ORGANIC LETTERS

2006
Vol. 8, No. 18
3987−3990

De Novo Asymmetric Synthesis of Milbemycin β_3 via an Iterative Asymmetric Hydration Approach

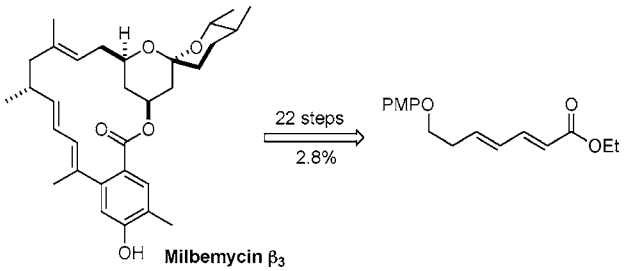
Miaosheng Li and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

george.odoherty@mail.wvu.edu

Received June 12, 2006

ABSTRACT



The enantioselective synthesis of the spiroketal/macrolide natural product milbemycin β_3 has been achieved in 22 steps and 2.8% overall yield from an achiral dienoate. The spiroketal ring system was installed by three sequential asymmetric hydrations followed by sprioketalization. Both the absolute and relative stereochemistry of milbemycin β_3 was introduced by two Sharpless asymmetric dihydroxylations, two π-allylpalladium-catalyzed reductions, and an iridium-catalyzed hydrogen migration/Claisen rearrangement to install the *C*-12 stereocenter.

Since their initial isolation and structural determination, the milbemycins[1,2] have attracted significant interest for their potential use as pesticides and pharmaceuticals. In addition to antibiotic activity, various members of this class of spiroketal/macrolide natural products have shown significant activity against various agricultural pests (e.g., mites, beetles, and tent caterpillars)[2,3] and parasites (e.g., nematodes, mites, ticks, and larvae of biting flies),[2,4] while displaying minimal cytotoxicity to plants and animals.[5] Pharmacological interest in the milbemycins reemerged after it was discovered that they are also potent efflux pump inhibitors.[6]

In addition to this array of fascinating biological activities, the milbemycin structural complexity has also attracted the attention of the synthetic community.[7,8] To date, several total syntheses of milbemycin β_3 have been completed,[7] along with various efforts to the spiroketal ring system.[8] While all of the previous syntheses of the milbemycin (**1**) derived their

(1) (a) Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kuwano, H.; Saito, A. *Tetrahedron Lett.* **1975**, *16*, 711−714. (b) Takiguchi, Y.; Ono, M.; Muramatsu, S.; Ide, J.; Mishima, H.; Terao, M. *J. Antibiot.* **1983**, *36*, 502−508. (c) Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120−1127.

(2) For a review see: (a) Shoop, W. L.; Mrozik, H.; Fisher, M. H. *Vet. Parasitol.* **1995**, *59*, 139−156. (b) Aoki, A. *J. Pestic. Sci.* **1992**, *19*, 245−247.

(3) Thamsborg S, Roepstorff A, Larsen M. *Vet. Parasitol.* **1999**, *84*, 169−186.

(4) Bowman, D. D.; Parsons, J. C.; Grieve, R. B.; Hepler, D. I. *Am. J. Vet. Res.* **1988**, *49*, 1986−1989.

(5) (a) Material Safety Data Sheet: Moxidectin: Fort Dodge Animal Health. (b) Fisher, M. H. *Pure Appl. Chem.* **1990**, *62*, 1231−1240.

(6) Chamberland, S.; Lee, M.; Lomovskaya, O. Milbemycin class efflux pump inhibitors for treating microbial infections and cancer. WO 98-US20916 19981001, 1999 AN1999:244572.

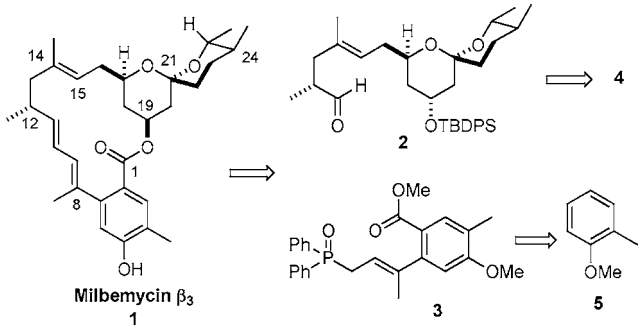
(7) (a) Smith, A. B.; III; Schow, S. R.; Bloom J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015−4018. (b) Schow, S. R.; Bloom J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2662−2674. (c) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708−4710. (d) Street, S. D. A.; Yeater, C.; Kocienski, P.; Campbell, S. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1386-1388. (e) Attwood, S. V.; Barrett, A. G. M.; Carr, R. A. E.; Robinson, G. *J. Chem. Soc., Chem. Commun.* **1986**, 479−481. (f) Baker, R.; O'Mahony, M. J.; Swain, C. *J. Chem. Soc., Chem. Commun.* **1985**, 1326−1328. (g) Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840−4856.

(8) (a) Yeater, C.; Street, S. D. A.; Kocienski, P.; Campbell, S. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1388−1389. (b) Baker, R.; O'Mahony, M. J.; Swain, C. *Tetrahedron Lett.* **1986**, *27*, 3059−3062. (c) Crimmins, M. T.; Bankaitis-Davis, D. M.; Hollis, W. G., Jr. *J. Org. Chem.* **1988**, *53*, 652−657. (d) Holoboski, M. A.; Koft, E. *J. Org. Chem.* **1992**, *57*, 965−969.

10.1021/ol061439k CCC: $33.50
Published on Web 08/08/2006

asymmetry from the chiral pool, we were interested in a de novo asymmetric approach that would use asymmetric catalysis to install the six stereocenters in milbemycin β_3 from achiral starting materials (**5** and **10**, Scheme 1).[9] Herein

Scheme 1. Milbemycin β_3 (**1**) and Its Retrosynthesis

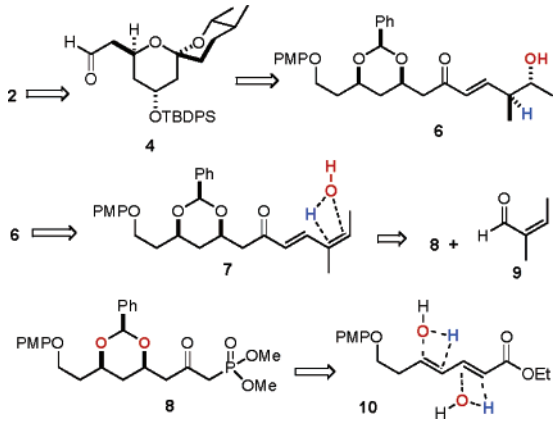


we describe our successful efforts to implement this strategy for the de novo synthesis of milbemycin β_3.

Retrosynthetically, we envisioned milbemycin β_3 (**1**) being prepared by an olefination/macrolactonization strategy. This transform divided the molecule into two halves, an achiral phosphine oxide **3**, which was first prepared by Smith,[10] and a silyl-protected hydroxyaldehyde **2**, which possessed both the spiroketal and the five chiral centers of milbemycin. Following the Barrett precedent, we planned to install the sixth chiral center during a Mitsunobu macrocyclization.[11]

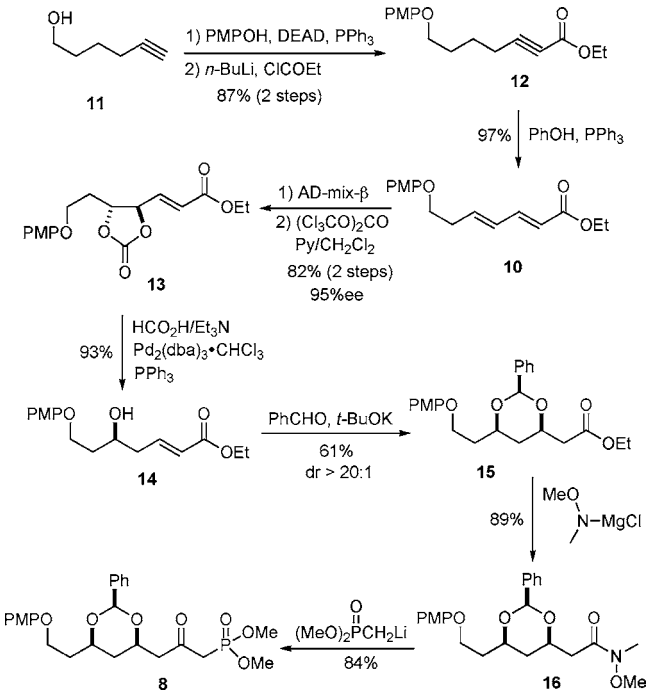
Using a transition-metal variant of the Smith's vinyl anion addition Claisen rearrangement, we planned to prepare **2** from spiroketal **4**, which in turn could be prepared from the partially protected tetraol **6**. Finally, we hoped to establish the four chiral centers and triol functionality of **6** by the iterative use of our asymmetric hydration protocol (i.e., **10** to **8** and **7** to **6**) (Scheme 2).[12]

Scheme 2. Retrosynthesis of Spiroketal **2**



In practice, dienoate **10** was prepared by a three-step protocol from commercially available **11** via protection, carboxylation, and ynoate isomerization.[13] Using our three-step asymmetric hydration protocol (dihydroxylation, carbonate formation, and palladium-catalyzed reduction),[12] dienoate **10** was regio- and enantioselectively transformed into δ-hydroxy enoate **14**, which in turn was diastereoselectively hydrated to form the protected 3,5-dihydroxy ester **15** using Evans' procedure.[14] The ester **15** was then converted into the β-ketophosphonate **8** via Weinreb amide **16** (75% for the two steps) (Scheme 3).

Scheme 3. Synthesis and Bis-hydration of Dienoate **10**



The last five carbons of the spiroketal portion of milbemycin β_3 came from angelaldehyde (**9**) and were installed via a Horner−Wadsworth−Emmons reaction with **8**. Exposure of ketophosphonate **8** to aldehyde **9** with Cs_2CO_3 as base produced the *E*,*Z*-dienone **7** in 82% yield (Scheme 4). Using a similar three-step sequence, as on dienoate **10**, dienone **7** was diastereoselectively hydrated (**7** to **17a**).[12] Regioselective dihydroxylation of **7** gave an inseparable diols **17a/b** in 58% yield and diastereocontrol.[15] Because of the distance between the relevant stereocenters, it was difficult to distinguish diastereomers **17a** and **17b** by ^{1}H NMR and

(9) While it did not exclusively use asymmetric catalysis, Emil Koft had previous demonstrated that the spiroketal portion of Milbemycin β_3 could be prepared from an achiral starting material, see: ref 8d.

(10) We prepared phosphine oxide **3** by a slightly modified variant of the Smith route, see Supporting Information and ref 7b.

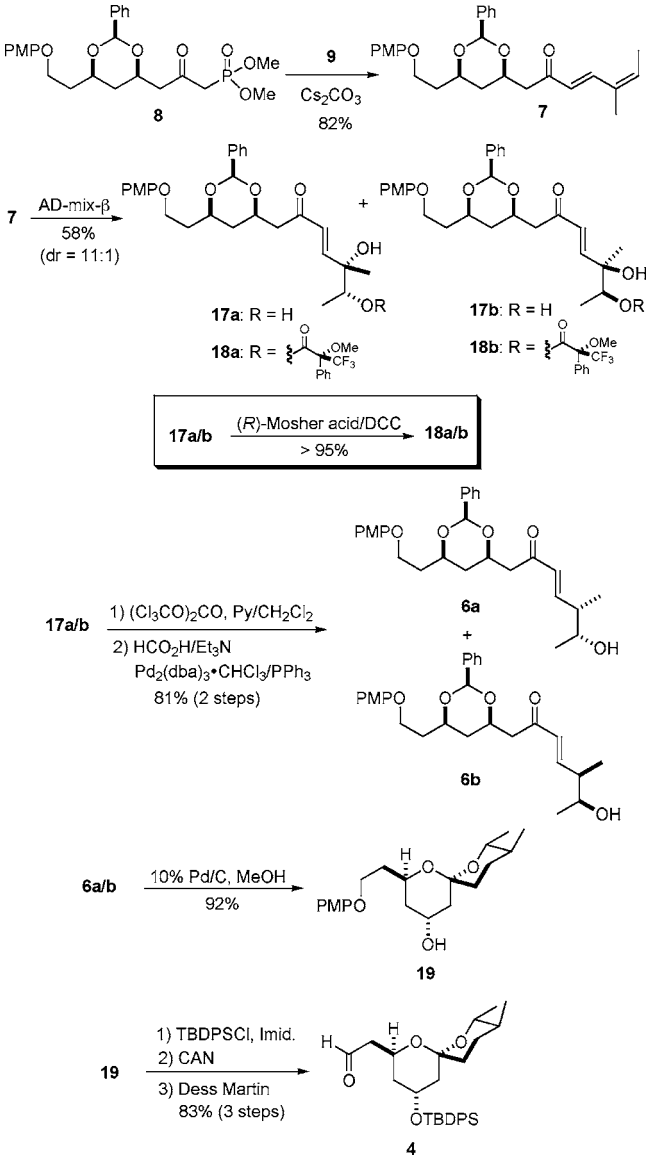
(11) Barrett had previously shown that the *C*-19 carboxylate could be installed by a Mitsunobu reaction, see: ref 7g and Mitsunobu, O. *Synthesis* **1981**, 1−28.

(12) For examples of the asymmetric hydration of unsubstituted dienoates (e.g. **10** to **8**), see: Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*(7), 1049−1052. Our study of the asymmetric hydration of substituted dienoates, will be published in due course.

(13) (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659−2660. (b) Trost, B.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933−35.

(14) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446−2453.

Scheme 4. Synthesis of Spiroketal **4** via Dienone Hydration



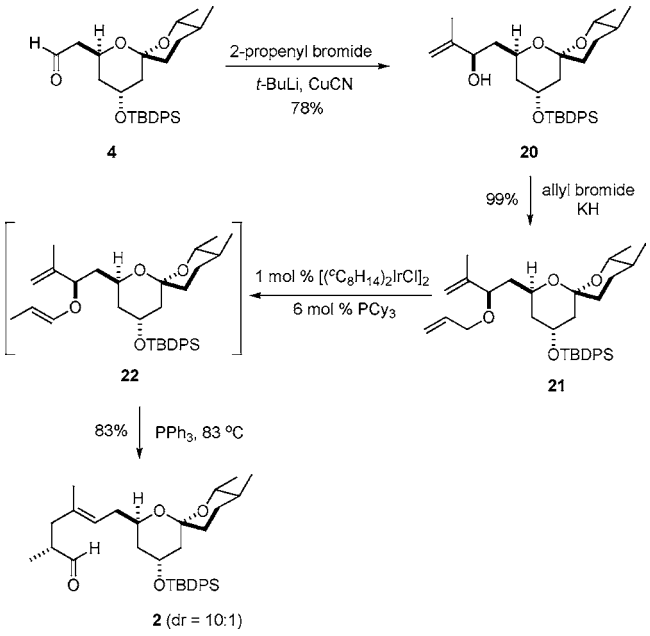
TLC. Thus, Mosher ester analysis (**17a/b** to **18a/b**, see the Supporting Information) was used to determine the diastereomeric ratio of **17a** to **17b** (dr = 11:1). The mixture of diastereomers **17a/b** was converted into cyclic carbonates and stereoselectively reduced with HCO_2H/Et_3N and catalytic palladium(0) in CH_2Cl_2/hexane to give alcohols **6a/b** (93%).[16] As with **17a/b**, the diastereomers **6a/b** were not easily differentiated by ^1H NMR or separated by chromatography. The diastereomeric alcohols **6a/b** were cleanly converted into spiroketal **19** via a one-pot hydrogenation/hydrogenolysis/spiroketalization procedure (92%). The minor diastereomeric impurity in **19** was easily removed by recrystallization from a mixture of EtOAc/hexanes (9:1). The *C*-19 alcohol was protected as the TBDPS-ether, the PMP-group was oxidatively removed with CAN and the *C*-15 alcohol was oxidized to the aldehyde with the Dess−Martin reagent in an 83% overall yield.

We next looked to extend the *C*-15 aldehyde to the *C*-11 aldehyde. Based on the Smith synthesis, we planned to establish the *C*-14/*C*-15 *E*-double bond and the *C*-12 stereocenter by a Claisen rearrangement. In contrast to Smith's use of an Ireland enolate rearrangement, we chose to use the isomerization-Claisen rearrangement (ICR) developed by Nelson.[17] This procedure has the added advantage of providing the aldehyde **2** directly.

When aldehyde **4** was exposed to a vinyl cuprate reagent, an exceedingly diastereoselective addition (dr > 20:1) occurred to give allylic alcohol **20** in good yield (78%). The allylic alcohol **20** was allylated with KH/AllylBr to give allylic ether **21** in nearly quantitative yield (99%). Following the Nelson protocol, allylic ether **21** was exposed to catalytic iridium and tricyclohexylphosphine. Under these conditions, allylic ether **21** cleanly rearranged to the *E*-enol ether **22**, at which point 6 mol % of PPh_3 was added and the dichloroethylene solution was refluxed. After heating for 24 h, an 83% yield of aldehyde **2** was isolated. While aldehyde **2** can be purified by SiO_2 chromatography, this leads to lower diastereoselectivity (dr = 4:1). The preferred procedure was to use the crude aldehyde in the subsequent transformation. Analysis of the crude ^1H NMR indicated that the diastereomeric ratio of crude **2** was on the order of 10:1 (Scheme 5).

Finally, with aldehyde **2** in hand, we set out to stitch the two fragments together via an olefination and lactonization. The *E*,*E*-diene of **23** was stereoselectively installed upon

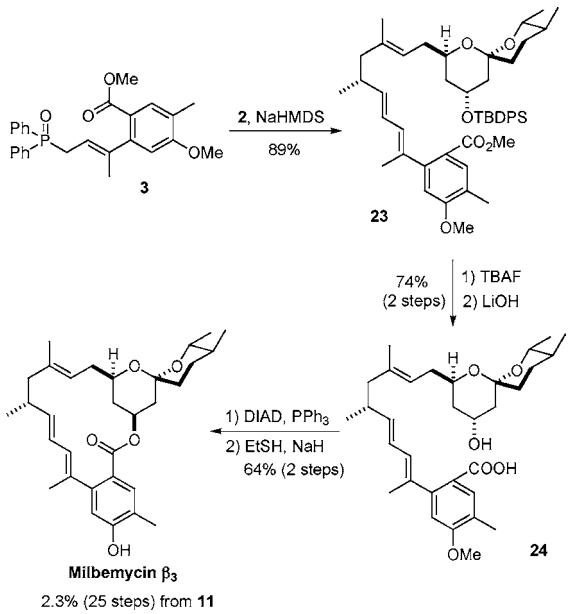
Scheme 5. Synthesis of Aldehyde **2** via an ICR Reaction



(15) Because most of the enantiomeric impurity in **7** is converted into the minor diastereomer ***ent*-17b** during the asymmetric dihydroxylation (**7** to **17a/b**), the major diastereomer diol **17a** was isolated in essentially enantiomeric pure form. Consequently, the minor diastereomer **17b** must be formed with lower enantiopurity. For other examples of this enantio-enriching phenomena, see: Ahmed, Md. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745−748.

(16) The CH_2Cl_2/hexane solvent mixture was critically important to ensure high yields for the palladium catalyzed reduction. For instance, use of THF as solvent gave a 1: 1 mixture of double bond regioisomers.

Scheme 6. Synthesis of Milbemycin β_3 (**1**) via a Macrolactonization



exposure of a crude solution of aldehyde **2** with the sodium salt of phosphine oxide **3**. Before the lactonization could commence, the silyl ether was removed (TBAF, 95%) and the methyl ester was hydrolyzed (LiOH, 78%). Then following the Barrett procedure the 19-*epi*-seco acid **24** was lactonized with DIAD/PPh_3 in good yield (79%). Using NaSEt the methyl protecting group was removed, providing 30 mg of synthetic material that was physically (mp, optical rotation)[18] and spectroscopically (^{1}H NMR, ^{13}C NMR, IR, and MS) identical to natural milbemycin β_3 (**1**) (Scheme 6).

In conclusion, a short de novo asymmetric synthesis of milbemycin β_3 (**1**) has been developed. This highly enantio- and diastereocontrolled route illustrates the utility of our dienoate/dienone asymmetric hydration strategy for natural product synthesis. In addition, it features the use of Nelson's isomerization−Claisen rearrangement (ICR) in a structurally complex setting. This approach provided milbemycin β_3 (**1**) in 2.3% overall yields from 5-hexyn-1-ol (**11**), which should be amenable to the preparation of its enantiomer. Further application of this approach to the synthesis of structurally more complex members of this class of compounds and biological testing is ongoing.

Acknowledgment. We are grateful to the NIH (GM63150) and NSF (CHE-0415469) for the support of our research program and NSF-EPSCoR (0314742) for a 600 MHz NMR and an LTQ-FT mass spectrometer at WVU.

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

OL061439K

(17) (a) Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000−13001. (b) Nelson, S. G.; Wang, K. *J. Am. Chem. Soc.* **2006**, *128*, 4232−4233.

(18) The synthetic material had a melting point range of 182−184 °C and an optical rotation of +99 (c = 0.25, MeOH) which is in good agreement with the literature value (Mp = 181−183 °C.; $[\alpha]_D$ = +102 (c = 0.17, MeOH)). The actual value for the optical rotation of milbemycin β_3 has been a source of disagreement. For an interesting discussion of this issue along with its resolution, see: ref 7 g.