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Epoxyamide-Based Strategy for the Synthesis of Polypropionate-Type Frameworks

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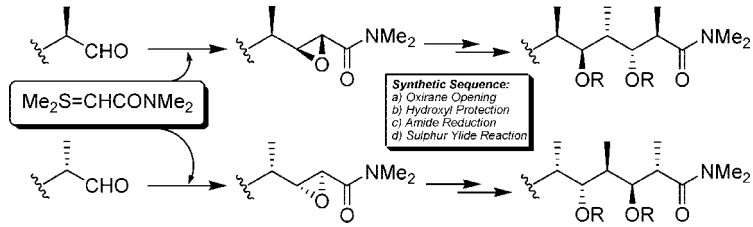

A new approach to the stereoselective synthesis of polypropionate-type frameworks is reported utilizing reactions of amide-stabilized sulfur ylides with chiral aldehydes. To establish a new strategy for macrolide fragment synthesis, the stereoselectivity of these reactions in the construction of epoxy amides was the most important aspect of this study. In this aspect, we found a strong influence of the protecting groups employed in the starting aldehydes upon the stereochemical outcome of their reactions with the sulfur ylide **1**. Thus, numerous aldehydes showed remarkable stereofacial differentiation, providing a major diastereoisomer, in contrast to others that displayed a poor or no stereoselectivity. Despite the difficulties encountered for some cases with respect to their diastereomeric yields, we were able to prepare various stereotetrads and stereopentads, thus enhancing the synthetic value of this new methodology for the preparation of typical polypropionate frameworks found in many natural products, in particular the macrolide class of antibiotics.

Introduction

The stereoselective synthesis of epoxides has represented one of the most outstanding chapters of the history of Organic Synthesis,[1] comprising an important number of significant contributions that have enabled the access of numerous scaffolds of great utility in total synthesis. Among these structural frameworks, a key structural motifs is that derived from the polypropionate biosynthetic pathway,[2] found in many diverse natural products. The macrolide-type antibiotics,[3] in particular, represent a prominent example of this type of compounds, owing to their biological properties and medicinal applications,[4] and have prompted the chemical community to design and develop diverse asymmetric synthetic methodologies[5] to achieve the total syntheses of members of this family of natural products.[6] Despite all the chemistry devoted to this field in the past 30 years,[7] it is gratifying that one can still find in the literature outstanding and elegant new contributions in this area.[8]

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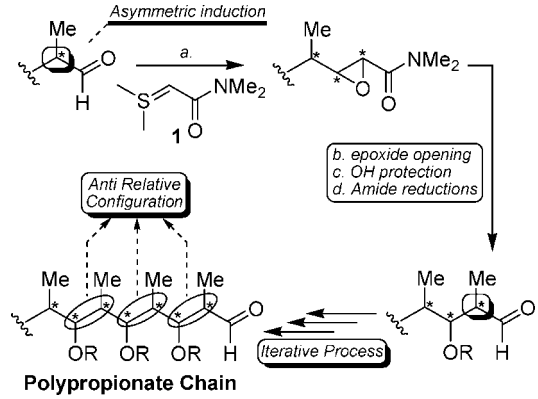
In this publication, we wish to report our synthetic studies on the stereoselective synthesis of macrolide fragments utilizing epoxy amides as key building blocks, which can be readily prepared by reaction of carbonyl compounds with amide-stabilized sulfur ylides.[9] Our experience and preliminary results in this field[10,11] prompted us to explore and exploit the chemistry of sulfur ylides for the stereoselective synthesis of this type of structural motifs. The general synthetic strategy is summarized in Scheme 1, and accordingly, a starting chiral aldehyde would react with sulfur ylide **1** in a stereoselective fashion induced by the presence of an asymmetric center in the α-position of the aldehyde. The resulting *trans* epoxy amide would then be subjected to a synthetic sequence that would entail an epoxide opening reaction mediated by an organocuprate reagent, followed by protection of the resulting alcohol, as a silyl ether for instance, and reduction of the amide to the aldehyde, which in turn would be ready for a second sequence of reactions with **1**. The sequence could be done iteritatively giving access to a polypropionate chain, whose stereochemistry would be a consequence of the asymmetric induction produced by the starting chiral aldehyde coupled with the *trans*-selectivity showed by the stabilized sulfur ylide reaction, providing the *anti* relative configuration between the highlighted chiral centers present in the resulting polypropionate chain (Scheme 1).[12]

SCHEME 1. General Synthesis of Polypropionate Chains by the Chemistry of Sulfur Ylides



Results and Discussion

To initiate the synthetic study, epoxy amide **2**[13] was chosen as a valid starting point for the preparation of the required chiral aldehyde. To this end, epoxy amide **2** was treated with lithium dimethylcuprate to obtain hydroxy amide **3** in an excellent 90% yield, followed by protection of the secondary alcohol of two different manners, to give the silylether **4** and benzylether **5**, respectively. The preparation of the aldehydes required a reduction of the amide function to the alcohol, mediated by the action of Super-H,[14] to furnish alcohols **6** and **7** in 96 and 73% yields respectively, followed by subsequent Swern oxidation,[15] that provided the corresponding aldehydes **8** and **9** in very good yields (90% for **8** and without purification for **9**). With both aldehydes in hand, we proceeded in exploring their reactions with the sulfur ylide **1**, which was prepared previously by treatment of its corresponding sulfonium salt with sodium hydride.[16] Thus, after exposure of aldehydes **8** and **9** to the action of 3.0 equivalents of **1** in methylene chloride for 8 h, the result was the obtention of separable mixtures of epoxy amides for both cases, **10a**:**10b** in a 85:15 ratio and 89% combined yield, for aldehyde **8**, and **11a**:**11b** in a 1:1 ratio and 85% combined yield, for aldehyde **9**. The different diastereomeric ratios found in both cases revealed the influence of the protecting group employed in alcohol **3** upon the stereochemical outcome. Additionally, these results also reflect the difficulty of predicting the stereochemical result in reactions of **1** with chiral aldehydes (Scheme 2). Given the poor or practically null stereoselectivity found for the reaction of **1** with aldehyde **9**, we opted to discard this product and to continue our synthetic studies with the silylether derivatives **10a**:**10b**.

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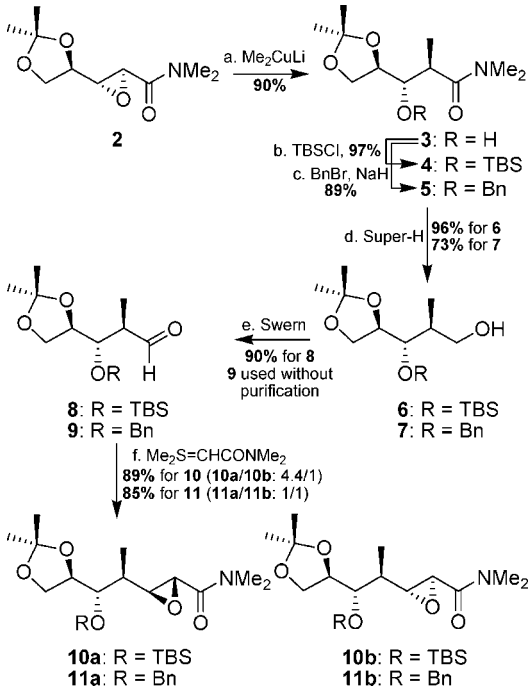
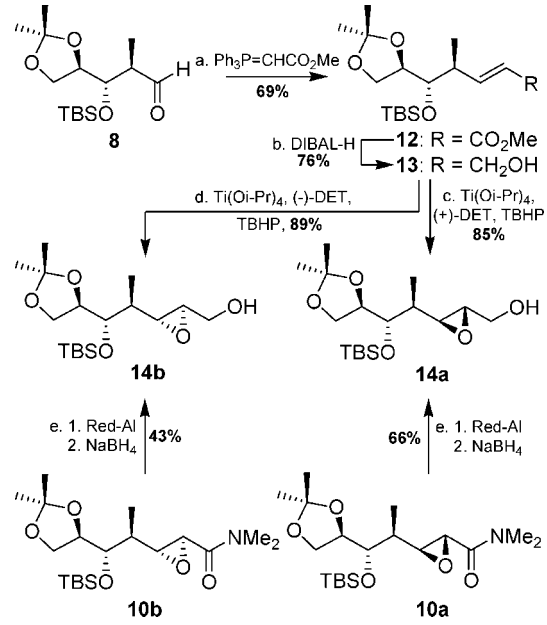
SCHEME 2. Synthesis of Epoxy Amides 10 and 11



SCHEME 3. Confirmation of Absolute Stereochemistry for Epoxy Amides 10a and 10b



To demonstrate the absolute configuration of epoxy amides **10a** and **10b**, which were established assuming a Felkin-Ahn model[17] for the addition process of **1** to aldehyde **8**, the epoxy alcohols **14a** and **14b** were independently prepared utilizing a Sharpless asymmetric epoxidation[18] of the corresponding allylic alcohol **13**, which was obtained by reduction of the α,β-unsaturated ester **12** with DIBAL-H in a 76% yield. In parallel, the epoxy amides **10a** and **10b** were subjected to the sequential action of Red-al[19] and $NaBH_4$ to obtain the corresponding epoxy alcohols **14a** and **14b** in moderate 66 and 43% overall yields respectively. A comparison of the spectroscopic properties of both epoxy alcohols obtained from the different synthetic routes unambigously established the stereochemistry as assigned (Scheme 3).

In order to proceed with the chain elongation proccess and to determine the viability of our delineated strategy for the construction of macrolide motifs, epoxy amide **10a** was subjected to the general synthetic sequence outlined in Scheme 1. Thus, **10a** was transformed into aldehyde **18** via a ring opening reaction of **10a** with lithium dimethylcuprate, to provide alcohol **15** in a 87% yield, followed by protection of the resulting alcohol **15** as the silyl ether to give the amide derivative **16**, which was reduced to alcohol **17** by treatment with Superhydride and finally oxidized to aldehyde **18** by the action of TEMPO/BAIB[20] or DMP.[21] Aldehyde **18** was then reacted with the sulfur ylide **1** under identical conditions as for **8**, to obtain in this case, a discouraging 1:1 mixture of diastereoisomers **19a**:**19b** in a 71% combined yield, which was inseparable by chromatographic methods. Considering that the stereochemistry at C-3 could influence the stereochemical induction of the sulfur ylide addition, the minor epoxy amide **10b** was transformed in a similar way into aldehyde **23** following the same synthetic pathway as described before for **18** and reacted with sulfur ylide **1**. However, this reaction also furnished an inseparable mixture of epoxy amides **24a**:**24b** in a 64% combined yield, although in a 2:1 ratio (Scheme 4).

The remarkable sensitivity displayed by these reactions toward the protecting groups employed in the starting aldehydes upon the stereochemical results, led us to consider a modification of the silyl protecting groups to other groups that would introduce a conformational constraint. In this sense, a cyclic acetal possessed these conformational features and, therefore, epoxy amide **15** was transformed into the acetal derivative **26** in a 82% yield via diol **25**. When amide **26** was treated with Super-H, the expected alcohol **27** was not formed under the conventional conditions consisting of treatment with 3.0 equiv of Super-H in THF at room temperature. Even after long periods of exposure and use of large excess of Super-H (15.0 equiv), only a small amount of alcohol **27** was obtained. This unexpected lack of reactivity displayed by amide **26** toward the potent reducting agent Super-H was ascribed to steric factors. This adverse result obligated us to investigate an alternative route. To this aim, alcohol **17**, previously described in Scheme 4, was protected as its pivaloate ester to obtain in virtually quantitative yield compound **28**, which, after treatment with TBAF afforded diol **29**. After protection of the 1,3-diol system of **29** as an acetal, the pivaloyl group of the resulting product, compound **30**, was efficiently removed by the action of DIBAL-H, to give the desired alcohol **27** in a 95% yield. Oxidation of **27** was undertaken with the oxidative system TEMPO/BAIB to obtain the aldehyde **31** in an excellent 95% yield. The aldehyde was then subjected to the action of sulfur ylide **1**, to provide a mixture of epoxy amides **32a**:**32b** in a 81% combined yield but in greater diastereoselectvity 4:1 in favor of the expected Felkin-Ahn adduct, **32a**, which was isolated as a pure diastereoisomer after purification by flash column chromatography (Scheme 5).

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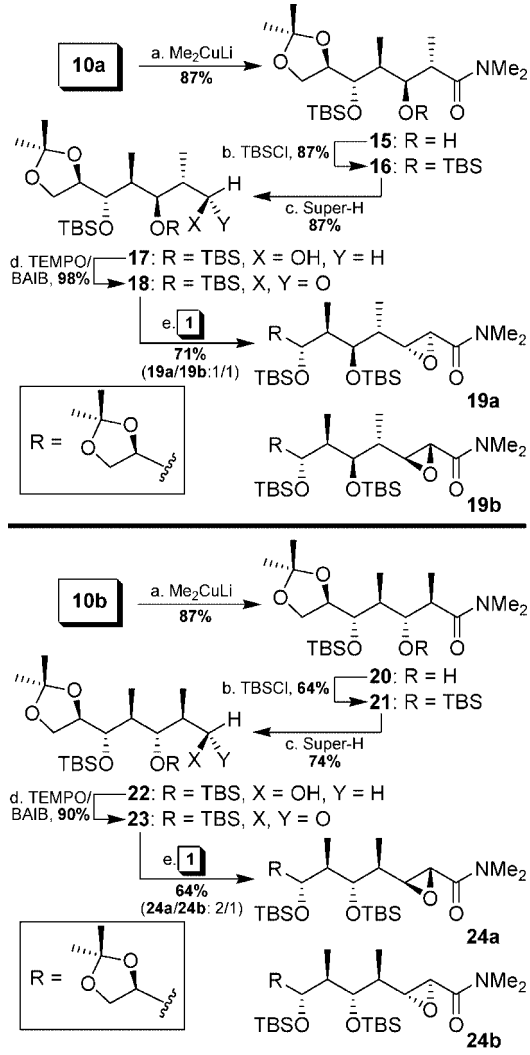
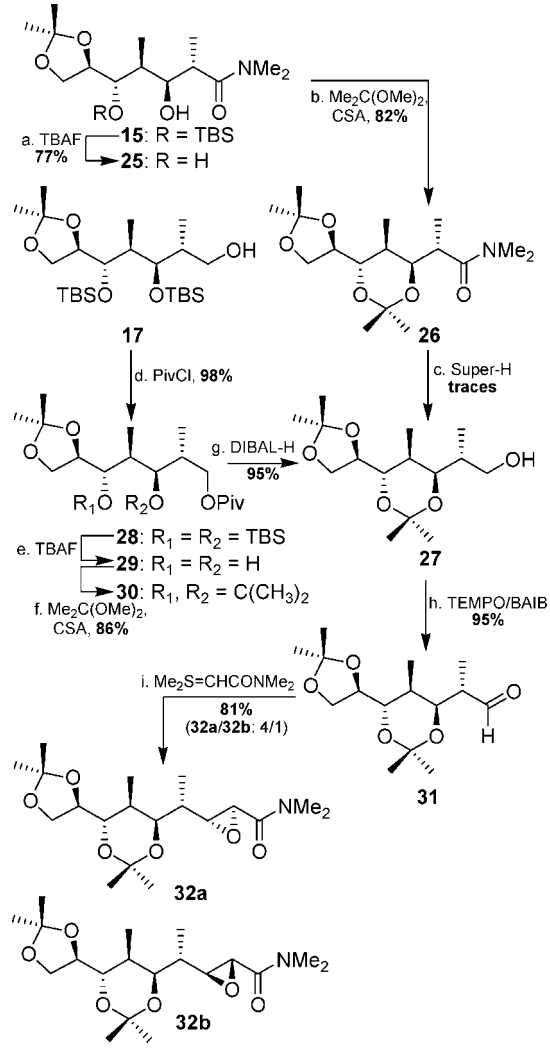
SCHEME 4. Synthesis of Epoxy Amides 19 and 24



SCHEME 5. Synthesis of Epoxy Amides 32a:32b



Before continuing with the construction of a longer polypropionate chain, we moved to confirm the stereochemical outcome of the previous epoxidation reactions in favor of the expected Felkin-Ahn adduct. In this sense, Sharpless asymmetric epoxidation was again the synthetic tool of choice to ascertain the stereochemical outcome. Therefore, allylic alcohols **34** and **36**, prepared from their corresponding Wittig products **33** and **35** respectively, were subjected to Sharpless epoxidations using (−)-DET to afford the corresponding epoxy alcohols **37** and **38** in 72 and 95% yields respectively and diastereomeric excesses (*d.e.*) greater than 95% for both cases. On the other hand, reduction of the mixture of epoxy amides **19a/19b** and **32a** were conducted by sequential reductive treatment with Red-Al and sodium borohydride as described previously for **10a** and **10b**. Thus, comparison of the epoxy alcohols obtained from these different routes allowed us to confirm the presence of epoxy alcohol **37** as major isomer for the mixture of epoxy amides **19a/19b**, and the formation of epoxy alcohol **38** for the epoxy amide **32a** (Scheme 6).

Following our synthetic plan toward macrolide fragments, the epoxy amide **32a** was treated with lithium dimethylcuprate to incorporate a new methyl group, obtaining hydroxy amide **39**, which was protected as the silyl ether **40** in a reasonable 63% yield over two steps. The silyl derivative **40** was subjected to reduction with Super-H, to provide alcohol **41** in a 63% yield, followed by oxidation with TEMPO/BAIB to afford aldehyde **42**, which displayed poor stability, therefore requiring its use without further purification. The crude aldehyde **42** was reacted with sulfur ylide **1**, to give to our delight, epoxy amide **43** in a 56% overall yield from **41**, as the only detectable epoxide. This epoxy amide **43** was then transformed into amide **45** in a 67% yield over two steps, consisting of ring opening reaction of the epoxy amide **43** and silyl protection of the resulting hydroxy amide **44** (Scheme 7).

With all the chemistry gathered on the synthesis of macrolide fragments, we turned our attention to chiral α-methyl aldehydes, extensively used in Organic Synthesis as key building blocks in the synthesis of polypropionate chains. Among them, aldehydes **46**,[22] **47**,[23] and **48**[24] were initially chosen to test their utilities in the stereoselective synthesis of epoxy amides. Thus,

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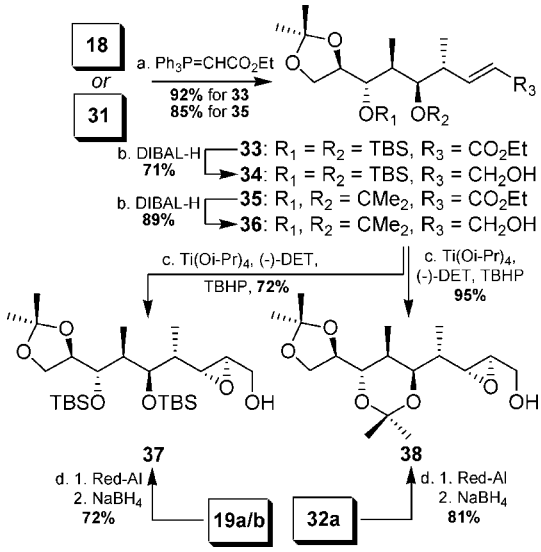
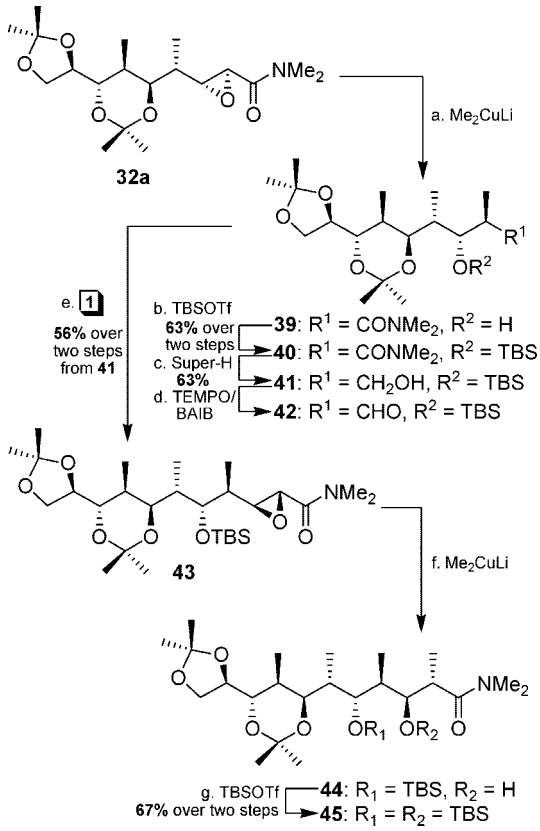
SCHEME 6. Confirmation of Absolute Stereochemistry for Epoxy Amides 19a and 32a



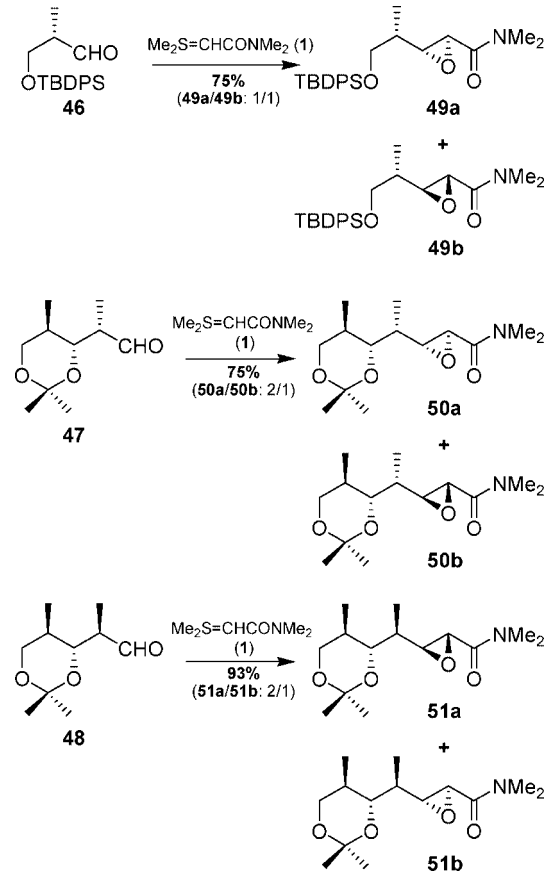
SCHEME 7. Synthesis of Macrolide Fragment 45



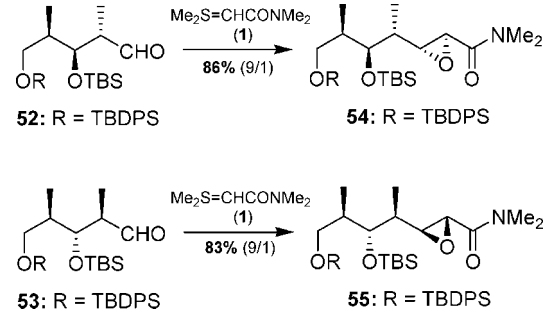
when **46** was treated with an excess of sulfur ylide **1**, a disappointing 1:1 mixture of inseparable epoxy amides **49a**:**49b** was obtained, albeit in a remarkable 75% yield. On the other hand, aldehydes **47** and **48** provided the formation of a 2:1 mixture of epoxy amides **50a**:**50b** and **51a**:**51b** in 75 and 93% combined yields respectively. In these cases, the separation of both diastereoisomers was acheivable by column chromatography (Scheme 8).

In light of the poor stereoselectivities obtained, we decided to investigate new aldehydes for their synthetic potential in these

SCHEME 8. Reaction of Simple Chiral Aldehydes with Sulfur Ylide 1 (I)



SCHEME 9. Reaction of Simple Chiral Aldehydes with Sulfur Ylide 1 (II)



reactions. In particular, we chose the bis-silylether aldehydes **52**[25] and **53**,[26] which, in contrast to the previous aldehydes, provided excellent diastereoselections in their reactions with **1**, giving the epoxy amides **54** and **55**[27] together with their diastereoisomers in 9:1 ratios, according to their ^{1}H NMR spectra, and very good combined yields (86 and 83% respectively) (Scheme 9).

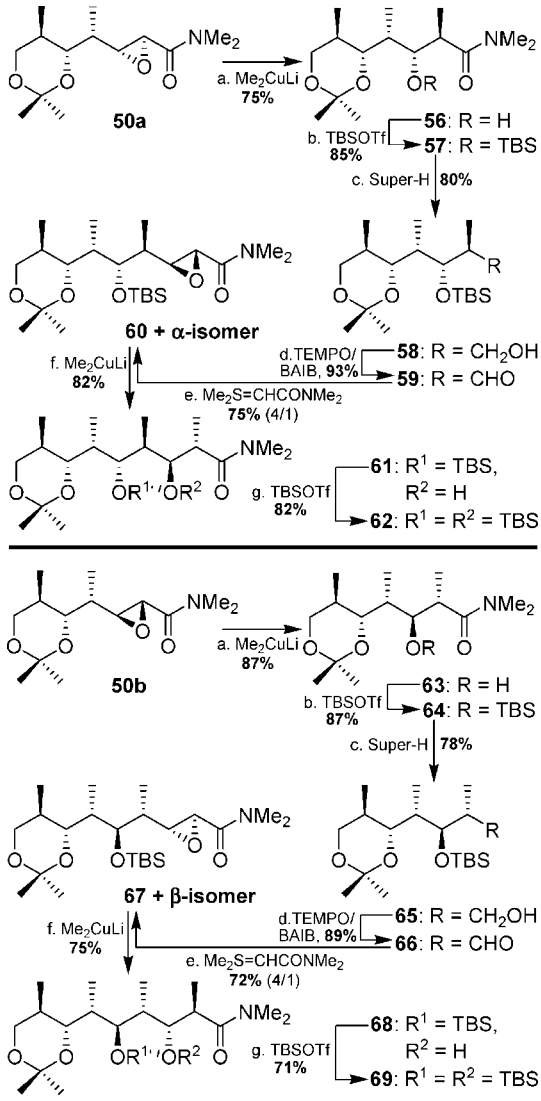
The last result was quite promising despite restricting the stereochemical diversity to the Felkin-Ahn addition product. For aldehydes **47** and **48**, despite providing poor stereoselectivities in their reactions with **1**, they supplied sufficient amounts of

(25) Kiyooka, S.-i.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967–7978.

(26) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275–4283.

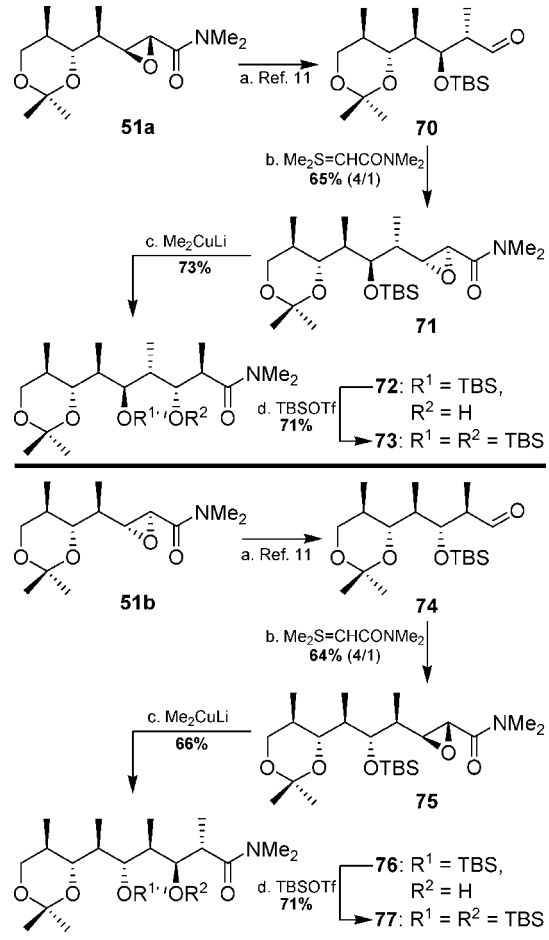
(27) For demonstration of stereochemistry of epoxy amides **54** and **55**, see Supporting Information.

SCHEME 10. Sulfur Ylide Methodology towards Polypropionate Chains (I)



both stereoisomers in enantiomerically pure forms after purification. Therefore, we pursued our goal of constructing long polypropionate chains by the synthetic course designed for this methodology with all the stereoisomers obtained from these reactions. Thus, ring opening reactions of the pure epoxy amides **50a** and **50b** were achieved by treatment with Gilman reagent, furnishing hydroxy amides **56** and **63** in 75 and 87% yields respectively, followed by protection of the secondary alcohols as silyl ethers, affording amides **57** and **64**. The transformation of both amides into the corresponding aldehydes **59** and **66** was accomplished in two steps, Super-H reduction and oxidation of the resulting alcohols by the action of TEMPO/BAIB. With both advanced aldehydes in hand, we proceeded with another sulfur ylide reaction by exposing **59** and **66** to an excess of sulfur ylide **1** (4.0 equiv). The results for both aldehydes were very similar in terms of chemical yields and stereoselectivities. In fact, for aldehyde **59**, the result was the obtention of a mixture of epoxy amide **60** together with its α-isomer in a 4.5:1 proportion and 75% combined yield, while aldehyde **66** afforded epoxy amide **67** in a 72% yield as a 4:1 mixture of diastereoisomers. Finally, epoxy amides **60** and **67** were treated again with lithium dimethylcuprate, and the resulting hydroxy amides **61** and **68**, obtained in 82 and 75% yields respectively, protected as their silyl ethers **62** and **69** by treatment with TBSOTf (Scheme 10).

SCHEME 11. Sulfur Ylide Methodology towards Polypropionate Chains (II)



In a similar way, the pure epoxy amides **51a** and **51b** were subjected to the same synthetic scheme as described before, to obtain aldehydes **70** and **74** respectively, which were reacted with an excess of **1** to afford epoxy amides **71** and **75** in good yields and expectable diastereomeric purities. Finally, oxirane ring openings of both epoxy amides by the action of the copper reagent followed by silylation of the resulting hydroxy amides provided compounds **73** and **77** (Scheme 11).[11]

Finally, to advance the elongation process of the polypropionate framework, we chose compounds **69** and **77** to proceed with one more reaction with sulfur ylide **1**. To this end, aldehyde **79** was prepared after reduction of **69** to alcohol **78**, by the action of Super-H (82%), followed by oxidation with TEMPO/BAIB (85%). Then, aldehyde **79** was exposed to an excess of ylide **1** under conventional conditions and after several days a disappointingly unexpected 2:1 mixture of epoxy amides **80a/80b** was obtained in a 58% yield. In contrast, aldehyde **82**, obtained from compound **77** following the same synthetic sequence as described before for **69**, afforded only one epoxy amide, epoxy amide **83**, in its reaction with sulfur ylide **1** in a very good 76% yield. This epoxy amide was then subjected to the introduction of a new methyl group via oxirane ring opening by the action of Gilman reagent, to give hydroxy amide **84** in a 73% yield, which was protected as its silyl ether **85** (Scheme 12). It is worth note this latter compound contains the C-3/C-13 fragment of

SCHEME 12. Sulfur Ylide Methodology towards Polypropionate Chains (III)

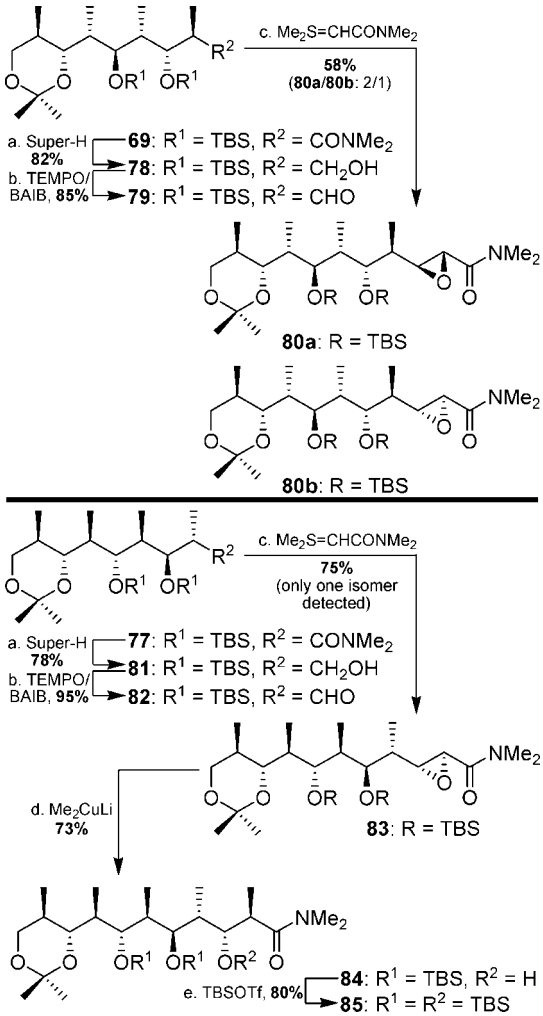


TABLE 1. Reaction of Chiral Aldehydes with Sulfur Ylide 1: A Summary

aldehyde	epoxy amide (% yield)	stereoselectivity (isomers ratio)
8	**10a/10b** (89%)	4.4:1
9	**11a/11b** (85%)	1:1
18	**19a/19b** (71%)	1:1
23	**24a/24b** (64%)	2:1
31	**32a/32b** (81%)	4:1
42	**43** (56%)	<95:5
46	**49a/49b** (75%)	1:1
47	**50a/50b** (75%)	2:1
48	**51a/51b** (93%)	2:1
52	**54** + β-epoxide (85%)	9:1
53	**55** + α-epoxide (83%)	9:1
59	**60** + α-epoxide (75%)	4:1
66	**67** + β-epoxide (72%)	4:1
70	**71** + β-epoxide (65%)	4:1
74	**75** + α-epoxide (64%)	4:1
79	**80a/80b** (75%)	2:1
82	**83** (76%)	<95:5

the ansa like antibiotic Streptovaricin U,[12b,28] whose total synthesis we are currently investigating.

(28) (a) Knoll, W. M. J.; Rinehart, K. L., Jr.; Wiley, P. F.; Li, L. H. *J. Antibiot.* **1980**, *33*, 249–251. (b) Miyashita, M.; Yamasaki, T.; Shiratani, T.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1997**, 1787–1788.

Conclusions

In conclusion, we have described the stereoselective synthesis of macrolide-type antibiotics motifs utilizing the addition of sulfur ylides to aldehydes. We have investigated the stereochemical control exerted by the starting chiral aldehydes, identifying the relevant role played by the protecting groups employed in the starting aldehydes. As demonstration of this, a collection of different aldehydes were subjected to reactions with sulfur ylide **1** and their stereoselectivities evaluated. These results are summarized in Table 1. Despite the poor stereoselectivities recorded for some cases, we have demonstrated the potential and applicability of this methodology for the construction of typical polypropionate frameworks with the synthesis of stereotetrads containing systems in form of compounds **45**, **62**, **69**, **73**, **77**, and the product **85**, which represents the C-3/C-13 fragment of the ansa like antibiotic Streptovaricin U.

Experimental Section

Sulfur Ylide 1. To a stirred suspension of N, N-Dimethylcarbamoylmethyl dimethylsulfonium chloride (260 mg, 1.42 mmol) in wet acetonitrile was added sodium hydride (68 mg, 1.69 mmol, 1.2 equiv, 60% dispersion in mineral oil) in one portion at 0 °C. After stirring at this temperature for 3 h, the crude mixture was filtered and the solution concentrated to obtain crude sulfur ylide **1** as a yellow oil.

General Procedures

Oxidation of Alcohols. Procedure A. To a solution of oxalyl chloride (2.0 equiv) in CH_2Cl_2 was added dropwise DMSO (4.0 equiv) at −78 °C. After stirring for 15 min, a solution of alcohol (1.0 equiv) in CH_2Cl_2 (0.1 M) was added dropwise at −78 °C. The solution was stirred for 30 min at −78 °C, and TEA (6.0 equiv) was added at the same temperature. The reaction mixture was allowed to warm to 0 °C over 30 min, and then Et_2O was added, followed by saturated aqueous NH_4Cl solution. The organic phase was separated, and the aqueous phase was extracted with Et_2O (twice). The combined organic solution was sequentially washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% EtOAc in hexanes) provided the corresponding aldehyde. **Procedure B.** To a solution of alcohol (1.0 equiv) in CH_2Cl_2 (0.1 M) was added Dess-Martin periodinane (DMP) (1.5 equiv) at 0 °C. After 0.5 h at this temperature, a saturated aqueous $NaHCO_3$ solution was added and the bilayer system was allowed to stir at 0 °C for an additional 0.5 h. The organic phase was then separated, the aqueous layer extracted with CH_2Cl_2 (twice), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude aldehyde was purified by flash column chromatography (silica gel, 5% AcOEt in hexanes) to obtain the corresponding aldehyde. **Procedure C.** To a solution of alcohol (1.0 equiv) in CH_2Cl_2 (0.1 M) was added iodobenzene diacetate (BAIB) (3.0 equiv) and TEMPO (0.3 equiv) at 0 °C. After 0.5 h at this temperature, a saturated aqueous $Na_2S_2O_3$ solution was added and the bilayer system was allowed to stir at 0 °C for an additional 0.5 h. The organic phase was then separated, the aqueous layer extracted with CH_2Cl_2 (twice), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude aldehyde was purified by flash column chromatography (silica gel, 5% AcOEt in hexanes) to provide the corresponding aldehyde.

Aldehyde 66. Obtained by procedure C in a 89% as a colorless oil: $R_f = 0.49$ (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D = +15.0$ ($c = 1.0$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.11$ (s, 6 H), 0.74 (d, $J = 6.3$ Hz, 3 H), 0.89 (d, $J = 7.0$ Hz, 3 H), 0.92 (s,

9 H), 1.14 (d, $J = 6.7$ Hz, 3 H), 1.37 and 1.44 (2 s, 6 H), 1.83−1.95 (m, 2 H), 2.74−2.81 (m, 1 H), 3.54 (dd, $J = 11.1$ Hz, 1 H), 3.66 (d, $J = 10.1$ Hz, 1 H), 3.73 (dd, $J = 11.2$, 4.8 Hz, 1 H), 3.99 (d, $J = 5.0$ Hz, 1 H), 9.85 (d, $J = 2.0$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.4$, 8.4, 11.3, 12.7, 18.1, 19.5, 25.8, 29.6, 30.2, 39.7, 50.5, 66.0, 74.9, 77.0, 97.8, 204.4.

Synthesis of Epoxy Amides. Aldehyde (1.0 equiv) was dissolved in CH_2Cl_2 (0.1 M), and *N*,*N*-dimethyl-2-(dimethylsulfuranylidene)-acetamide **1** (3.0−4.0 equiv) was added at room temperature. The reaction mixture was stirred at room temperature until the reaction was complete as judged by TLC (ca. 12 h). The solvents were removed by concentration under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 50% AcOEt in hexanes) to provide the corresponding epoxy amide in a wide range of yields and stereoselectivities (see Table 1).

Epoxy Amide 67. Epoxy amide **67** was obtained together with its β-epoxide isomer in a 72% total yield as a 4:1 diastereomeric mixture: Colorless oil; $R_f = 0.34$ (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = -0.05$ and −0.03 (2 s, 6 H), 0.61 (d, $J = 6.7$ Hz, 3 H), 0.80 (s, 9 H), 0.84 (d, $J = 7.2$ Hz, 3 H), 1.02 (d, $J = 7.0$ Hz, 3 H), 1.24 and 1.31 (2 s, 6 H), 1.69 (dq, $J = 7.0$, 2.1 Hz, 1 H), 1.72−1.76 (m, 1 H), 1.79−1.85 (m, 1 H), 2.88 and 3.09 (2 s, 6 H), 3.14 (dd, $J = 8.0$, 2.0 Hz, 1 H), 3.44 (dd, $J = 10.0$, 5.7 Hz, 1 H), 3.48 (d, $J = 2.0$ Hz, 1 H), 3.55 (dd, $J = 5.4$, 2.1 Hz, 1 H), 3.57−3.60 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.6$, −4.5, 7.8, 12.6, 16.1, 18.0, 19.2, 25.8, 29.7, 30.3, 35.8, 36.6, 38.9, 39.6, 53.9, 60.0, 65.9, 75.4, 79.0, 97.6, 167.4; FAB HRMS (NBA) *m/e* 466.2968, M + Na^+ calcd for $C_{23}H_{45}NO_5Si$ 466.2965.

Reaction of Epoxy Amides with Lithium Dimethylcuprate. To a suspension of CuI (2.0−3.0 equiv) in THF was added dropwise MeLi (1.6 M in Et_2O, 4.0−6.0 equiv) at 0 °C. The resulting colorless solution of Me_2CuLi was added to a solution of epoxy amide (1.0 equiv) in THF at 0 °C. The reaction mixture was stirred for 0.5−3.0 h at this temperature and quenched by careful addition of aqueous saturated NH_4Cl solution, followed by dilution with Et_2O. After separation of both phases, the aqueous phase was extracted with Et_2O twice and the combined organic layers were sequentially washed with aqueous saturated NH_4Cl solution, water and brine. After treatment with $MgSO_4$, the solvents were removed by reduced pressure to obtain a crude product which was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to afford the corresponding ring opened product.

Hydroxy Amide 68. Hydroxy amide **68** was obtained in a 75% as a colorless oil: $R_f = 0.29$ (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D = -19.8$ ($c = 0.6$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.01$ and 0.05 (2 s, 6 H), 0.63 (d, $J = 6.7$ Hz, 3 H), 0.83 (s, 9 H), 0.92 (d, $J = 7.3$ Hz, 3 H), 0.94 (d, $J = 6.9$ Hz, 3 H), 0.97 (d, $J = 7.2$ Hz, 3 H), 1.26 and 1.34 (2 s, 6 H), 1.73−1.83 (m, 1 H), 1.89 (q, $J = 7.0$ Hz, 1 H), 1.90−1.98 (m, 1 H), 2.78 (q, $J = 7.0$ Hz, 1 H), 2.91 and 3.00 (2 bs, 6 H), 3.42 (dd, $J = 11.4$ Hz, 1 H), 3.53 (d, $J = 10.4$ Hz, 1 H), 3.62 (dd, $J = 11.5$, 5.1 Hz, 1 H), 3.67 (dd, $J = 6.4$, 1.8 Hz, 1 H), 4.20 (bd, $J = 7.8$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.4$, −3.9, 8.7, 12.4, 12.7, 18.2, 19.7, 26.0, 29.6, 30.2, 35.6, 37.3, 38.2, 38.5, 39.7, 65.9, 74.1, 74.8, 81.5, 97.6, 167.2; FAB HRMS (NBA) *m/e* 482.3280, M + Na^+ calcd for $C_{24}H_{49}NO_5Si$ 482.3278.

Silylation of Hydroxy Amides. Procedure A. A solution of hydroxy amide (1.0 equiv) in DMF (0.1 M) was treated with tertbutyldimethylsilyl chloride (TBSCl) (1.2 equiv) at 25 °C in the presence of imidazole (2.5 equiv). After 12 h at this temperature, the reaction mixture was quenched by addition of MeOH, followed by addition of aqueous saturated NH_4Cl solution and dilution with Et_2O. After separation of both phases, the aqueous phase was extracted with Et_2O, the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed by reduced pressure to obtain a crude product which was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford the corresponding silyl ether. **Procedure B.** A solution of hydroxy amide (1.0 equiv) in CH_2Cl_2 (0.1 M) was treated with tertbutyldimethylsilyl trifluoromethanesulphonate (TBSOTf) (1.2 equiv) at 0 °C in the presence of 2,6-lutidine (1.5 equiv). After 0.5 h at 0 °C, the reaction mixture was quenched by addition of MeOH, followed by addition of aqueous saturated NH_4Cl solution and dilution with Et_2O. After separation of both phases, the aqueous phase was extracted with Et_2O, the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed by reduced pressure to obtain a crude product which was purified by flash column chromatography (silica gel) to afford the corresponding silyl ether.

Silyl Ether 69. Silyl ether **69** was obtained by procedure B in a 71% as a colorless oil: $R_f = 0.54$ (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D = -30.7$ ($c = 0.4$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = -0.07$, 0.01, 0.03 and 0.12 (4 s, 12 H), 0.66 (d, $J = 6.7$ Hz, 3 H), 0.79 (s, 9 H), 0.83 (d, $J = 7.0$ Hz, 3 H), 0.84 (s, 9 H), 0.86 (d, $J = 7.4$ Hz, 3 H), 0.95 (d, $J = 6.8$ Hz, 3 H), 1.26 and 1.31 (2 s, 6 H), 1.64−1.73 (m, 1 H), 1.79−1.86 (m, 2 H), 2.80 (q, $J = 7.0$ Hz, 1 H), 2.84 and 2.99 (2 s, 6 H), 3.42 (dd, $J = 11.2$ Hz, 1 H), 3.48 (dd, $J = 7.6$, 4.3 Hz, 1 H), 3.52 (dd, $J = 10.3$, 1.0 Hz, 1 H), 3.61 (dd, $J = 11.6$, 5.1 Hz, 1 H), 4.15 (dd, $J = 7.8$, 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -3.9$, −3.4, −3.3, 8.5, 9.8, 13.0, 13.8, 18.5, 18.9, 26.1, 29.7, 31.9, 35.7, 37.3, 40.1, 40.2, 41.4, 66.3, 73.5, 74.2, 76.6, 97.8, 174.5; FAB HRMS (NBA) *m/e* 596.4138, M + Na^+ calcd for $C_{30}H_{63}NO_5Si_2$ 596.4143.

Reduction of Amides with Super-H. A solution of amide (1.0 equiv) in THF (0.1 M) was treated with lithium triethylborohydride (Super-H) (1 M in THF, 3.0 equiv) at room temperature. The reaction mixture was stirred at room temperature until the reaction was complete as judged by TLC (ca. 8 h). The excess of Super-H was carefully quenched by addition of MeOH, and the resulting solution was diluted with Et_2O and washed with saturated aqueous NH_4Cl solution. The organic phase was separated, the aqueous layer was extracted with Et_2O (twice), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude product that was purified by flash column chromatography (silica gel, 20% AcOEt in hexanes) to afford the corresponding alcohol.

Alcohol 78. Alcohol **78** was obtained from amide **69** in a 82% yield: colorless oil; $R_f = 0.41$ (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D = -17.5$ ($c = 2.0$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.01$, 0.04, 0.05 and 0.06 (4 s, 12 H), 0.64 (d, $J = 6.6$ Hz, 3 H), 0.79 (d, $J = 7.2$ Hz, 3 H), 0.84 (s, 9 H), 0.85 (s, 9 H), 0.94 (d, $J = 7.2$ Hz, 3 H), 1.00 (d, $J = 7.1$ Hz, 3 H), 1.26 and 1.34 (2 s, 6 H), 1.68−1.77 (m, 2 H), 1.83−1.88 (m, 1 H), 1.96−2.04 (m, 1 H), 3.43 (dd, $J = 11.3$ Hz, 1 H), 3.53 (dd, $J = 11.1$, 4.7 Hz, 1 H), 3.62 (dd, $J = 11.5$, 5.1 Hz, 1 H), 3.64−3.67 (m, 2 H), 3.74 (dd, $J = 8.4$, 2.0 Hz, 1 H), 3.83 (dd, $J = 11.2$, 4.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.5$, −3.4, −3.3, 9.6, 11.8, 12.8, 15.9, 18.3, 19.5, 26.0, 26.2, 29.6, 30.3, 37.6, 39.0, 43.9, 64.9, 66.1, 74.3, 74.6, 79.0, 97.8; FAB HRMS (NBA) *m/e* 555.3882, M + Na^+ calcd for $C_{28}H_{60}O_5Si_2$ 555.3877.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds, and ^{1}H- and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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