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De Novo Formal Synthesis of (−)-Apicularen A via an Iterative Asymmetric Hydration Sequence

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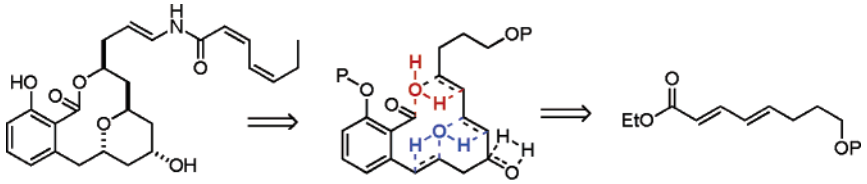
ABSTRACT



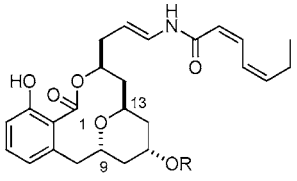
A de novo approach to the formal total synthesis of the macrolide natural product (−)-apicularen A has been achieved in 18 steps from achiral starting materials. Both the absolute and relative stereochemistries of apicularen A were introduced by a Sharpless asymmetric dihydroxylation, a π-allyl-palladium catalyzed reduction, a stereoselective reduction, and a base-promoted transannulation to install the C-9 stereocenter.

Since its isolation and structural determination by Jansen and co-workers,[1] apicularen A has attracted significant interest due to its extremely potent antitumor activity. Apicularen A showed remarkable cytotoxicities against nine human cancer lines at quite low concentration ($IC_{50} \sim 0.1-3$ ng/mL). This activity persisted even with the multidrug resistant line, KB-VI ($IC_{50} \sim 0.4$ ng/mL).[1b] Recently, the mode of action for the apicularens was demonstrated to occur via the selective inhibition of the mammalian V-ATPases,[2] which are responsible for regulating the intracellular pH. Interestingly, although apicularen A and B were equipotent inhibitors of V-ATPases, apicularen A is ~100 times more toxic to cancer cells.[1b] This switch in activity controlled by glycosylation has peaked our interest in the synthesis of both apicularen A and B, as well as other glycosylated potential prodrugs (Scheme 1).

In addition to its fascinating biological activities, the structural novelty of apicularen A has also attracted the attention of the synthetic community. To date, several total syntheses of apicularen A have been completed,[3] along with several formal total syntheses and various efforts to the unique bicyclic ring system.[4] Whereas all of the previous syntheses of the apicularen A derived their asymmetry by a resolution or from the chiral pool, we were interested in a de novo asymmetric approach that would use asymmetric catalysis to install the four stereocenters in apicularen A from achiral starting materials. Herein, we describe our successful efforts to implement this strategy for the de novo formal total synthesis of apicularen A.

Retrosynthetically, we envisioned apicularen A (**1**) and apicularen B (**2**) as being derived from the known macrolide

Scheme 1. Biological Activity of (−)-Apicularen A and B[2b]



	GI of M1 cell line (IC_{50})	V-ATPases inhibition (IC_{50})
1	1.4 nM	~.5 μM
2	190 nM	~.5 μM

(-)-Apicularen A, **1**, R = H
(-)-Apicularen B, **2**, R = *N*-acetyl-β-glucosamine

(1) (a) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075−1080. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913−919.

(2) (a) Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114−120. (b) Huss, M.; Sasse, F.; Kunze, B.; Jansen, R.; Steinmetz, H.; Ingenhorst, G.; Zeeck, A.; Wieczorek, H. *BMC Biochem.* **2005**, *6*, 13.

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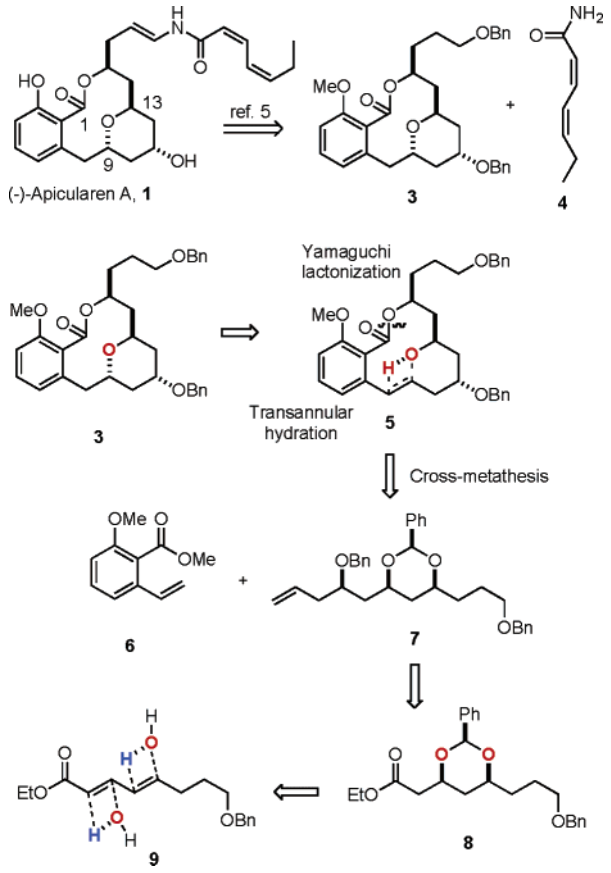
3 and the amide side chain **4**, which have been successfully used by Maier for the synthesis of **1**.[5] In our strategy (Scheme 2), the macrolide **3** could be derived from macrolactone **5**, which in turn could be obtained by cross metathesis of styrene **6** and alkene **7**. The homoallylic alcohol stereochemistry in the differentially protected tetraol **7** was planned to

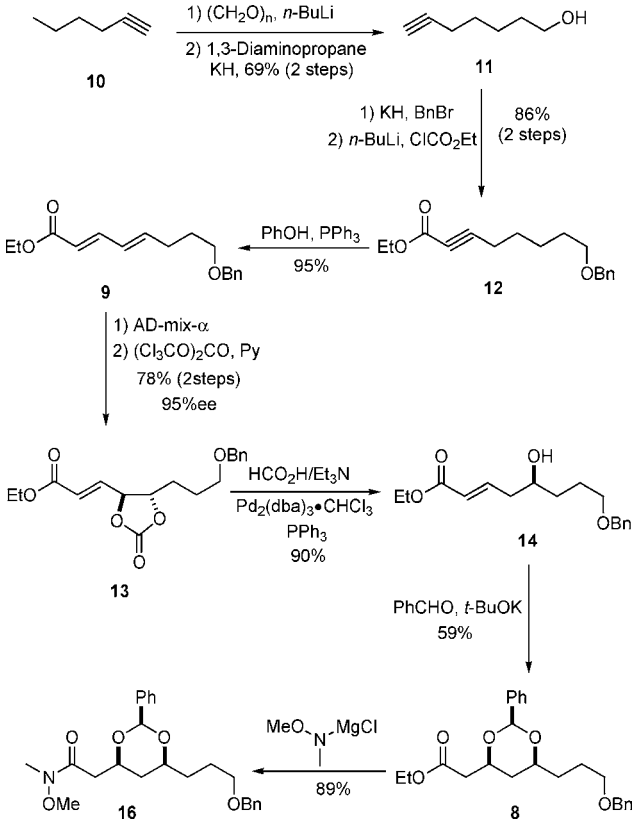
Scheme 2. Retrosynthesis of (−)-Apicularen A (**1**)



be introduced by the diastereoselective introduction of an allyl group to the benzylidene-protected triol **8**.[6] Previously, we have been successful at preparing protected 3,5-dihydroxy esters from 2,4-dienoates.[6,7] Thus, we envisioned using this four-step asymmetric bishydration protocol for the preparation of benzylidene acetal **8** from dienoate **9**.

To access useful quantities of dienoate **9**, an efficient five-step approach was developed (Scheme 3). The route featured the KAPA-promoted alkyne zipper reaction[8] and the Ph_3P-promoted ynoate to dienoate isomerization, developed by Trost.[9] Treatment of the lithium acetylide of **10** with paraformaldehyde gave a good yield (87%) of a propargylic alcohol, which when exposed to the KAPA reagent readily isomerized to the terminal heptynol **11** (79%). The primary alcohol in **11** was easily protected as a benzyl ether (KH/BnBr, 92%), and the terminal alkyne was carboxylated (*n*-BuLi/$ClCO_2Et$, 93%) to give ynoate **12**. Exposure of alkynoate **12** to the Rychnovsky variant of the Trost isomerization (Ph_3P/PhOH) cleanly gave dienoate **9** in excellent yield (95%) and near perfect double bond stereoselectivity.

Scheme 3. Synthesis of Dienoate **9** and Its Bishydration



We next turned to our three-step asymmetric hydration protocol (dihydroxylation, carbonate formation, and palladium-catalyzed reduction) to convert dienoate **9** into δ-hydroxyenoate **14**. In practice, dienoate **9** was dihydroxylated under the Sharpless conditions to give a diol, which

(3) (a) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217−1220. (b) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701−3704. (c) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425−2430. (d) Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5821−5823.

(4) (a) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549−5552. (b) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104−116. (c) Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357−3360. (d) Kühnert, S.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643−646. (e) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, *43*, 8507−8510. (f) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289−1292.

(5) Although Maier's endgame seemed ideal for our purpose, his use of a stoichiometric amount of $(CF_3CO_2)_2Hg$ to set the transannular ether bridge in macrolide **3** (see ref 3d) was viewed as needing to be replaced with an environmentally more benign yet equally stereoselective process.

(6) (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777−2780. (b) Tosaki, S. Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495−498. (c) Smith, C. M.; O'Doherty, G. A. *Org. Lett*, **2003**, *5*, 1959−1962.

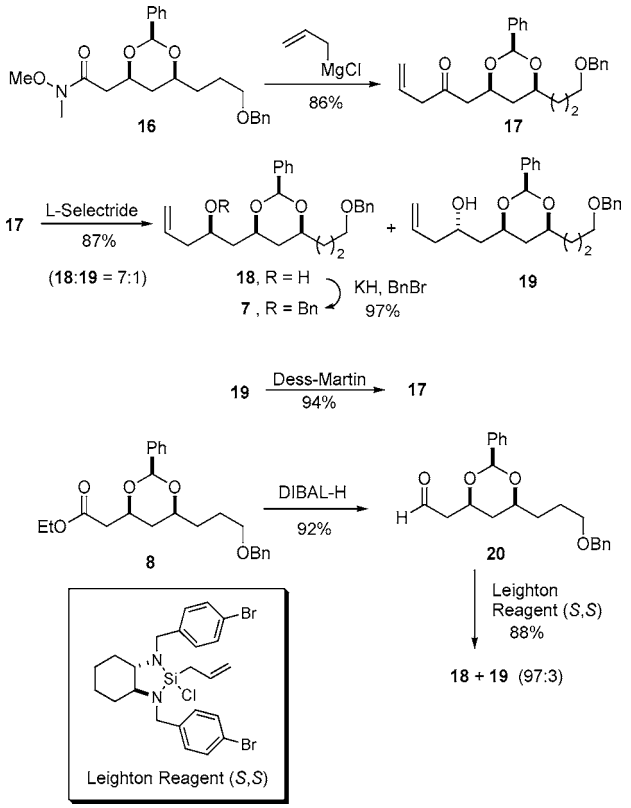
(7) (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049−1052. (b) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987−3990.

(8) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891−892. (b) Kimmel, T.; Becker, D. *J. Org. Chem.* **1984**, *49*, 2494−2496.

(9) (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659−2660. (b) Trost, B.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933−7935.

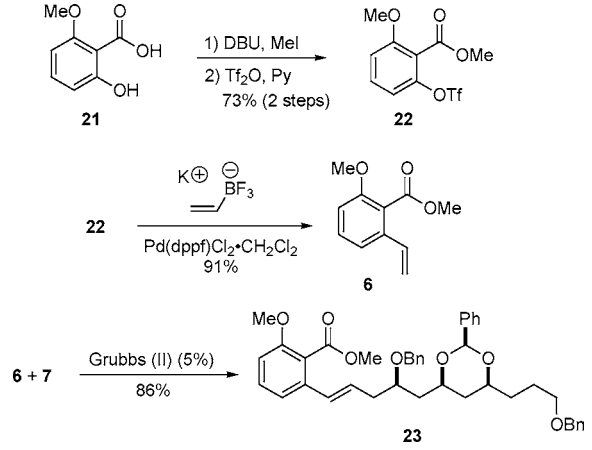
was cyclized into carbonate **13** in good overall yield (78%). Exposure of carbonate **13** to the palladium(0)-catalyzed reduction conditions (HCO_2H/Et_3N) provided δ-hydroxy enoate **14** in good yield (90%). With the initial chiral center introduced in δ-hydroxy enoate **14**, the remaining double bond was diastereoselectively hydrated and protected to form the benzylidene acetal **8** using Evans' procedure (PhCHO/*t*-BuOK, 59%).[10] The ester **8** was then converted into Weinreb amide **16** (ClMgN(OMe)Me) in 89% yield (Scheme 3).[11]

Scheme 4. Synthesis of Intermediate **7** via Stereoselective Reduction or Asymmetric Allylation



Exposure of Weinreb amide **16** to allylmagnesium chloride cleanly formed the ketone **17** in 86% yield (Scheme 4). Reduction of the ketone under various conditions resulted in different ratios of diastereomers **18** and **19**. Our optimized conditions used L-selectride, which produced homoallylic alcohols **18** and **19** in a ratio of 7:1. The two diastereomers **18** and **19** were separable by careful chromatography. The undesired isomer **19** can be recycled by a Dess−Martin oxidation back to ketone **17** (94%). Alternatively, treatment of aldehyde **20**, which was formed by Dibal-H reduction of ester **8** (92%), with the Leighton reagent formed the desired homoallylic alcohol **18** in high diastereoselectivity (97:3) and high yield (88%).[12] Finally, the alcohol in **18** was protected as a benzyl ether to provide the cross metathesis precursor **7**.

Scheme 5. Synthesis of Salicylate **23** via Cross-Metathesis Reaction



We next looked at the synthesis of styrene fragment **6** (Scheme 5). Selective monomethylation[13] of commercially available salicylic acid **21** (DBU/MeI, 82%) was followed by treatment of the remaining phenol group with Tf_2O to give triflate **22** (89%). The Molander[14] trifluoroborate variant of the Suzuki−Miyaura[15] coupling was then used to convert the triflate **22** to the styrene **6** (91%).

The merging of the two alkenes **6** and **7** via an olefin cross metathesis reaction was then investigated. Treatment of **6** (2 equiv) and **7** with the second-generation Grubbs reagent (5% Grubbs II)[16] provided the cross metathesis product **23** in good yield (86%) and high trans stereoselectivity (Scheme 5).

In preparation for the macrolactone assembly (Scheme 6), the benzylidene protection group in **23** was removed with mildly acidic conditions (4:1 $AcOH/H_2O$, 80 °C) to form diol **24** (82%).[17] Then, the methyl ester **24** was hydrolyzed with LiOH.[18] Applying a modified Yamaguchi lactonization[19] procedure to the seco acid **25** selectively produced the 12-membered macrolactone **6** (67%) over the 10-membered ring. With the macrolactone established, we next looked for an

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

(11) (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. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

(12) Previous approaches to apicularen A used the Brown AllylBIpc$_2$ reagent; see: refs 3b, 3c, 4b, and 4f. We have found that the Leighton reagent works equally well in terms of stereochemical outcome and allows for a significantly simpler product isolation procedure. See: Kubota, K.; Leighton, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 946−948.

(13) Mal, D. *Synth. Commun.* **1986**, *16*, 331−335.

(14) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107−109.

(15) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

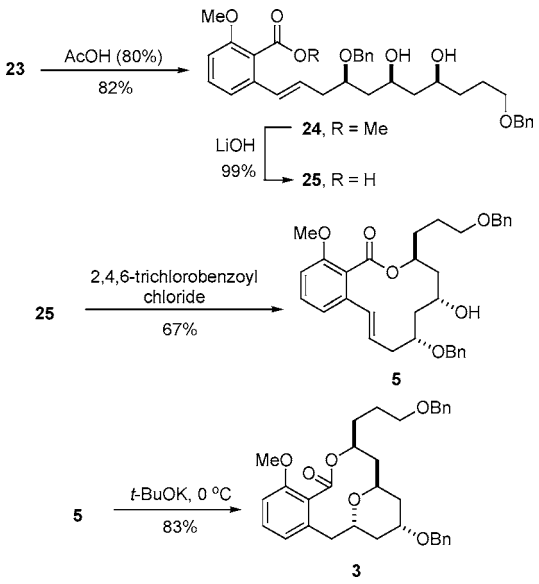
(16) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(17) Efforts to lactonize diol **24** under various basic conditions (NaH, KH, or *t*-BuOK) caused either decomposition of the starting material or no reaction.

(18) Petri, A. F.; Kuhnert, S. M.; Scheufler, F.; Maier, M. E. *Synthesis* **2003**, *6*, 940−955.

(19) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Mulzer, J.; Mareski, P. A.; Buschmann, J.; Luger, P. *Synthesis* **1992**, *1*, 215−234.

Scheme 6. Completion of the Formal Synthesis of (−)-Apicularen A



alternative to the Maier transannular etherification.[3d] After numerous fruitless investigations, including Au(I)[20] and Pt(II)[21] catalysts, we eventually found that the tetrahydropyran could be formed under basic (*t*-BuOK, 1 equiv) conditions. Significantly, only one diastereomer was formed under these conditions and in good yield (83%).[22] The desired target macrolide **3** was physically (mp, optical rotation) and spectroscopically (^{1}H NMR, ^{13}C NMR, IR, and MS) identical to the material previously reported by Maier.[3d]

In conclusion, a short formal de novo asymmetric synthesis of apicularen A has been developed. This highly enantio- and diastereocontrolled route illustrates the utility of our dienoate asymmetric hydration strategy for natural product synthesis. In addition, this approach features a cross metathesis reaction, a Yamaguchi lactonization, and a base-mediated transannular etherification. Further application of this approach to the synthesis of other members of this class of compounds and biological testing are ongoing.

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

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(20) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966−6967.
(21) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536−9537.

(22) The high diastereoselectivity associated with this transannular cyclization (**5** to **3**) has precedent in the work of Rizzacasa. See refs 4e and 4f. Our results suggest the possibility of an olefin migration preceding cyclization, in the Rizzacasa model study, instead of the proposed 6-endo-dig cyclization. See ref 4e.