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Asymmetric Synthesis of All Eight Seven-Carbon Dipropionate Stereotetrads

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Abstract: Enantiopure cycloheptadienyl sulfones **6** and **7** are diastereoselectively epoxidized to yield epoxyvinyl sulfones **8**, **9**, **14**, and **16** in high yields and diastereomeric ratios. Syn and anti methylation of epoxides **8**, **9**, **14**, and **16** enables access to all eight possible diastereomeric stereotetrads, seven of which are commonly found in polypropionate natural products. Anti methylations of the above epoxides are possible by either the reaction of methyl organometallics promoted by copper(I), or via reaction with trimethylaluminum to yield stereotetrads **11**, **12**, **22**, and **24**. Syn methylations are achieved via Lawton S_N2' reaction in the case of stereotetrads **10, 15**, and **38**, while stereotetrad **13** is accessed by an oxidation/reduction alcohol inversion sequence from stereotetrad **11**. All stereotetrads were obtained in high diastereomeric ratios and yields, and their relative stereochemistry was confirmed by X-ray crystallography. Oxidative cleavage of the cyclic stereotetrads yields termini-differentiated acyclic heptanyl stereotetrads ready for use in building larger fragments in the course of target syntheses.

Introduction

Polypropionates constitute a large family of natural products that are biosynthesized by the condensation of two or more propionic acid units.[1]

Many polypropionate natural products have been found to possess medicinally relevant biological activities. Important examples bearing the dipropionate stereotetrad include aplyronine A (**1**),[2] apoptolidine (**2**),[3] discodermolide (**3**)[4] (Figure 1), erythronolide B,[5] oleandolide,[6] amphotericin B,[7] and dictyostatin.[8] Of particular relevance to our research are the anti-actin agent aplyronine A (**1**), the apoptosis inducer apoptolidine (**2**), and the anti-tubulin compound discodermolide (**3**) (Figure 1). All three compounds show high promise as anticancer agents, with discodermolide (**3**) currently in clinical trials.[9] While there are ample examples of a family of natural products having members that differ by alcohol or methyl stereochemistry, to our knowledge, there are no examples where an *entire stereotetrad* has been substituted. When one considers the steric and electronic nature of the 1,3-dimethyl and 1,3-diol moieties of polypropionates, it can be argued that these segments are ideal conformational control elements, and their systematic substitution might provide analogues that exhibit conformational populations with improved binding to a target receptor. A synthetic approach systematically exploring the structure−activity relationships of a *single stereotetrad would require 16 total syntheses if all enantiopure diastereomers were incorporated.* Clearly, such an approach would rightly be disparaged as a mindless 'fishing expedition'. However, armed with substrate−enzyme X-ray structural information combined with *in silico* modeling, one should be empowered to select the most optimal "unnatural" targets for synthesis and testing.

Before undertaking the (still considerable) effort of several computationally inspired total syntheses, it was deemed prudent to demonstrate our ability to deliver significant quantities of all eight diastereomers potentially needed for the designer-SAR study.

Only a few methods used for the construction of polypropionate natural products are deemed of general utility, mostly relying on asymmetric aldol[10] and crotylation[11] chemistry.

(1) (a) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477. (b) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677.
(2) (a)Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020. (b) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Tsukada, I.; Tsuboi, T.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7441.
(3) Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 872 and references therein.
(4) (a)Kalesse, M. *ChemBioChem* **2000**, *1*, 171. (b) Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193 and references therein.
(5) (a) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falk, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620. (b) Oleinick, N. L. In *Antibiotics*; Corcoran, J. W., Hahn, F. E., Eds.; Springer-Verlag: New York, 1975; Vol III, pp 396−419.
(6) (a) Sobin, B. A.; English, R. A.; Celmer, W. D *Antibiot. Annu.* **1955**, *2*, 827. (b) Hochstein, F. A.; Els, H.; Celmer, W. D.; Shapiro, B. L.; Woodward, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 3225. (c) Celmer, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 1797. (d) Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *J. Am. Chem. Soc.* **1978**, *100*, 6733.
(7) Vandeputte, J.; Wachtel, J. L.; Stiller, E. T. *Antibiot. Annu.* **1956**, 587.
(8) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, *J. M. J. Chem. Soc., Chem. Commun.* **1994**, *9*, 1111. (b) Paterson, I.; Britton, R.; Delgado. O.; Wright, A. E. *Chem. Commun.* **2004**, *6*, 632.
(9) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004**, *67*, 1216.
(10) For excellent reviews: (a) Mahrwald, R., Ed. *Modern Aldol Reactions*; Wiley-VCH: New York, 2004. (b) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: New York 2000; p 249.
(11) For key reviews: (a) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: New York, 2000; p 403. (b) Denmark, S. E.; Almstead, M. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: New York, 2000; p 299.

10.1021/ja071217x CCC: $37.00

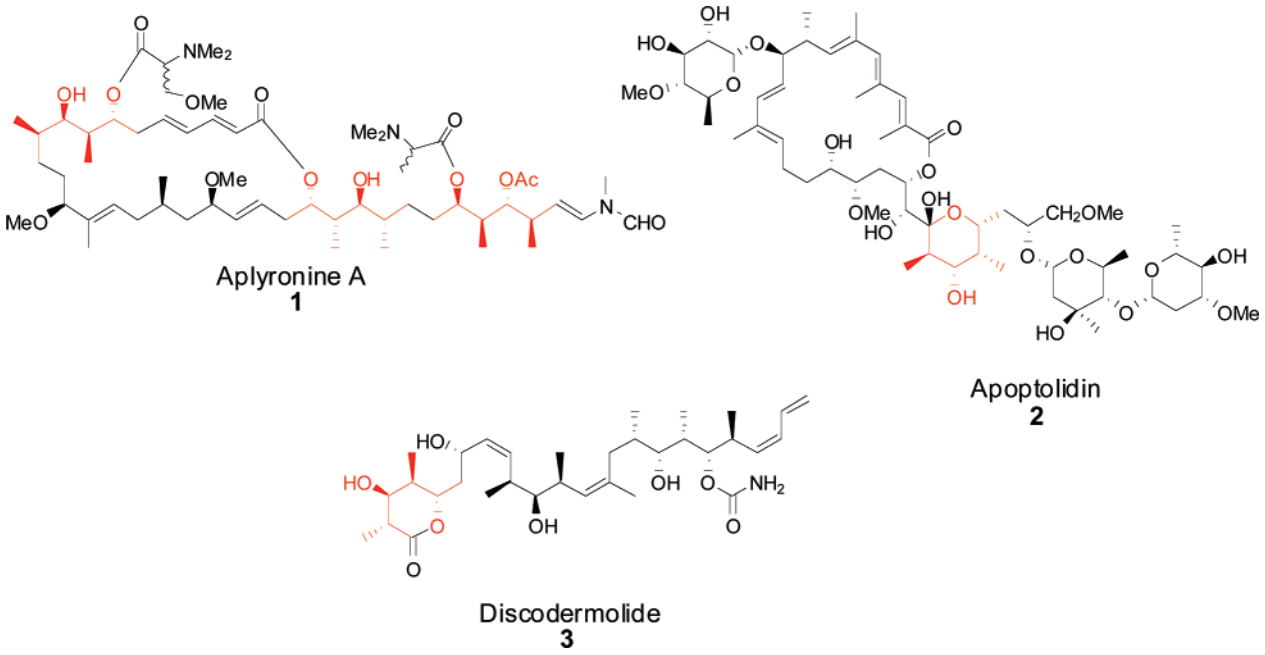


Figure 1. Dipropionate unit in natural products.

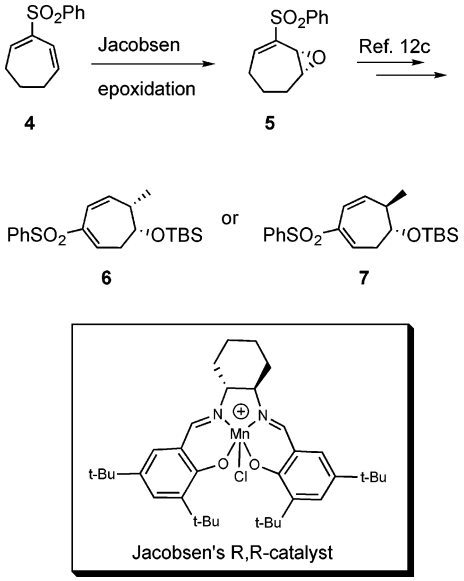
We envisioned a method for synthesis of the entire family of diastereomeric stereotetrads based on our previous experience with vinylsulfone chemistry.[12] Pivotal to this strategy is the use of environmentally friendly scalable synthetic methods. Hence, we elected to rely on substrate control whenever possible, and in cases where substrate control failed, asymmetric catalysts rather than stoichiometric reagents and auxiliaries were adopted.[13] Accordingly, the initial asymmetry was installed via catalytic asymmetric Jacobsen epoxidation.[14] All subsequent asymmetric centers were established with achiral reagents relying on substrate directed epoxidations, except epoxide **14** which was accessible only by double stereoselective reagent control via a second catalytic Jacobsen epoxidation. In seven of the eight stereotetrads it was possible to develop direct methods for stereoselectively installing the methyl group, while the eighth target relied on epimerization. Details of construction of the eight stereotetrads are discussed below.

Synthetic Plan

The synthetic plan begins with *syn*- and *anti*-dienyl sulfones **6** and **7**[12c] which are prepared from achiral dienyl sulfone **4**,[12a,15] available on the kilogram scale, wherein the first asymmetry is introduced via Jacobsen catalytic asymmetric epoxidation (Scheme 1).[12a]

Diastereoselective epoxidation of *syn*-dienyl sulfone **6** was correctly anticipated to afford epoxide **8** or **9** as a function of the reagent employed. Both **8** and **9** can be methylated from the beta face to give stereotetrads **10** and **12** or from the alpha face to give stereotetrads **11** and **13** respectively (Scheme 2). Likewise, *anti*-dienyl sulfone **7** can be epoxidized from either face followed by diastereoselective methylation of the resultant epoxides to produce the remaining four stereotetrads.

Scheme 1



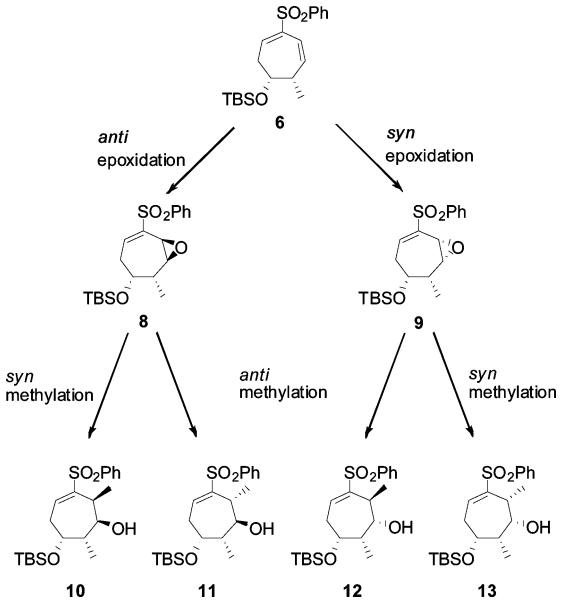
Essential to this plan was the ability to control the diastereoselectivity of each of the epoxidation and the methylation events.

During a study targeting the total synthesis of aplyronine A (**1**),[16] we previously demonstrated the synthesis of diastereomeric stereotetrads **10** and **15** by 1,2-*syn* methylation of epoxyvinyl sulfones **8** and **14** (Scheme 3). Furthermore, we have generally shown[12g] that epoxyvinyl sulfones can be attacked by methyl anion equivalents to give 1,2-*anti* addition products. Hence, a campaign for synthesis of all eight stereoterads was initiated. Moreover, since enantiopure epoxyvinyl sulfone **5** and

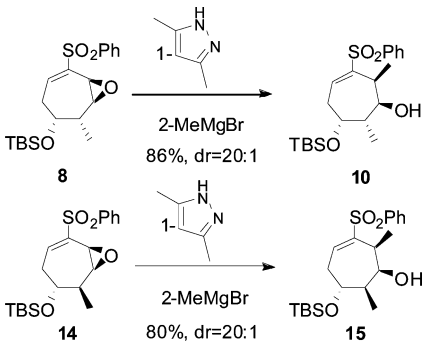
(12) (a) Park, T.; Torres, E.; Fuchs, P. L. *Synthesis* **2004**, *11*, 1895. (b) Tong, Z.; Ma, S.; Fuchs, P. L. *J. Sulfur Chem.* **2004**, *25*, 1. (c) Torres, E.; Chen, Y.; Kim, I.; Fuchs, P. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 3124. (d) Chen, Y.; Evarts, J.; Torres, E.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 3571. (e) Jiang, W.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2000**, *2*, 2181. (f) Evarts, J. B.; Fuchs, P. L. *Tetrahedron Lett.* **1999**, *40*, 2703. (g) Hentemann, M.; Fuchs, P. L. *Tetrahedron Lett.* **1999**, *40*, 2699. (h) Hentemann, M.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 5615.
(13) Fuchs, P. L. *Tetrahedron* **2001**, *57*, 6855.
(14) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
(15) Meyers, D. J.; Fuchs, P. L. *J. Org. Chem.* **2002**, *67*, 200.

(16) El-Awa, A.; Fuchs, P. L. *Org. Lett.* **2006**, *8*, 2905.

Scheme 2



Scheme 3



its enantiomer are available on the mole scale[12a] using ~1% of commercially available Jacobsen salen-Mn catalysts, access to all 16 possible stereotetrads is now possible.

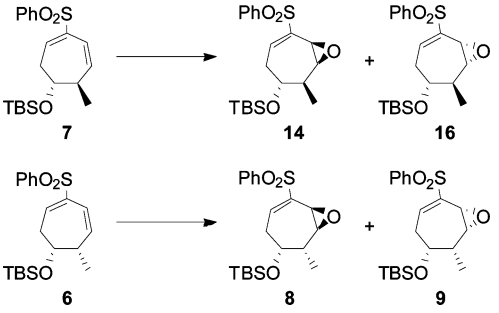
Results and Discussion

Epoxidations. Previous investigations by our group have indicated that *anti*-dienyl sulfone **7** is epoxidized with either antipode of Jacobsen's catalyst to give epoxides **14** and **16** in high selectivity (Table 1, entries 1 and 2). On the other hand, *syn*-dienyl sulfone **6** reacts with Jacobsen's *R,R*-catalyst to selectively give epoxide **8** (Table 1, entry 6). Perhaps not surprisingly, **6** is completely inert toward the α-face specific, Jacobsen *S,S*-catalyst (Table 1, entry 5).[17]

We envisioned that the existing asymmetric centers in **6** and **7** could be exploited in substrate-directed epoxidations with achiral reagents since the allylic methyl groups in **6** and **7** exert steric effects favoring anti epoxidations. Alternatively, the homoallylic silyl ethers present in both substrates can direct syn epoxidations by virtue of hydrogen bonding to the oxygen lone pairs. Therefore, judicious selection of the epoxidizing agent is critical in obtaining the desired epoxide in good selectivity, especially in the case of **6**, where both control elements have opposed facial biases. In the event, epoxidation of **6** with DMDO (dimethyldioxirane) quantitatively generated

(17) Torres, E. Ph. D. Thesis, Purdue University, May 2004. Also see ref 15.

Table 1. Epoxidation of Dienyl Sulfones **6** and **7**



entry	starting material	reagents	selectivity	yield (%)
1	**7**	Jacobsen's *R,R*-catalyst	**14:16** 50:1[a]	68[a]
2	**7**	Jacobsen's *S,S*-catalyst	**14:16** 1:10[a]	70[a]
3	**7**	CF_3COOOH	**14:16** >1:50[b]	100[b,c]
4	**6**	Jacobsen's *R,R*-catalyst	**8:9** 50:1[a]	72[a]
5	**6**	Jacobsen's *S,S*-catalyst	no reaction	0
6	**6**	DMDO	**8:9** 26:1[b]	100[b,c]
7	**6**	CF_3COOOH	**8:9** 1:10[b] (1:30)[d]	100[b] (71)[d]

[a] Yield and selectivity after flash column chromatography. [b] Crude yield and selectivity. [c] The crude epoxide showed high purity and did not need subsequent purification. [d] Yield and selectivity after crystallization.

epoxide **8** with a 26:1 selectivity (Table 1, entry 6).[18] Conversely, trifluoroperacetic acid gave epoxide **9** in a 10:1 selectivity, which was easily improved to 30:1 after crystallization from methanol (Table 1, entry 7).[19] In the former case, the absence of a hydrogen bond donor group in DMDO resulted in dominance of steric control from the methyl moiety, while the latter conditions featured hydrogen bonding of trifluoroperacetic acid to the silyl ether oxygen lone pair which substantially exceeded the steric bias of the methyl group. When using trifluoroperacetic acid with compound **7**, both control elements favored formation of epoxide **16**, resulting in formation of a single diastereomer in quantitative yield (Table 1, entry 3). Securing epoxide **14** via substrate-directed selectivity was not possible, requiring double stereoselection via Jacobsen's catalyst (Table 1, entry 1).

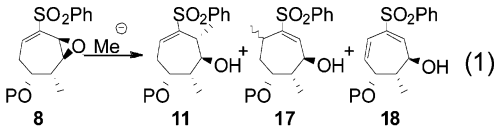
Anti Methylations. With all four epoxides in hand, investigation of anti methylation chemistry was initiated. Several literature reports have established that good 1,2-*anti* selectivity can be achieved in reaction of vinyl epoxides with different organometallic methylating agents.[20] Among these reagents are lithium tetramethylaluminate, lithium trimethylzincate,[20a] the combination of methyllithium or methyl Grignard with boron trifluoride,[20b] and a chiral copper(I) catalyst paired with dimethylzinc.[20c] Those reports represented an appropriate point

(18) Unless otherwise indicated, all ratios reported in this publication are based on ^{1}H NMR integrations.

(19) The crude NMR showed a quantitative conversion and 10:1 epoxidation selectivity.

(20) (a) Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* **2004**, 2151. (b) Alexakis, A.; Vrancken, E.; Mangeney, P.; Chemla, F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3352. (c) Pineschi, M.; Moro, F. D.; Crotti, P.; Bussolo, V. D.; Macchia, F. *J. Org. Chem.* **2004**, *69*, 2099.

Table 2. 1,2-*anti* Methylation of Epoxide **8**



P= TBS

entry	reagent and conditions	products and selectivity
1	Me_3Al/ rt/ DCM	**11:10**[a] 50:30
2	$Li(Me_4Al)$/ rt/ THF	complex mixture
3	$Li(Me_3Zn)$/ rt/ THF	**18**
4	MeMgBr/ rt/ THF	bromohydrin **11b** (10%)[b,c]
5	MeMgBr/ $BF_3{\cdot}OEt_2$ Et_2O/ −78 °C	bromohydrin **11b** (60%)
6	MeLi/ $BF_3{\cdot}OEt_2$ Et_2O/ −78 °C	**11:17**[d]**:18** 63:25:12
7	MeMgBr/ CuI (cat.) Et_2O/ −40 °C	**11:17**[e] 1:1
8	Me_2Zn/ Li_2CuCl_4 (cat.) Tol/ rt	**17**[f]
9	MeLi/ CuI(2:1) Et_2O/ −20 °C	**11:17**[d]**:6** 77:10:13
10	MeLi/CuCN (1:1) THF/ −75 °C	**11:17**[g] 11:89
11	MeLi/CuCN(2:1) Et_2O/ −78 °C	**11:17**[d] 63 :37
12	MeMgBr/CuI (2:1) Et_2O/ 0 °C	**11:17**[d]**:6** 46: 44: 10
13	MeLi/MeMgBr (1:1) CuI (cat)/ Et_2O/ −40 °C	**11:17**[d]**:6** 91:7:2

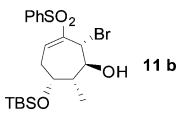
[a] The remaining 20% was an unidentified product. [b] 90% of the starting material was recovered. [c] See ref 22. [d] **17** was formed as a mixture of epimers. [e] **17** was formed as a single diastereomer. [f] **17** was formed as a single diastereomer epimeric to that in entry 7. [g] **17** was formed as a single epimer; the same as in entry 8.

of departure, although none of them had been applied to epoxyvinyl sulfones.

The results of screening different reagents for the 1,2-*anti* methylation of epoxide **8** are summarized in Table 2. Reaction of trimethylaluminum with epoxide **8** produced some **11**, but in low selectivity, along with syn methylation product **10** and an unidentified side product (Table 2, entry 1), while tetramethylaluminate gave a complex mixture of products (Table 2, entry 2). The zincate led mainly to base-promoted 1,4-elimination,[21] generating dienylic alcohol **18** (Table 2, entry 3). The use of boron trifluoride in conjunction with methylmagnesium bromide or methyllithium delivered bromohydrin **11b**[22] in the former instance and low selectivity for **11** in the latter (Table 2, entries 5 and 6). Although copper-promoted reactions of organometallics are known to predominantly favor 1,4-additions to vinyl epoxides,[23] there were several reports in the literature revealing that seemingly slight changes in reaction conditions, or including additives, resulted in striking changes in product distributions.[24] Hence, we launched a screening study

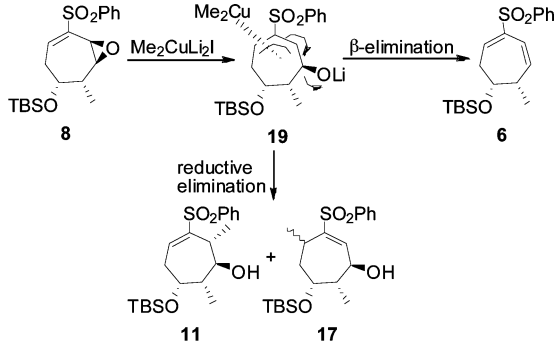
(21) (a) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064. (b) Thummel, R. P.; Rickborn, B. *J. Org. Chem.* **1971**, *36*, 1365.

(22) Bromohydrin structure:



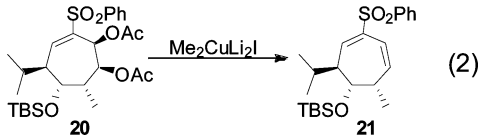
(23) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

Scheme 4



of organocopper reagents and methyl metals. Before trying the different combinations of organocopper reagents, it was determined that MeMgBr is very unreactive toward epoxide **8**, yielding 10% of the bromohydrin **11b**[22] along with recovery of 90% of the starting material after 2 days at room temperature in tetrahydrofuran (Table 2, entry 4). Copper-catalyzed addition of MeMgBr was very clean, but gave a 50:50 mixture of 1,2-*anti* **11** combined with the unassigned 1,4 adduct **17** (Table 2, entry 7). Varying the temperature between −60 °C to room temperature, the copper(I) source or solvent had negligible effect on the reaction. The 1,4-addition product **17** was formed as a single diastereomer in some instances, and as a mixture of epimers in others (Table 2).[25] Switching to dimethylzinc gave mostly 1,4-addition (Table 2, entry 8). Interestingly, the 1,4-product from the dimethylzinc reaction was epimeric to that from the Grignard reaction. Gilman's cuprate[26] gave the best selectivity thus far: 8:1 in favor of **11** (Table 2, entry 9). However, the reaction was accompanied with the formation of dienyl sulfone **6**, presumably by elimination of lithium alkoxide from the electron rich π-allyl copper intermediate **19** (Scheme 4).

Compound **20**, bearing the allylic acetate, a much better nucleofuge than lithium alkoxide, suffered β-elimination to provide **21** with no methylation being observed.[27]



Varying the reaction conditions (temperature, solvent, copper source) gave variable product ratios, with the most selective example shown in entry 9. Lower-order cyanocuprate gave good selectivity toward 1,4-addition consistent with studies by Marino et al.[28] Both the Lipshutz cuprate[29] and magnesiocuprate[24a] did not offer any advantage over Gilman's cuprate (Table 2, entries 11 and 12).

(24) (a) Lipshutz, B. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley: New York, 2002; p 665. (b) Taylor, R. J. K., Ed. *Organocopper Reagents a Practical Approach*; Oxford University Press: Oxford, 1994.

(25) The relative stereochemistries of the various 1,4-addition products were not determined.

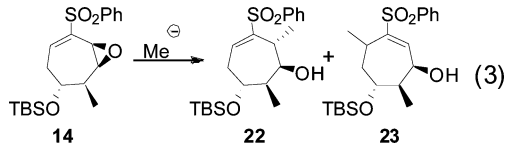
(26) (a) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1.

(27) Similar eliminations are precedents in the literature, see: (a) Hegedus, L. S.; Cross, J. *J. Org Chem.* **2004**, *69*, 8492. (b) Ibuka, T.; Chu, G.; Yoneda, F. *Tetrahedron Lett.* **1984**, *25*, 3247. (c) Logusch, E. W. *Tetrahedron Lett.* **1979**, *20*, 3365. (d) Ruden, R. A.; Litterer, W. E. *Tetrahedron Lett.* **1975**, *16*, 2043. (e) Nilsson, A.; Ronlan, A. *Tetrahedron Lett.* **1975**, *16*, 1107.

(28) Marino, J. P.; Jaen, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.

(29) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135 and references therein.

Table 3. 1,2-*anti* Methylation of Epoxide **14**



14 **22** **23**

entry	reagent and conditions	products and selectivity
1	Me_3Al/ rt/ CH_2Cl_2	**22:23** 5:1
2	MeMgBr/ CuI (cat.) Et_2O/ −35 °C	**22:23** 1:4
3	MeLi/ CuI(2:1) Et_2O/ −70 °C	**22:23** 14:1

Finally, when a 1:1 mixture of methyllithium and methylmagnesium bromide was cannulated to a solution of **8** in ether at −40 °C with suspended copper(I) iodide, stereotetrad **11** was obtained in 91:7:2 selectivity with respect to **17** and **6**, with an 80% isolated yield of pure **11** after flash column chromatography (Table 2, entry 13).[30] The rationale for employing the MeLi−MeMgBr combination was based upon the fact that the copper-catalyzed Grignard reaction was clean and reproducible yet not selective. However, Gilman's cuprate showed good selectivity for **11**, but was neither clean nor uniformly reproducible. Therefore, a reagent with hybrid properties was expected to result in better selectivity and yield, which proved to be the case. The actual species in the latter reaction is postulated to be dimethylmagnesium, as it has been reported that dimethylmagnesium can be prepared by mixing MeLi and MeMgX.[31]

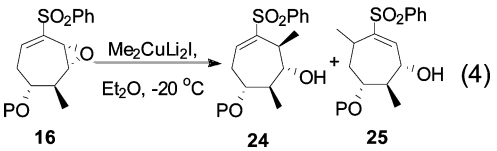
Having gained good experience with the anti methylation reaction of **8**, we next investigated the reaction of **14** starting with those reagents that had performed well (Table 3). Treatment of **14** with Me_3Al resulted in a 5:1 mixture of **22** and **23** respectively.[32] Cu(I)-catalyzed addition of MeMgBr furnished a reversed selectivity pattern giving **22** and **23** in a 1:4 ratio.

Finally, Gilman's reagent in ether at −70 °C gave **22**/**23** in 14:1 ratio, and a 62% isolated yield of pure **22** after flash column chromatography (Table 3, eq 3).

While Me_3Al and Cu(I)-catalyzed MeMgBr reagent gave unfavorable results, epoxide **16** reacted favorably with Gilman's reagent to give stereotetrad **24** in 10:1 selectivity with respect to the 1,4-addition product **25** with no diene **7** observed, and in 71% yield of pure **24** after chromatographic purification (Table 4, eq 4).

Since copper(I)-promoted reactions of epoxides **8**, **14**, and **16** were satisfactory, it was surprising that epoxide **9** exclusively gave 1,4-addition with both Gilman's reagent and the Cu(I)-catalyzed Grignard reagent. Me_3Al reacted with **9** to give 10:1 selectivity in favor of the desired 1,2-*anti* addition product **12**. However, the ratio varied between 2:1 and 13:1 depending on the number of equivalents of both Me_3Al and H_2O. After an extended systematic study,[33] it was determined that the optimum protocol consists of four equivalents of Me_3Al combined with

Table 4. 1,2-*anti* Methylation of Epoxide **16**

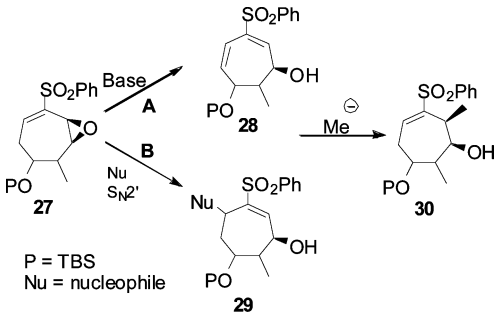


16 P= TBS **24** **25**

Selectivity= 10:1
Yield= 71%

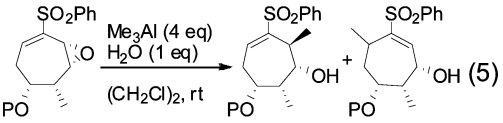
entry	reagent and conditions	products and selectivity
1	Me_3Al/ rt/ CH_2Cl_2	complex mixture
2	MeMgBr/ Li_2CuCl_4 (cat.) Et_2O/ −35 °C	**25**
3	MeLi/ CuI(2:1) Et_2O/ −20 °C	**24:25** 10:1

Scheme 5



27 **28** **29** **30**

one equivalent H_2O, which gave 100:1 selectivity and 87% isolated yield of **12** (eq 5).[34]



9 P= TBS **12** **26**

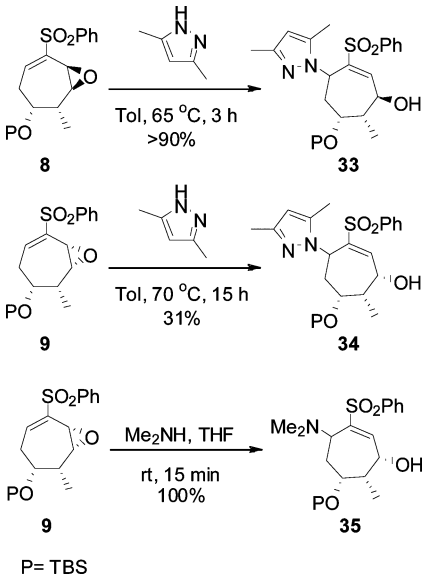
Selectivity= 100:1
Yield= 87%

Syn Methylations. The plan for achieving syn methylation relied upon converting the epoxyvinyl sulfone to an allylic alcohol with the double bond conjugated to the sulfone group. This structural arrangement was expected to enable OH-directed syn methylation to the vinyl sulfone. The desired result can be achieved in two possible ways (**A** or **B**, Scheme 5). Treatment of the epoxyvinyl sulfone **27** with a base should foster 1,4-elimination of the epoxide moiety, leading to cross-conjugated dienylic alcohol **28**. Subsequent OH-directed methylation would then give syn methylation product **30**. Alternatively, 1,4-addition to **27** with a hybrid species bearing nucleophilic/ nucleofugic properties would give allylic alcohol **29**. Subsequent reaction of **29** with a methyl anion would yield **30** by a Lawton S_N2' reaction (Scheme 5).[35]

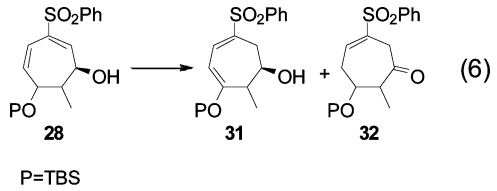
In practice, **28** proved to be unstable, giving silyl enolether **31** or ketone **32** under various conditions (eq 6). This isomerization which involves a formal 1,5-hydrogen migration, was quite fast, with a half-life of about 12 h under neutral conditions,

(30) Relative and absolute stereochemistries of all stereotetrads were determined by X-ray crystallography of the stereotetrads themselves or derivatives. See Supporting Information.
(31) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; p 62.
(32) **23** was obtained as a single diastereomer, and its relative stereochemistry was not determined.
(33) The results of that study will be published in due course.
(34) For precedence to the necessity of H_2O with Me_3Al in the reaction with epoxides see: Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483. However, in that publication and the ensuing ones from the same group 10 equivalents of Me_3Al and 5 equivalents of H_2O were necessary.
(35) Brocchini, S. J.; Eberle, M.; Lawton, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5211 and references therein.

Scheme 6



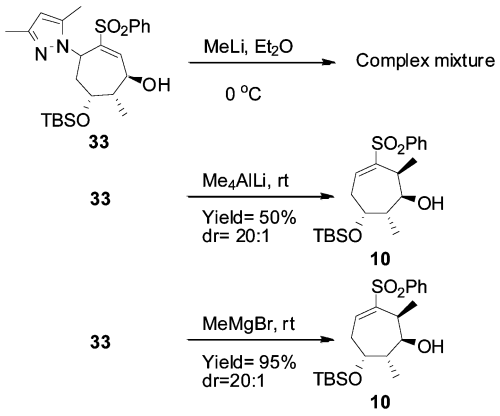
and is much faster under basic conditions.[36] Since generation of **28** is performed under basic conditions, it was invariably accompanied by 20−30% of **31** and/or **32**.



Moreover, addition of a methyl anion equivalent to **28** would generate an allyl anion bearing a β-OTBS group. Therefore, β-elimination may ensue, forming a conjugated diene with loss of one of the asymmetric centers of the stereotetrad's asymmetric centers.[37] Therefore, path **A** was abandoned (Scheme 5). Path **B** requires the nucleophile undergoing addition to epoxyvinyl sulfone **27** to possess several desirable properties: It should add regioselectively in a 1,4-fashion, should be weakly basic to avoid formation of **28**, and should have good nucleofugacity, so that it can be displaced simultaneously with the addition of the methyl moiety to **29**, i.e. the methyl group should perform an S_N2' reaction to directly generate **30**.

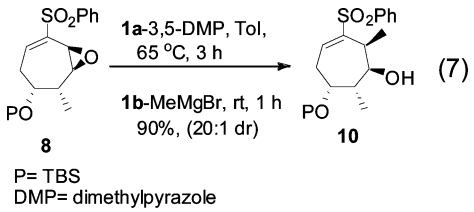
Screening to identify the optimal Lawton S_N2' nucleophile was performed on epoxides **8**, **9**, and **14**, with all three epoxides showing similar trends. Ethylthiol, pyrrole, and acetone cyanohydrin all returned the starting material. Thiolates,[38] imidazole, and iodide exclusively gave 1,2-addition. Cyanide fostered base-promoted elimination of the epoxide, yielding the dienylic alcohol. Dimethylamine gave clean and quantitative 1,4-addition to epoxide **9**, affording **35** (Scheme 6),[39] consistent with results previously demonstrated with five- and six-membered epoxyvinyl sulfones.[40] Nevertheless, since dimethylamide anion is a poor leaving group, it typically requires an additional nitrogen alkylation or oxidation step to enable C−N bond scission.[41]

Scheme 7



The search for a better nucleophile/nucleofuge was continued, with the azole moiety being the optimal compromise. Although pyrrole was totally unreactive, treatment of epoxide **8** with 3,5-dimethylpyrazole resulted in a virtually quantitative yield of the coveted Lawton S_N2' product **33** as a single diastereomer (Scheme 6).[16] Unfortunately, epoxide **9** reacted sluggishly with 3,5-dimethylpyrazole to give the desired adduct **34** in only 31% yield after 15 h in toluene at 70 °C (Scheme 6). Poor selectivity in the ensuing methylation step discouraged optimization of the yield of **34**.

Testing the syn methylation event was initiated with adduct **33**. Methyllithium resulted in complex mixtures (Scheme 7). While lithium tetramethylaluminate gave diastereomerically pure product **10**, the reaction failed to proceed beyond 50% conversion, even employing a larger excess of reagent.[42] Finally, treatment of **33** with three equivalents of methylmagnesium bromide in ether at room temperature gave 95% yield of stereotetrad **10** with 20:1 sy*n* selectivity (Scheme 7).[16] The selectivity of this reaction showed little solvent dependence, allowing a single-pot operation as follows: Epoxide **8** is first stirred with 3,5-dimethylpyrazole in toluene at 65 °C for 3 h, and allowed to reach room temperature followed by slow addition of MeMgBr and stirring at room temperature for an additional hour to give **10** in 90% yield and 20:1 selectivity (eq 7).



Epoxide **14** behaved similarly to **8** upon sequential treatment of 3,5-dimethylpyrazole and MeMgBr.[16] However, the MeMgBr step showed an interesting temperature dependence. Conducting the reaction at 0 °C afforded a 1:1 mixture of stereotetrads **15** and **22**. Running the reaction at −45 °C favored **22** by a factor of 4, while performing the reaction at 36 °C both reversed and amplified the selectivity to 20:1 in favor of **15** (Scheme 8).[43]

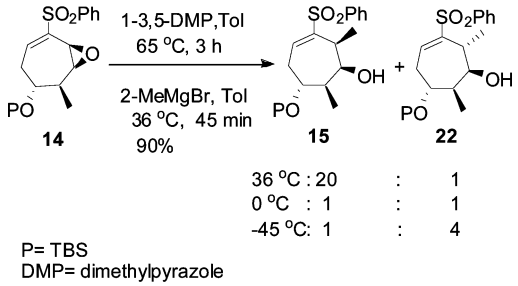
(36) While this reaction appears to involve an interesting competition between two 1,5-H migrations, we have not investigated the specifics of this process. We have previously observed a similar process in the 5-membered ring series. See: Saddler, J. C.; Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2110.

(37) In fact, that pathway is used to install the first methyl group very early on in the sequence used to make diad **13**. See footnote 12c.

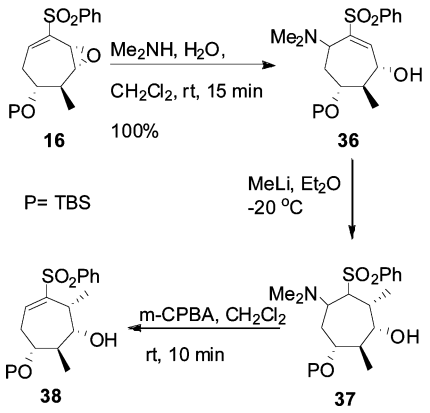
(38) Early experiments were performed either with benzyl or ethyl thiolates in combination with Lewis acids and resulted in exclusive 1,2-addition. However, later on we discovered that sodium thiolates in THF at −70 °C give good 1,4-selectivity.

(39) **33**, **34**, and **35** each was formed as a single diastereomer; however, their relative stereochemistries were not determined.

Scheme 8



Scheme 9

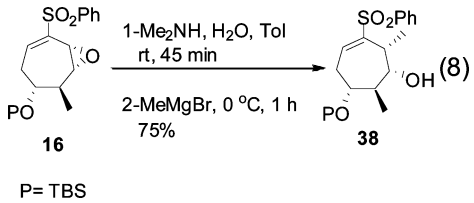


In contrast to epoxides **8** and **14**, reaction of 3,5-dimethylpyrazole with epoxide **16** gave a mixture of products with the desired adduct as a minor component.

Hence, Me_2NH was tested with **16**, giving a quantitative yield of 1,4-adduct **36** in 15 min at room temperature (Scheme 9).[44] Treatment of **36** with methyllithium at −20 °C for 90 min gave **37** in high selectivity. Amine **37** was then converted to stereotetrad **38** via Cope elimination[45] mediated by *m*-chloroperbenzoic acid (Scheme 9).

To determine if the magnesium counterion had any advantage over lithium, **36** was treated with MeMgBr at 0 °C, surprisingly resulting in direct formation of **38** in 25:1 diastereoselectivity and 75% yield.

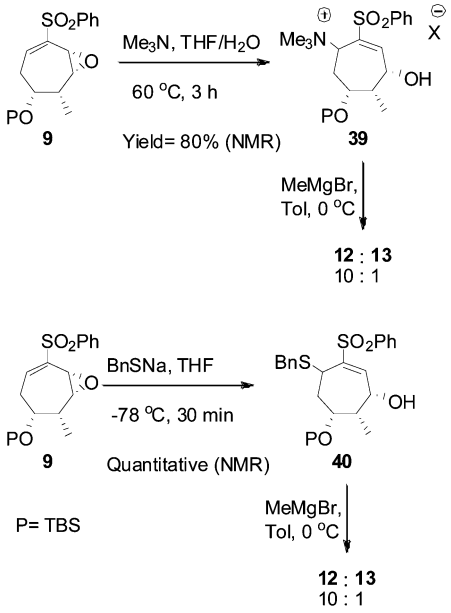
This may be explained by the stronger energy of the N−Mg bond relative to that of the N−Li bond,[46] rendering the formation of magnesiumdimethylamide species much more favorable than lithiumdimethylamide. In addition, the whole sequence starting from **16** was done in a single pot similar to the case of tetrads **10** and **15** giving tetrad **38** in 75% yield (eq 8).



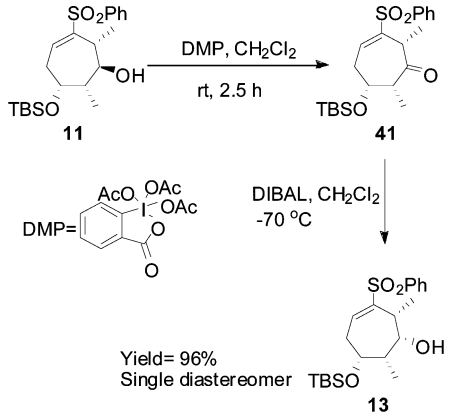
(8)

The final task was to make the eighth stereotetrad **13**. Since dimethylamine adduct **35** was in hand, it was subjected to methyllithium addition followed by oxidative Cope elimination.

Scheme 10



Scheme 11



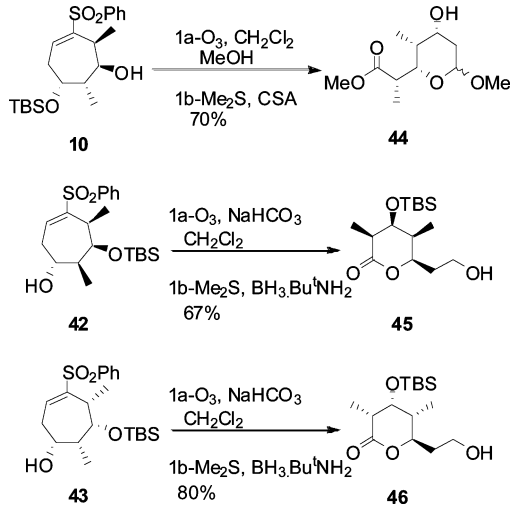
Unfortunately this led to formation of a 10:1 mixture of **12** and **13** in favor of the undesired anti addition product **12**. Switching to Grignard reagent or varying temperature or solvent did not offer much advantage. 3,5-Dimethylpyrazole adduct **34** reversed the selectivity, but gave only a mediocre 2:1 ratio in favor of **13**.

The improved result from the 3,5-dimethylpyrazole adduct encouraged the screening of more nucleophiles for the Lawton S_N2' reaction of epoxide **9**. Trimethylamine and sodium benzylthiolate both added in 1,4 fashion; however, both adducts **39** and **40** reacted with MeMgBr to predominantly give anti adduct **12** (Scheme 10).

These results suggested that the strong bias favoring formation of **12** is hard to override. Therefore, we elected to pursue an epimerization strategy. Tetrad **11** was quantitatively oxidized to ketone **41** via the Dess−Martin reagent.[47] Reduction of **41** after cooling to −70 °C, with diisobutylaluminum hydride in the same reaction pot, gave the final tetrad **13** in an overall yield of 96% as a single diastereomer (Scheme 11).

(40) Pan, Y.; Hardinger, S. A.; Fuchs, P. L. *Synth. Commun.* **1989**, *19*, 403.
(41) (a) Donaldson, R. E.; Saddler, J. C.; McKenzie, A. T.; Byrn, S.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167. (b) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137. (c) Hutchinson, D. K.; Hardinger, S. A.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1425. (d) Pan, Y.; Hutchinson, D. K.; Nantz, M. H.; Fuchs, P. L. *Tetrahedron* **1989**, *45*, 467.
(42) With both MeLi and Me_4AlLi various solvents and temperature ranges were tested yet without significant improvement.
(43) (a) See ref 16 for a proposition about this selectivity pattern. (b) In ref 16 we report that a 20:1 dr was obtained at room temperature. However, we later on found out that actually higher temperature (36 °C) is required to attain such ratio, and the previous result was due to the exotherm resulting from fast addition of MeMgBr.
(44) **36** was formed as a single diastereomer; however, its relative stereochemistry was not confirmed.
(45) Cope, A. C.; Foster, T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929.

Scheme 12



Because of scalability and economic issues, we also demonstrated that Swern oxidation[48] can replace the Dess−Martin protocol; however, the latter reagent required aqueous workup between the oxidation and reduction steps to remove the $Et_3N\cdot$HCl.

Oxidative Cleavage of the Stereotetrads. To be viable for use in synthesis of polypropionate natural products, the above stereotetrads have to be rendered acyclic and further functionalized and/or coupled with additional segments. Toward that end, we have subjected tetrads **10**, **42**,[49] and **43**[50] to ozonolytic cleavage to yield termini-differentiated stereotetrads **44**, **45**, and **46** (Scheme 12).[51]

Conclusion

All eight diastereomeric stereotetrads, seven of which are present in known polypropionate natural products, have been synthesized in high stereoselectivities and yields. Both antipodes of **5**, the first chiral intermediate in our synthetic scheme, are equally easily accessible; therefore, access to all 16 enantiomers of the eight diastereomeric tetrads is possible. Oxidative cleavage of the cyclic stereotetrads has been demonstrated, thus making termini-differentiated acyclic tetrads available for routine use in target syntheses.

Acknowledgment. We thank Arlene Rothwell and Karl Wood for providing MS data. We are most grateful to Professor Mark Lipton for his collaborative efforts in calculating unnatural targets bearing polypropionates (and related) tetrads.

Note Added after ASAP Publication. After this article was published ASAP on June 14, 2007, an error was discovered in the drawing of Jacobsen's catalyst in Scheme 1. The corrected version was published ASAP on July 2, 2007.

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

JA071217X

(46) A recent theoretical study shows that H_2N-MgH bond dissociation energy is 356.3 kJ/mol while that of H_2N-Li bond dissociation is 302.4 kJ/mol which is equal to a difference of 53.9 kJ/mol (12.9 kcal/mol). See: Mo, O.; Yanez, M.; Eckert-Maksic, M.; Maksic, Z. B.; Alkorta, I.; Elguero, J. *J. Phys. Chem. A* **2005**, *109*, 4359.
(47) Dess, P. B.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 5294.
(48) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
(49) **42** was obtained from **15** by a protection/selective deprotection operation. See ref 16.
(50) **43** was obtained from **13** by a protection/selective deprotection operation. See Supporting Information.
(51) For previous examples of ozonolytic cleavage of vinylsulfones from our lab see refs 12c, 12d, 12g, and 16.