

Asymmetric Synthesis of Quaternary Centers. Total Synthesis of (–)-Malyngolide

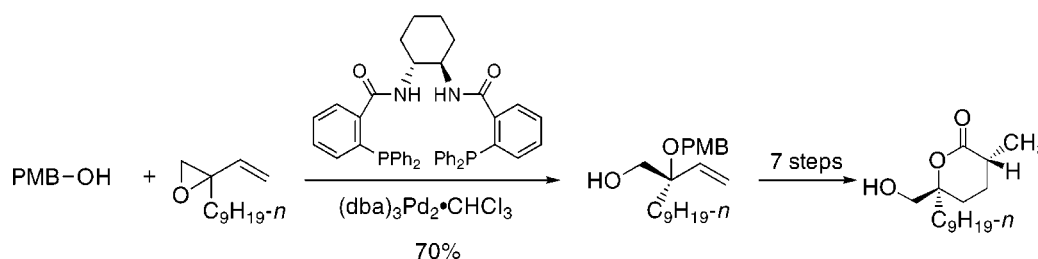
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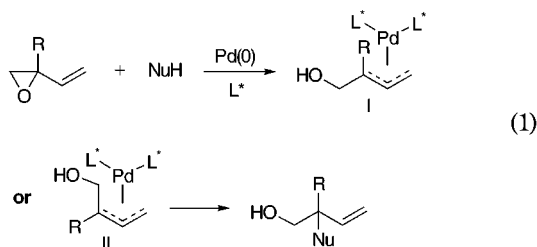
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ABSTRACT



The deracemization of 3-nonyl-3,4-epoxybut-1-ene with Pd(0) in the presence of chiral ligands using *p*-methoxybenzyl alcohol as a nucleophile proceeds regio- and enantioselectively to form the monoprotected vinylglycidol in 99% ee. This chiral building block was converted in seven steps to (–)-malyngolide, an antibiotic showing significant activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*. An interesting aspect involves controlling the diastereoselectivity of protonation of an enolate via a distal hydroxyl group.

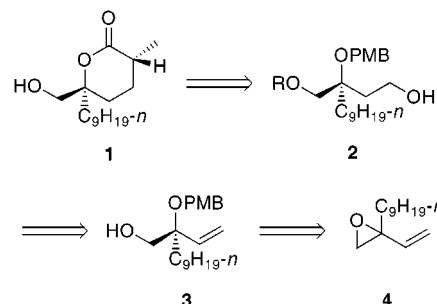
The regio- and enantioselective alkylation of vinyl epoxides using the Pd-catalyzed asymmetric allylic alkylation (AAA) offers a potentially powerful approach to vinylglycidols as chiral building blocks.¹ A particularly challenging task, the stereocontrolled creation of quaternary centers, as shown in eq 1, appears to be approachable by this strategy. Given the



working model, a key question becomes the effect of the size of the R group on the process both in terms of regio- and enantioselectivity. A particularly nettlesome aspect is

the question of the geometry of the intermediate π -allylpalladium complexes I and II. Since they lead to enantiomeric products and the syn-anti isomerization involving the substituted terminus would not be expected to occur at appreciable rates;² if both are formed kinetically, only low ee's can be expected. We chose to explore this issue in the context of a total synthesis of (–)-malyngolide (**1**) whose retrosynthetic analysis is outlined in Scheme 1. The target should

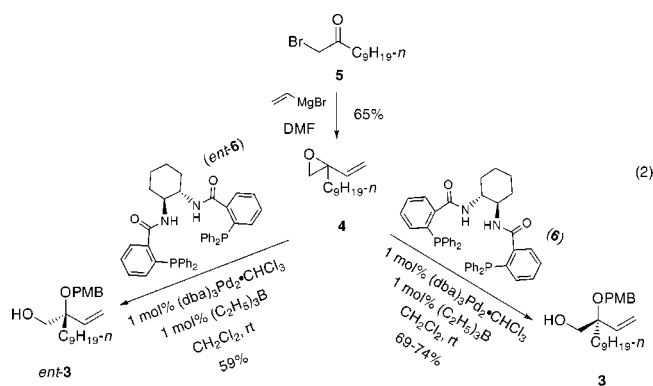
Scheme 1. Retrosynthetic Analysis of (–)-Malyngolide



(1) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702; Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 8649.

be accessible by chain extension of the primary alcohol of **2** with a propionate equivalent. Hydroboration-oxidation of **3** which could derive asymmetrically from racemic **4** would constitute a short efficient synthesis. (–)-Malyngolide, an antibiotic possessing significant activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, was isolated from the blue green alga *Lyngbya Majuscula*.³ The first asymmetric synthesis by Mukaiyama involves use of a chiral auxiliary.^{4a} Most syntheses employ either chiral auxiliaries or building blocks from the “chiral pool”.^{4–6} Few employ asymmetric catalysis⁷ which allows equal access to either enantiomer.

An advantage of the deracemization of vinyl epoxides via AAA is the ease of access of the substrate. The known bromoketone **5**⁸ produced from 2-undecanone by the procedure of Zav'ylov⁹ reacts with vinylmagnesium bromide to produce epoxide **4**¹⁰ directly in 65% yield (see eq 2).¹¹



Exposure of a 1:1 mixture of racemic epoxide **4** and *p*-methoxybenzyl alcohol to 1 mol % of a palladium(0) catalyst and 3 mol % of ligand **6** in the presence of 1 mol % of triethylboron gave PMB ether **3**¹⁰ as the exclusive regioisomer. Chiral HPLC analysis established the ee as 97–99%. Alternatively, the enantiomeric ether *ent*-**3** was obtained by simply changing the ligand to *ent*-**6**.

(2) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642. Also see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074.

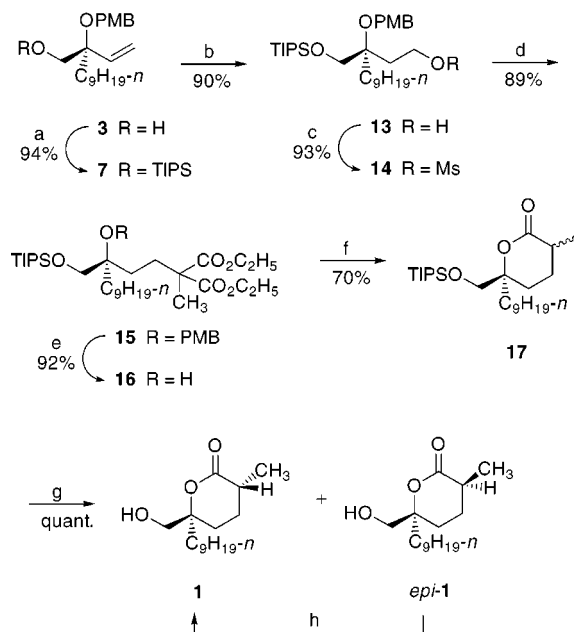
(3) Cardllina, J. H., II; Moore, R. E.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1979**, *44*, 4039.

(4) Chiral auxiliary syntheses: (a) Sakito, Y.; Tanaka, S.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 1223. (b) Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111. (c) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576. (d) Guingant, A. *Tetrahedron: Asymmetry* **1991**, *2*, 415. (e) Enders, D.; Knopp, M. *Tetrahedron* **1996**, *52*, 5805. (f) Maezaki, N.; Matsumori, Y.; Shogaki, T.; Soejima, M.; Tanaka, T.; Ohishi, H.; Iwata, C. *Chem. Commun.* **1997**, 1755. (g) Winter, E.; Hoppe, D. *Tetrahedron* **1998**, *54*, 10329. (h) Maezaki, N.; Matsumori, Y.; Shogaki, T.; Soejima, M.; Ohishi, H.; Tanaka, T.; Iwata, C. *Tetrahedron* **1998**, *54*, 13087.

(5) Chiral pool syntheses: (a) Pougny, J.-R.; Rollin, P.; Sinay, P. *Tetrahedron Lett.* **1982**, *23*, 4929. (b) Ho, P.-T.; Wong, S. *Can. J. Chem.* **1985**, *63*, 2221. (c) Tokunaga, Y.; Nagano, H.; Shiota, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 581. (d) Trinh, M.-C.; Florent, J.-C.; Monneret, C. *Tetrahedron* **1988**, *44*, 6633. (e) Honda, T.; Imai, M.; Keino, K.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2677. (f) Ichimoto, I.; Machiya, K.; Kiriha, M.; Ueda, H. *Agric. Biol. Chem.* **1990**, *54*, 657. (g) Matsuo, K.; Hasuiki, Y.; Kado, H. *Chem. Pharm. Bull.* **1990**, *38*, 2847. (h) Nagano, H.; Ohno, M.; Miyamae, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2814. (i) Ohira, S.; Ida, T.; Moritani, M.; Hasegawa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 293. (j) Matsuo, K.; Matsumoto, T.; Nishiaki, K. *Heterocycles* **1998**, *48*, 1213. (k) Carda, M.; Castillo, E.; Rodriguez, S.; Marco, J. A. *Tetrahedron Lett.* **2000**, *41*, 5511.

With the availability of the vinylglycidol **3** with high enantiopurity, the stage is now set for the synthesis of either enantiomer of malyngolide. The initial strategy examined the introduction of the additional required propionate unit in an intramolecular fashion. Thus, the silylated vinylglycidol **7** (see Scheme 2) was deprotected to the alcohol **8** (eq 3).

Scheme 2. Synthesis of (–)-Malyngolide^a



^a (a) TIPSO/SO₂CF₃, (C₂H₅)₃N, CH₂Cl₂, 0 °C; (b) 9-BBN–H, 4 mol % of (Ph₃P)₃RhCl, THF, rt; H₂O₂, NaOH, THF, 50 °C; (c) CH₃SO₂Cl, (C₂H₅)₃N, CH₂Cl₂, –78 °C; (d) CH₃CH(CO₂C₂H₅)₂, NaH, PhCH₃, 100 °C; (e) DDQ, CH₂Cl₂, H₂O, rt; (f) NaOH, H₂O, C₂H₅OH, reflux; HOAc; PhCH₃, reflux; (g) TBAF, THF, 0 °C; (h) see text.

Acylation of the magnesium alkoxide of **8**¹² selectively produced the tertiary propionate **9** uncomplicated by any silyl migration. On the other hand, the migration of the propionate

(6) Other asymmetric syntheses: (a) Noda, Y.; Kikuchi, M. *Synth. Commun.* **1985**, *15*, 1245. (b) Giese, B.; Rupaner, R. *Liebigs Ann. Chem.* **1987**, 231. (c) Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron* **1991**, *47*, 6967. For enzymatic synthesis that permits access to single enantiomers, see: (d) Sato, T.; Maeno, H.; Noro, T.; Fujisawa, T. *Chem. Lett.* **1988**, 1739. (e) Suemune, H.; Harabe, T.; Xie, Z.-F.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 4337.

(7) Catalytic asymmetric syntheses: (a) Flörke, H.; Schaumann, E. *Liebigs Ann.* **1996**, 147. (b) Konno, H.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 6023. (c) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 3631.

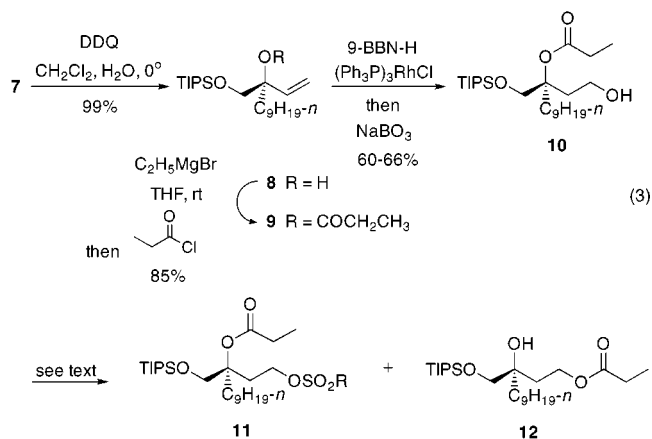
(8) Bryant, M. W.; Smith, R. A. J.; Wong, L. *Aust. J. Chem.* **1982**, *35*, 2529.

(9) (a) Zav'ylov, S. I.; Kravchenko, N. E.; Ezhova, G. I.; Sitkareva, I. V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1989**, *38*, 2152. (b) Zav'ylov, S. I.; Ezhova, G. I.; Sitkareva, I. V.; Dorofeeva, O. V.; Zavozi, A. G.; Rumyantseva, E. E. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1989**, *38*, 2204.

(10) This compound has been satisfactorily characterized spectroscopically and the elemental composition has been established by combustion analysis or high-resolution mass spectrometry.

(11) Sato, S.; Matsuda, I.; Izumi, Y. *J. Organomet. Chem.* **1989**, 359, 255.

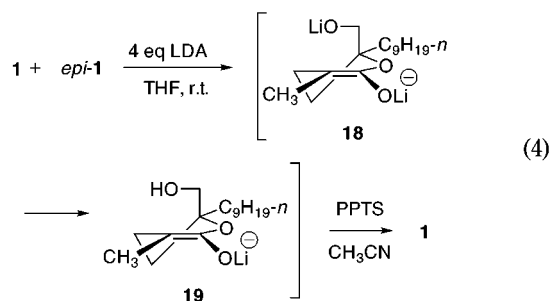
(12) Krafft, M. E.; Dasse, O. A.; Jarrett, S.; Fievre, A. *J. Org. Chem.* **1995**, *60*, 5093.



occurred in early attempts to form the alcohol **10**. Use of hydroboration catalyzed by Wilkinson's catalyst¹³ with sodium perborate as oxidant¹⁴ avoided the problem and allowed clean formation of **10**. However, attempts to activate the alcohol toward displacement by making the sulfonate **11** led predominantly to the acyl-migrated product **12**.

Switching to an intermolecular alkylation strategy avoided the issue as shown in Scheme 2. Again, rhodium-catalyzed hydroboration, to form alcohol **13**,¹⁰ was preferred, but otherwise the sequence to the mesylate **14** and subsequently the alkylation product **15**¹⁰ proceeded straightforwardly. After oxidative removal of the PMB,¹⁵ hydrolysis of the hydroxy diester **16** and acidification to effect decarboxylation, followed by heating, gave the monosilyl derivative **17** as a 1:1 mixture of (–)-malyngolide **1** and its C-2 epimer quantitatively.

Enhancement of the desired epimer **1** was envisioned to be possible as outlined in eq 4. If the dianion **18** would adopt

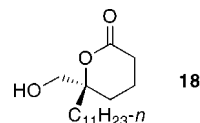


the conformation depicted, initial protonation of the more basic alkoxide oxygen, to form alcohol **19**, could then lead

(13) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878. Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671.

to internal delivery of the proton to form **1**. In the event, addition of 4 equiv of LDA in THF to the 1:1 mixture followed by inverse quenching into a solution of PPTS in acetonitrile gave a 3:1 mixture of **1**:*epi*-**1** from which pure **1** was isolated in 61% yield, pure *epi*-**1** in 20% yield, and a mixture of **1** and *epi*-**1** in 5% yield. Recycling the latter two fractions just once would raise the yield of pure **1** to 76%.

This nine-step route from bromoketone **5** provided enantiomerically pure (–)-malyngolide in 12.5% overall yield which can be improved to 16.5% overall yield with one recycling. This strategy allows access to other interesting targets. For example, tanikolides (**18**), recently isolated from



the marine cyanobacterium *Lyngbya majuscula*, shows antifungal and brine-shrimp toxicity.¹⁶ Clearly, this target is easily accessed by this strategy starting from 2-tridecanone using *ent*-**6** as the ligand for the dynamic kinetic asymmetric transformation (DYKAT) and malonate for the chain extension.

The DYKAT of vinyl epoxides nicely accommodates rather bulky groups. This observation strongly indicates that the initial palladium-promoted ionization generates only one geometric isomer, I or II, regardless of the length of R. These results suggest a broad scope for this deracemization of 3-substituted vinyl epoxides.

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Supporting Information Available: Characterization data for **1**, **3**, **4**, **7**, **13**, and **15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

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

(16) Singh, I. P.; Milligan, K. E.; Gerwick, W. H. *J. Nat. Prod.* **1999**, *62*, 1333.