

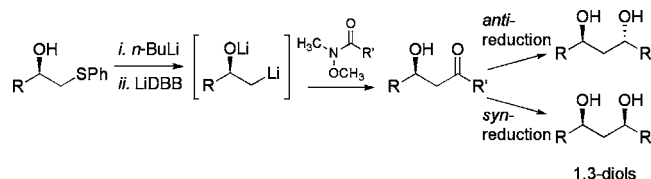
Polyol Synthesis with β -Oxyanionic Alkylolithium Reagents: Syntheses of Aculeatins A, B, and D

Viengkham Malathong and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California,
Irvine, California 92697-2025
srychnov@uci.edu

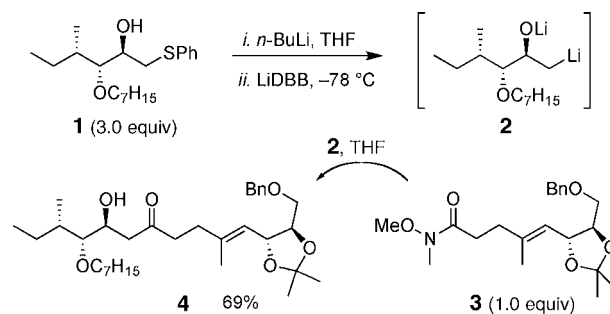
Received July 15, 2009

ABSTRACT



Synthesis of ketone aldol products using a non-aldol route was developed. The β -phenylthio alcohols were prepared from optically pure oxiranes. Deprotonation and reductive lithiation generated the key intermediate, a β -oxyanionic alkylolithium reagent. Addition to a Weinreb amide produced the β -hydroxy ketone in >90% yield using only 1.5 equiv of the phenylthio alcohol. Stereoselective reduction of the ketone led to either the *syn*- or *anti*-1,3-diol. This simple, convergent sequence was used to prepare aculeatins A, B, and D from a common intermediate.

Ketone aldol reactions are very useful for the construction of polyacetate and polypropionate natural products.¹ They allow carbon chains to be joined together to make much larger structures and are often the key disconnection in the retrosynthesis.² We recently reported an alternative sequence (Scheme 1) in which a β -oxyanionic alkylolithium reagent (**2**) was prepared and added to a Weinreb amide (**3**) to produce a β -hydroxy ketone (**4**). The sequence was used to prepare most of the carbon skeleton of amphidinol 3.³ This strategy nicely complements the traditional aldol sequence and offers several advantages, including the direct introduction of the stereogenic center from a chiral building block. Other groups have begun to adopt this method.⁴ One limitation is the use of a large excess of the alkylolithium reagent (3–4 equiv). In this Letter, we have

Scheme 1. Aldol Product from β -Oxyanionic Alkylolithium Reagents³

reinvestigated the generation of β -oxyanionic alkylolithium reagents and demonstrated that with normal precautions to exclude moisture, as little as 1.5 equiv of the alkylolithium precursor results in excellent yield of the coupled product. The utility of the improved procedure was demonstrated in a unified synthetic approach to aculeatins A, B, and D.

The β -oxyanionic alkylolithium reagents have been prepared by

(1) (a) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237–4313.
(b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506–7525.

(2) For recent examples of strategic aldol reactions in synthesis, see: (a) Evans, D. A.; Kvaerno, L.; Dunn, T. B.; Beauchemin, A.; Raymer, B.; Mulder, J. A.; Olhava, E. J.; Juhl, M.; Kagechika, K.; Favor, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 16295–16309. (b) Dunetz, J. R.; Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 16407–16416. (c) Bock, M.; Dehn, R.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9134–9137. (d) Lu, L.; Zhang, W.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 7253–7255. (e) Lanners, S.; Norouzi-Arasi, H.; Salom-Roig, X. J.; Hanquet, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7086–7089.

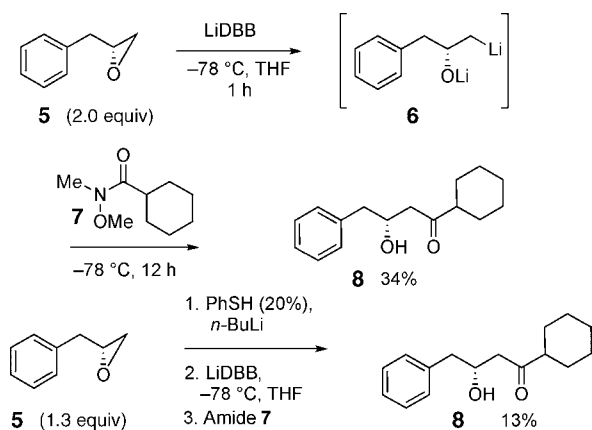
(3) Huckins, J. R.; De Vicente, J.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4757–4760.

(4) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047–5050.

a number of methods that include mercury–lithium exchange⁵ and reductive lithiation of chlorohydrins,⁶ oxiranes,⁷ and β -phenylthio alcohols.⁸ A few complex β -oxyanionic alkyllithium reagents have been prepared by reduction of oxiranes,^{7,9} but these reagents have not been used widely in synthesis. The β -phenylthio alcohols are typically prepared by nucleophilic opening of oxiranes; thus the most direct route to the alkyllithium reagents would be by direct reduction of oxiranes.

Reductive lithiation and coupling of a model oxirane is presented in Scheme 2. The reductive lithiation of oxirane **5**

Scheme 2. Aldol Products Formed by Reductive Lithiation of Oxiranes



generated β -oxyanionic alkyllithium **6**, which coupled only poorly with the Weinreb amide **7** to give the expected product in 34% yield. Both Cohen^{7b} and Yus^{7c} reported good yields for reductive lithiation of oxiranes followed by addition to aldehydes. Presumably the issue is not with the generation of the anion but rather with the coupling efficiency with the much less reactive Weinreb amide under these conditions.¹⁰ We considered the possibility that added thiophenol might catalyze the reduction of the oxirane or stabilize the alkyllithium agent. The addition of 20 mol % of thiophenol to the reaction did neither and actually resulted in a lower yield of product. Although oxiranes have been

reduced and added to aldehydes with excellent results,⁷ in our hands they did not add to a Weinreb amide efficiently.

Table 1. Optimized Coupling Between β -Oxyanionic Alkyllithium and Electrophiles

9: equiv	electrophile	equiv	product	yield
1.5		1.0		92–94%
1.0		1.0		68–85%
1.0		1.1		56%
1.0		1.0		52–60%
1.0		1.5		92% ^{b,c}

^a Compound **9** (100 mg) was titrated with *n*-BuLi with 1,10-phenanthroline as an indicator at 0 °C. The alkoxide was reduced with LiDBB at –78 °C for 1 h, followed by addition of the electrophile and stirring for 12 h. Isolated yields are reported and ranges are given for multiple runs.

^b The mixture was stirred for 2 h after addition of the electrophile. ^c The *syn*- and *anti*-diols were isolated as a 47:53 mixture of diastereomers.

Lithiation of β -phenylthio alcohols was much more effective, Table 1. The model phenylthio alcohol **9** was prepared from oxirane **5** using catalytic LiClO₄.¹¹ The alcohol **9** was dissolved in THF with 1,10-phenanthroline and titrated with *n*-BuLi to prepare the alkoxide and to remove all traces of water. The reductive lithiation was carried out with LiDBB (lithium 4,4'-di-*tert*-butylbiphenylide, Freeman's reagent)¹² at –78 °C in THF. The first entries in Table 1 show the addition to Weinreb amide **7**. With 1.5 equivalents of **9**, the product **8** was isolated in excellent yield. Reducing the ratio of phenylthio alcohol **9** and Weinreb amide **7** to 1:1 gave 68–85% of the product, a surprisingly good outcome.¹³ One reaction using the phenylthio

(10) Reductive lithiation of oxirane **5** with LiDBB and quenching with 1.5 equiv of isobutyraldehyde resulted in 59% of compound **12**. In a side-by-side reaction, quenching the alkyllithium with 1.0 equiv of Weinreb amide resulted in <20% of ketone **8**, accompanied by a significant amount of allylbenzene.

(11) Azizi, N.; Saidi, M. R. *Catal. Commun.* **2006**, *7*, 224–227.

(12) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.

(5) (a) Barluenga, J.; Fananas, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798–4801. (b) Barluenga, J.; Fananas, F. J.; Yus, M. *J. Org. Chem.* **1981**, *46*, 1281–1283.

(6) (a) Barluenga, J.; Florez, J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1153–1154. (b) Barluenga, J.; Florez, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 3019–3026. (c) Najera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289–300.

(7) (a) Bartmann, E. *Angew. Chem., Int. Ed.* **1986**, *25*, 653–655. (b) Cohen, T.; Jeong, I. H.; Mudryk, B.; Bhupathy, M.; Awad, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528–1536. (c) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2997–3008. (d) Dorigo, A. E.; Houk, K. N.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 8976–8978. (e) Grobely, Z. *Eur. J. Org. Chem.* **2004**, 2973–2982.

(8) (a) Foubelo, F.; Gutierrez, A.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 4837–4840. (b) Foubelo, F.; Gutierrez, A.; Yus, M. *Synthesis* **1999**, 503–514.

(9) (a) Soler, T.; Bachki, A.; Falvello, L. R.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 493–517. (b) Falvello, L. R.; Foubelo, F.; Soler, T.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2063–2066. (c) Yus, M.; Soler, T.; Foubelo, F. *Tetrahedron: Asymmetry* **2001**, *12*, 801–810. (d) Yus, M.; Maci, B.; Gúmez, C.; Soler, T.; Falvello, L. R.; Fanwick, P. E. *Tetrahedron* **2005**, *61*, 3865–3871.

alcohol **9** as the limiting reagent only gave 56%, but this result could certainly be improved upon. The use of a morpholine amide **10** was also effective, but resulted in slightly diminished yields compared with the Weinreb amide. Aldehydes are much better electrophiles, and generated the 1,3-diol **12** in 92% yield using phenylthio alcohol **9** as the limiting reagent. As expected, the 1,3-diol was produced as a 1:1 mixture of diastereomers, underscoring the need for an alternative strategy to introduce the second stereogenic center. Using a modest excess (1.5 equiv) of the phenylthio alcohol led to >90% yields of the desired aldol product.

The aculeatins A–D have attracted significant attention from synthetic chemists. They were isolated by Heilmann from the rhizomes of *Amomum aculeatum* and were reported to have significant antiprotozoal and antiplasmodial activity.¹⁴ In addition, they show low to submicromolar activity against KB cell lines, and aculeatin A was found to be active against MCF-7 (human breast cancer cells) using an in vivo hollow fiber assay.¹⁵ The synthesis of racemic aculeatin A and B was first reported by Wong,¹⁶ followed by enantioselective syntheses by Marco.¹⁷ Synthesis of aculeatin D was first reported by Baldwin.¹⁸ A number of other syntheses have followed, all of which use a final phenol oxidation to assemble the spirocyclic system.¹⁹ The aculeatins are interesting synthetic targets and promising lead compounds in a number of important therapeutic areas.

The retrosynthetic analysis of the aculeatins is presented in Figure 1. Aculeatin A and B are epimeric at the acetal center, with A having the thermodynamically favored configuration.^{17b} Similarly, aculeatin D is thermodynamically disfavored with respect to its C6 epimer. The final step is a biomimetic cyclization using a dithiane in place of the C6 ketone.¹⁶ *syn*-1,3-Diol **13** is the precursor to A and B, whereas *anti*-1,3-diol **14** is the precursor to aculeatin D. Both diols share a common 2*R*-configuration (aculeatin numbering), and they will be derived from the common intermediate **15** by stereoselective reduction. The key building blocks for

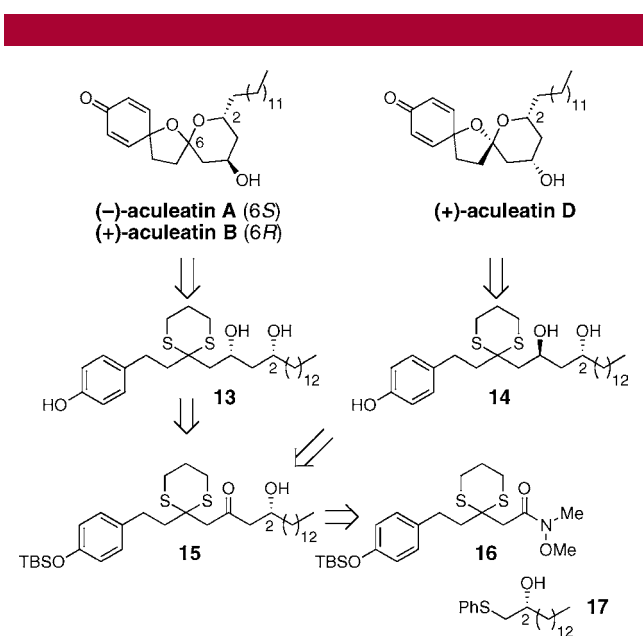
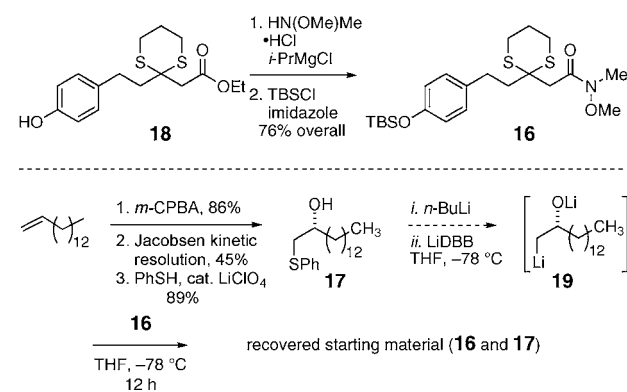


Figure 1. Structures and unified retrosynthetic analyses of aculeatins A, B, and D.

the planned syntheses are Weinreb amide **16** and the optically pure phenylthio alcohol **17**.

Synthesis of the building blocks and an initial attempt at the coupling reaction are shown in Scheme 3. Dithiane **18** was

Scheme 3. Synthesis of Aculeatin Precursors and an Attempted Coupling Reaction



(13) The reaction was quenched with NH_4Cl (aq) and did not show any indication of racemization or retro-aldol side reactions. When the reaction was quenched with $\text{MeOH}-d_4$, we observed partial deuteriation at the positions adjacent to the ketone but not at the benzylic position. Traces of retro-aldol product may be present, but apparently the forward aldol reaction is unfavorable. In cases where the yields of **8** were modest, most of the unreacted Weinreb amide **7** was recovered.

(14) (a) Heilmann, J.; Mayr, S.; Brun, R.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2000**, *83*, 2939–2945. (b) Heilmann, J.; Brun, R.; Mayr, S.; Rali, T.; Sticher, O. *Phytochemistry* **2001**, *57*, 1281–1285. (c) Salim, A. A.; Su, B.-N.; Chai, H.-B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. *Tetrahedron Lett.* **2007**, *48*, 1849–1853.

(15) Chin, Y.-W.; Salim, A. A.; Su, B.-N.; Mi, Q.; Chai, H.-B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. *J. Nat. Prod.* **2008**, *71*, 390–395.

(16) Wong, Y.-S. *Chem. Commun.* **2002**, 686–687.

(17) (a) Falomir, E.; Alvarez-Bercedo, P.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2005**, *46*, 8407–8410. (b) Alvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 9641–9649.

(18) Baldwin, J. E.; Adlington, R. M.; Sham, V. W. W.; Marquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353–2363.

(19) (a) Chandrasekhar, S.; Rambabu, C.; Shyamsunder, T. *Tetrahedron Lett.* **2007**, *48*, 4683–4685. (b) Peuchmaur, M.; Wong, Y.-S. *Synlett* **2007**, 2902–2906. (c) Peuchmaur, M.; Wong, Y.-S. *J. Org. Chem.* **2007**, *72*, 5374–5379. (d) Peuchmaur, M.; Saidani, N.; Botte, C.; Marechal, E.; Vial, H.; Wong, Y.-S. *J. Med. Chem.* **2008**, *51*, 4870–4873. (e) Ramana, C. V.; Srinivas, B. J. *J. Med. Chem.* **2008**, *73*, 3915–3918. (f) Suresh, V.; Selvam, J. J. P.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1509–1513. (g) Zhen, Z.-B.; Gao, J.; Wu, Y. *J. Org. Chem.* **2008**, *73*, 7310–7316.

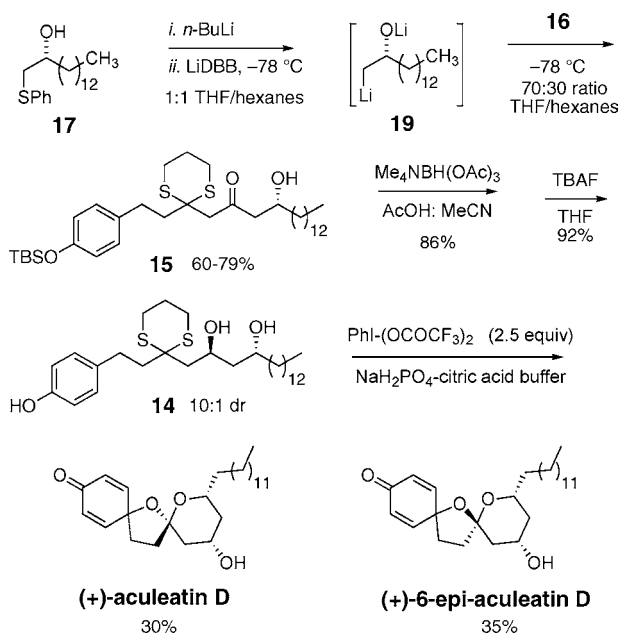
prepared by Wong's procedure.^{19d,16} Formation of the Weinreb amide²⁰ and protection of the phenol led to the coupling partner **16**. The optically pure hydroxy phenylthio alcohol **17** was prepared by epoxidation of 1-pentadecene, followed by Jacobsen kinetic resolution.²¹ The thiophenol addition was catalyzed by LiClO_4 to give optically pure²² phenylthio alcohol **17** in 34% overall yield. The initial coupling experiments, using the conditions reported in Table 1, gave none of the desired aldol product and returned both the Weinreb

(20) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. (b) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

amide **16** and the phenylthio alcohol **17**. Recovery of **17** indicated that the reductive lithiation reaction had failed.

The failure of the lithiation reaction led us to reoptimize the conditions for the coupling. The obvious difference between the reactive phenylthio alcohol **9** and the unreactive **17** was the long alkyl chain in **17**. We hypothesized that the lipophilic alkoxide formed by deprotonation of **17** was not available for reduction, possibly because it separated into a different phase or perhaps formed micelles in the THF solution. In an effort to avoid the hypothesized phase separation, we investigated different solvents and additives.²³ The lithiation was successful when the reaction was conducted in a 1:1 mixture of THF and hexanes, Scheme 4.

Scheme 4. Synthesis of Aculeatin D

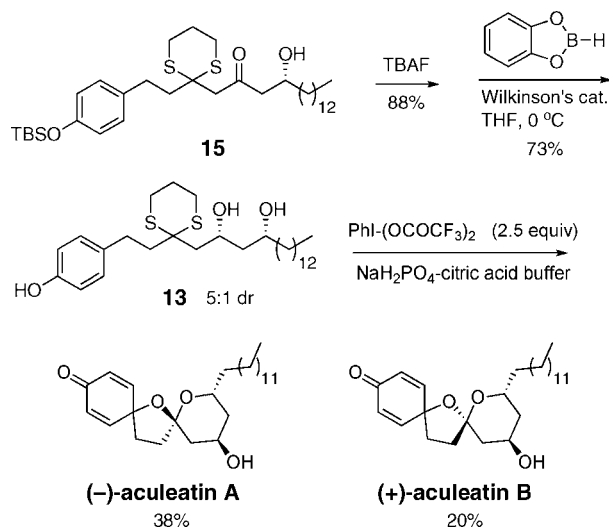


Addition of Weinreb amide **16** in THF resulted in a final solvent mixture of 70:30 THF/hexanes and delivered the aldol adduct **15** in 60–79% yield using 1.5 equiv of phenylthio alcohol **17**.²⁴ Ketone **15** is the common intermediate for all three aculeatins. Anti reduction using Evans' method²⁵ and deprotection led to *anti*-1,3-diol **14** as a 10:1 dr in very good yield. The final oxidative cyclization was conducted under citrate-buffered conditions^{19g} to generate aculeatin D in 30% yield, accompanied by the separable C6 epimer in 35% yield. Without the added buffer, only the C6 epimer was produced.^{19g} Aculeatin D was prepared in 7 steps from 1-pentadecane.

The synthesis of aculeatin A and B is shown in Scheme 5. Attempts to reduce **15** to the *syn*-diol using Narasaka's conditions (EtOBt₂, NaBH₄)²⁶ led to very slow and unselective reduction of the ketone. The steric crowding from the dithiane may slow the addition, and competing boron

coordination with the sulfur atoms may reduce the selectivity. Eventually we found that Evans' catecholborane procedure²⁷ was effective on the deprotected phenol and generated the *syn*-1,3-diol **13** with 5:1 dr. Oxidative deprotection and cyclization using Wu's buffered conditions gave aculeatin A (38%) and aculeatin B (20%).^{19g} The small amount of

Scheme 5. Synthesis of Aculeatin A and B



aculeatin D and its epimer were separated by chromatography at this stage. The NMR data for synthetic aculeatins A, B, and D were all identical to the literature data, and the optical rotations were consistent with the assigned configurations.

The β -oxyanionic alkylolithium addition to a Weinreb amide is a practical segment-coupling reaction to assemble β -hydroxy ketones. The aculeatins A, B, and D were prepared from a common intermediate using this method. This coupling reaction enables convergent synthesis of polyol chains and will be a valuable tool in natural product synthesis.

Acknowledgment. This work was supported by the National Institute of General Medicine (GM-043854) and by a generous gift from the Schering-Plough Research Institute. The S. T. Li foundation also provided financial support. V.M. thanks the Department of Education (GAANN) for a predoctoral fellowship.

Supporting Information Available: Characterization data and experimental procedures for all compounds described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL901623H

(21) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

(22) Compound **17** [$[\alpha]_D^{24} -27.2$ (c 0.99, CHCl₃)] was found to be a single enantiomer (>98% ee) by ¹H NMR analysis of the *R* and *S* Mosher's ester derivatives.

(23) Toluene/THF mixtures were also effective. Other additives (LiCl, HMPA) did not lead to any coupled product.

(24) The coupling of Weinreb amide **16** was attempted without the TBS protecting group, but neither the phenol nor the phenoxide was sufficiently soluble in the THF/hexanes mixture to react with the alkylolithium reagent.

(25) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(26) (a) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233–2338. (b) Chen, K.-M.; Hardtman, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.

(27) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190–5192.