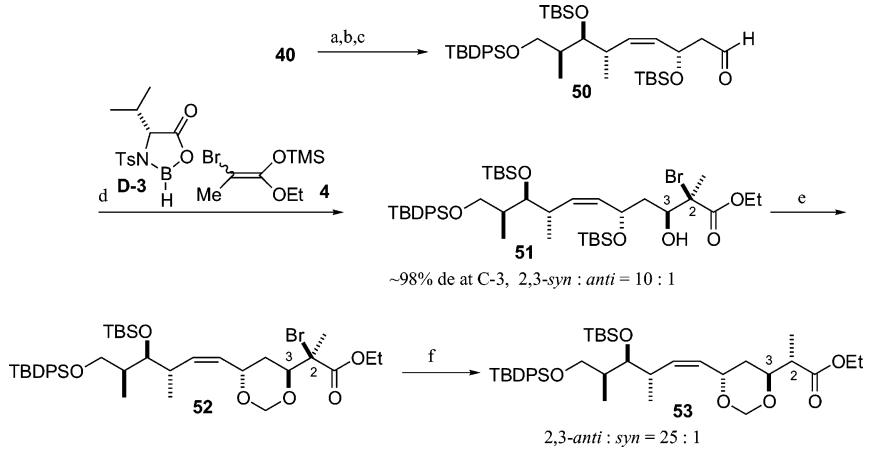


from the reaction. Only decomposed compounds were produced, presumably owing to the sensitivity of the acetonide group to $TiCl_4$ (Scheme 13).

We also examined a new 1,3-diol cyclization system that is effective for debromination, via the *exo*-cyclic mode, to produce a 4,5-anti configuration in segment **B**. A reaction sequence led inadvertently to a resolution favorable to a stable ring-closure. The following reaction sequence of TBS protection, DIBALH reduction, and a Swern oxidation of **40** provided aldehyde **50** in good overall yield. The aldol reaction of **50** with chiral borane **D-3** furnished α-bromo ester **51** in 89% yield with almost complete selection (~98% de) at C-3, accompanied by isomers at C-2 (2,3-syn:anti = 10:1). This is also a result of catalyst (promoter) control. Protection of the hydroxy group at C-3 of **51** with dimethoxymethane in the presence of P_2O_5 eventually gave a cyclic acetal **52** in good yield along with the simultaneous deprotection of the neighboring TBS group. The subsequent radical debromination resulted in excellent anti selection (2,3-anti:syn = 25:1) to give **53**, with the *exo*-cyclic effect, mentioned above (Scheme 14). Thus, the remarkable efficiency of our strategy was again verified in establishing the additional two stereocenters at C-4 and C-5 of segment **B**. A sequence of the Mukaiyama aldol reaction, designed to proceed through a chelation pathway, and subsequent radical reduction were expected to result in the 2,3-*syn*-3,4-*anti* selection. Actually, the $TiCl_4$-mediated aldol reaction of **54** with **4** occurred, producing the 3,4-anti (3,5-syn) product **55** with excellent anti selection (~98% de) along with the minor isomers at C-2 (2,3-syn:anti = ~15:1). Debromination with Bu_3SnH and Et_3B in the presence of $MgBr_2{\cdot}OEt_2$ resulted in a considerably high 2,3-syn selection to give **56** with a ratio of 13:1. The alcohol **56**, having the correct stereochemistry, was converted to the final protected **57**, equivalent to segment **B** (Scheme 15).

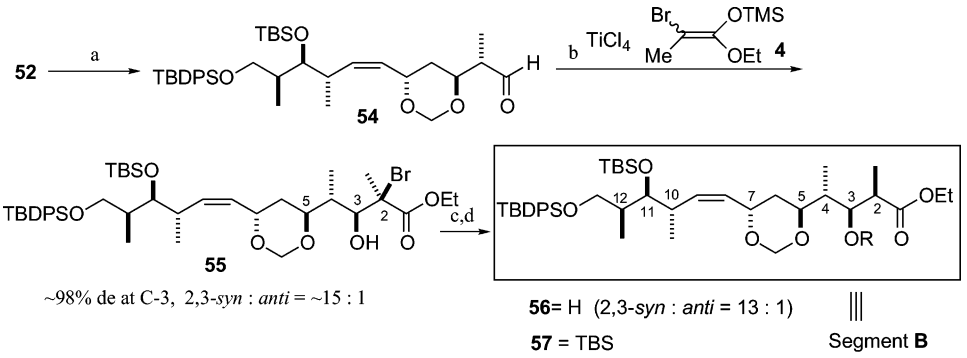
The eight stereogenic centers in the C_1-C_{13} segment **B** of (+)-discodermolide were unequivocally introduced by four aldol reactions with a quite high level of selection. The strategy, based on the iterative aldol reactions, could be effectively used for the straightforward synthesis of polypropionate frameworks. In addition, a series of reactions leading to the formation of **57** related to the natural segment **B** were applied to the epimeric **41** to provide the reverse configuration at C-2, C-3, C-4, C-5,

SCHEME 14[a]



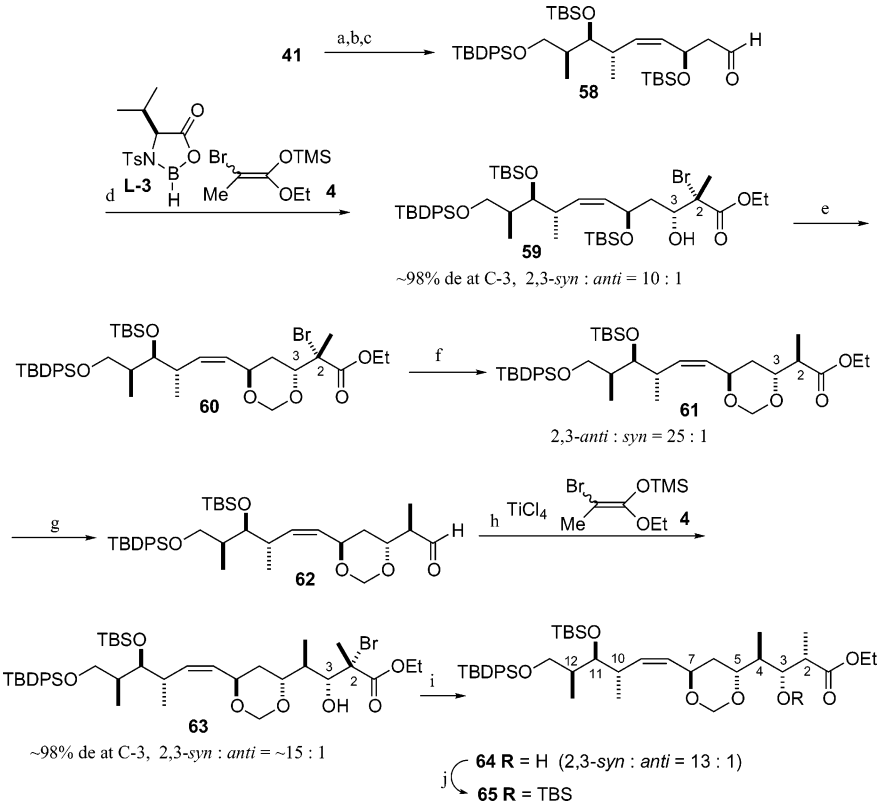
[a] Reaction conditions: (a) TBSOTf, 2,6-lutidine, rt, 1 h (87%). (b) DIBALH, CH_2Cl_2, −78 °C, 3 h (80%). (c) Swern oxidation (90%). (d) L-TsValine, $BH_3{\cdot}THF$, **4**, −78 °C (89%). (e) $CH_2(OCH_3)_2$, $CHCl_3$, P_2O_5, rt, 1 h (80%). (f) Bu_3SnH, Et_3B, toluene, −78 °C, 3 h (85%).

SCHEME 15[a]



[a] Reaction conditions: (a) DIBALH, CH_2Cl_2, −78 °C, 3 h (90%). (b) $TiCl_4$, **4**, −78 °C, 30 min (78%). (c) Bu_3SnH, Et_3B, $MgBr_2{\cdot}OEt_2$, −78 °C, 15 h (80%). (d) TBSOTf, 2,6-lutidine (97%).

SCHEME 16[a]

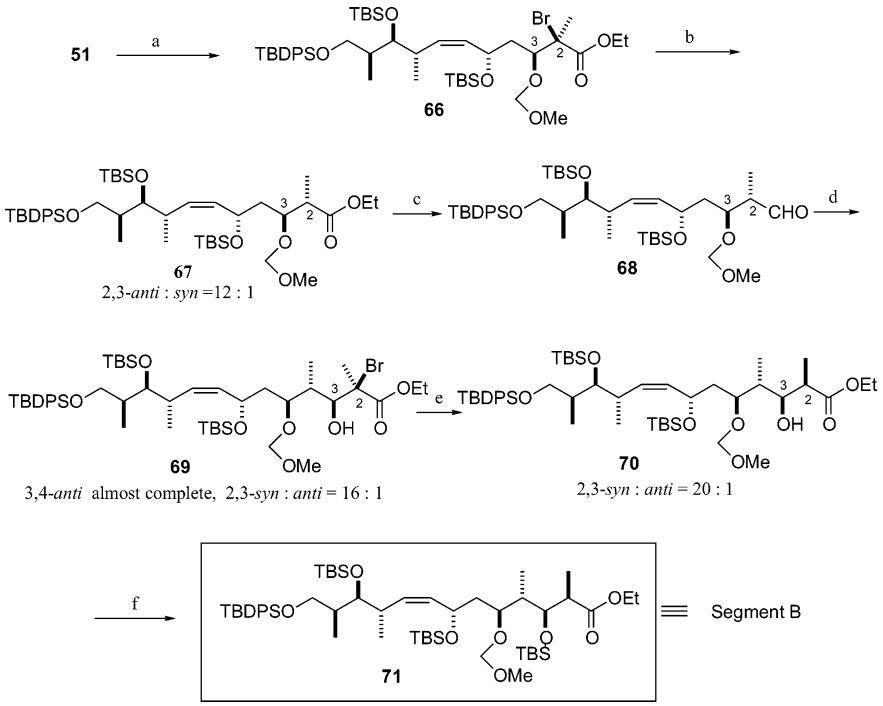


[a] Reaction conditions: (a) TBSOTf, 2,6-lutidine, rt, 1 h (87%). (b) DIBALH, CH_2Cl_2, −78 °C, 3 h (80%). (c) Swern oxidation (90%). (d) L-TsValine, $BH_3{\cdot}THF$, **4**, −78 °C (89%). (e) $CH_2(OCH_3)_2$, $CHCl_3$, P_2O_5, rt, 1 h (80%). (f) Bu_3SnH, Et_3B, toluene, −78 °C, 3 h (85%). (g) DIBALH, CH_2Cl_2, −78 °C, 3 h (90%). (h) $TiCl_4$, **4**, −78 °C, 30 min (78%). (i) Bu_3SnH, Et_3B, $MgBr_2{\cdot}OEt_2$, −78 °C, 15 h (80%). (j) TBSOTf, 2,6-lutidine (97%).

and C-7 in segment **B**. Without observing any special influence of the existing left-hand stereocenters, all the sequential reactions took place through the chiral oxazaborolidinone-promoted aldol reaction with **L-3** to **59**, cyclization to **60**, anti-debromination to **61**, $TiCl_4$-mediated aldol reaction to **62**, syn-debromination to **64**, and TBS protection to the final **65** (Scheme 16). Such a trial to synthesize isomeric discodermolides seems to be available for stimulating cancer-drug research.

An Improved Route to Segment B. The formation of the simplest acetal ring, as exemplified by **52**, was very effective in permitting the promising path to *exo*-cyclic performance in the debromination process. Furthermore, the stable ring was resistant to the strong Lewis acid, $TiCl_4$. On the other hand, the characteristics of the stable acetal ring represent a weak point in the total synthesis of (+)-discodermolide since the selection of more severe reaction conditions, inconvenient for the other protection groups, involved in the compounds in question, must be anticipated at the stage of the opening of the acetal ring. We previously succeeded in inducing considerably good anti selection independent of the *exo*-cyclic mode.[7] The good 2,3-*anti*-predominance (~10:1) in the radical debromination is expectedly achieved via the dipole mode, enhanced by MOM protection of the *β*-hydroxy group. An improved route was developed as follows (Scheme 17).

SCHEME 17[a]



[a] Reaction conditions: (a) Methylal, P_2O_5, 20 min (75%). (b) Bu_3SnH, Et_3B, toluene, −78 °C, 3 h (89%). (c) DIBALH, CH_2Cl_2, −78 °C, 2 h (68%). (d) $TiCl_4$, **4**, −78 °C, 30 min (72%). (e) Bu_3SnH, Et_3B, $MgBr_2$, −78 °C (89%). (f) TBSOTf, 2,6-lutidine, rt (92%).

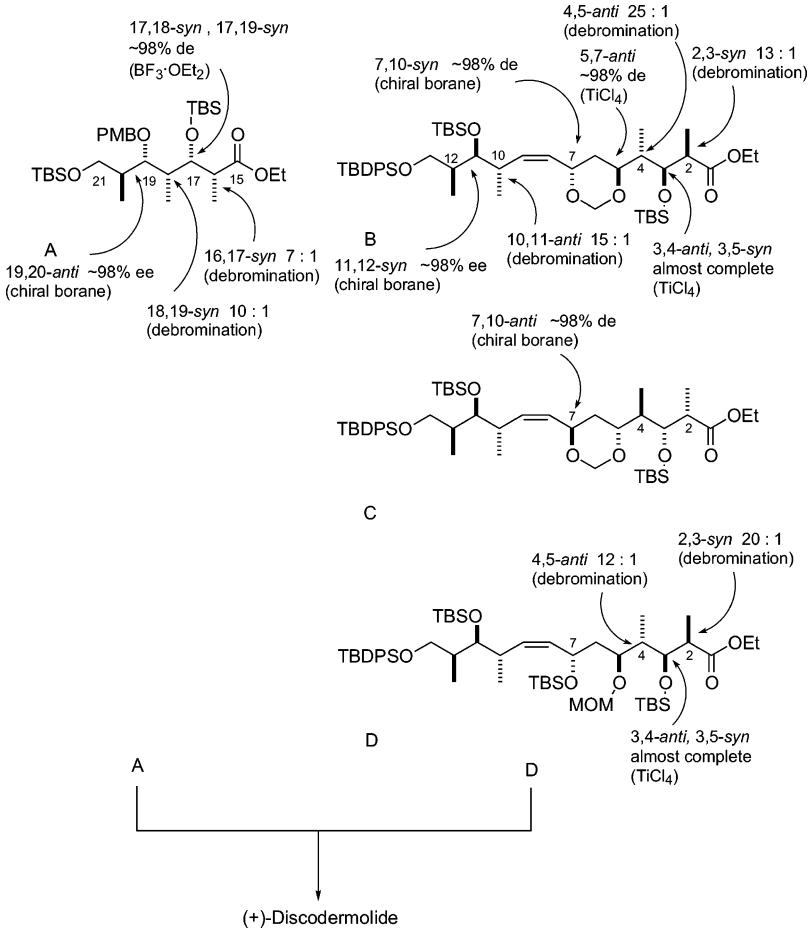


FIGURE 8. The total selectivities achieved in the stereoselective sequence of constructing 13 stereogenic centers.

Mild conditions (methylal, P_2O_5, rt, 20 min) of protection at the β-hydroxy group of **51** allowed the production of the corresponding MOM protected compound **66** avoiding the over-reaction to a cyclic acetal such as **52**. As expected, the radical reduction of **66** by treatment with Bu_3SnH and Et_3B in toluene at −78 °C resulted in fairly good anti selection (12:1) to preferentially give **67** in good yield. After the direct conversion of **67** to **68** by DIBALH reduction, the $TiCl_4$-mediated aldol reaction of **68** with **4** actually proceeded so as to exclusively give the 3,4-*anti* **69** via chelation control, withparticipation of the β-MOMO moiety; the applied conditions of dilution (ca. 10 times) and a short reaction time (30 min) presumably avoided decomposition of the MOMO moiety. Excellent selectivity was obtained in the above aldol reaction where 3,4-anti formation is almost complete and 2,3-syn selection occurred in a ratio of 16:1. In the next radical debromination step, 2,3-syn selection was addressed, which can be considered to occur via chelation conditions. Chelation with $MgBr_2$ did not necessarily permit protection at the β-hydroxy group to lead to a considerably high syn selection.[4] It is noteworthy that nonprotection might be more practical provided an appropriate syn selection is achieved under the conditions used due to the elimination of the protection and deprotection steps. The direct debromination of **69** led to the formation of 2,3-*syn* **70** with excellent selection (20:1). Finally, the normal TBS protection of **70** gave **71** as an equivalent of segment **B**, which is practically available for the synthesis of (+)-discodermolide.

Conclusions

The 13 stereogenic centers, essential for the total synthesis of (+)-discodermolide, can be constructed with high selectivities, as shown in Figure 8. The synthetic equivalent **A**, related to the $C_{15}-C_{21}$ segment, was prepared through very short paths constituted of a chiral oxazaborolidinone-mediated aldol reaction of the racemic aldehyde, derived from a readily available diol, and a BF_3-assisted aldol reaction; both aldol reactions were accompanied by diastereodivergent radical debromination reactions. The synthetic equivalent **B**, related to the C_1-C_{13} segment, could be prepared through the same enantioselective aldol reactions with the chiral borane, a diastereoselective aldol reaction with the chiral borane, and two $TiCl_4$-assisted aldol reactions. Isomer **C** at C-2 to C-7 was also prepared in similar selectivities. Furthermore, the equivalent **D**, which was intended to furnish substitutents more suitable for elongation, could also be prepared under the improved reaction conditions. After some modifications of the final known palladium(0)-*cross*-coupling reaction[2c,f,10] can be developed for the subunits **A** and **D**, the frame of (+)-discodermolide would be complete. The successful results obtained above indicate that numerous complex polyketide frames can be constructed on the basis of the Lewis acid-mediated aldol reaction strategy to divergently give highly enantioselective *syn*- and *anti*-propionates (chiral borane) and highly diastereoselective *syn*- and *anti*-propionates in polypropionate chains ($BF_3{\cdot}OEt_2$ and $TiCl_4$), respectively.

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Supporting Information Available: General methods and experimental procedures containing spectroscopic data for **2**, **4**, **5**, **6**, **7**, **8**, **9**, **11**, **12**, **14**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **26**, **27**, **29**, **30**, **31**, **32**, **33**, **38**, **40**, **41**, **50**, **51**, **52**, **53**, **54**, **55**, **56**, **57**, **58**, **59**, **60**, **61**, **62**, **63**, **64**, **65**, **66**, **67**, **68**, **69**, **70**, and **71**. This material is available free of charge via the Internet at http://pubs.acs.org.

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