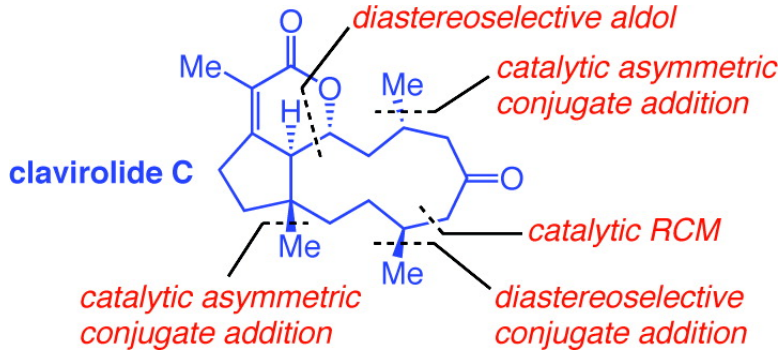
Communication

Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis

M. Kevin Brown, and Amir H. Hoveyda

J. Am. Chem. Soc., **2008**, 130 (39), 12904-12906 • DOI: 10.1021/ja8058414 • Publication Date (Web): 09 September 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 09/09/2008

Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis

M. Kevin Brown and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

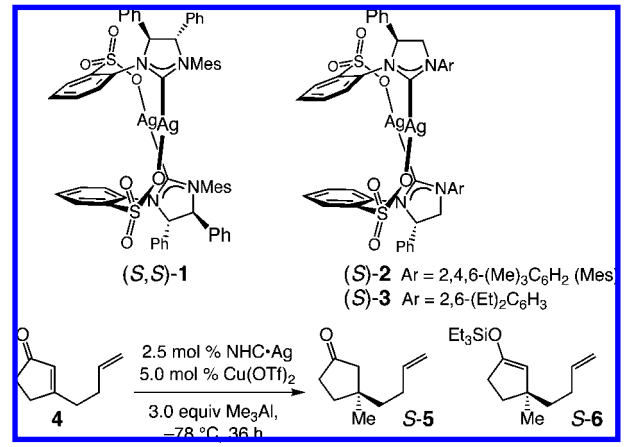
Received July 25, 2008; E-mail: amir.hoveyda@bc.edu

Clavirolide C, a member of the dolabellane family of diterpenes isolated from Pacific soft coral *Clavularia viridis*, contains a characteristic *trans*-bicyclo[9.3.0]tetradecane core structure (Scheme 1).[1,2] Our interest in this natural product stems from the viewpoint that an efficient and enantioselective total synthesis of clavirolide C would demonstrate and, perhaps more importantly, challenge the utility of the state-of-the-art in catalyst and synthesis methodology.[3] From the perspective of total synthesis,[4] two of the more demanding structural attributes of this class of natural products are the strained 11-membered carbocycle and the all-carbon quaternary stereogenic center[5] that resides at the fusion of the medium ring and the cyclopentane moiety. Herein, we disclose the first enantioselective total synthesis of clavirolide C, featuring the application of chiral amino acid based ligands in Cu-catalyzed asymmetric conjugate addition (ACA) reactions[6] and a Ru-catalyzed ring-closing metathesis (RCM).[7] More noteworthy is that the present initiative has spawned the development of a protocol for NHC·Cu-catalyzed ACA of alkylaluminum reagents to β-substituted cyclopentenones, one of the more difficult substrate sets for this class of transformations.

The retrosynthesis analysis adopted in our approach to clavirolide C is outlined in Scheme 1. We envisioned a route that would contain three stereoselective conjugate additions, leading to control of stereochemistry at C8, C4, and the critical all-carbon quaternary stereogenic center, C1. The stereochemical outcome of the conjugate addition to cyclo-undecenone **I** (stereochemistry at C4) might be addressed by utilization of the conformational preferences of the medium ring (substrate control)[8] or through the use of an appropriate chiral complex (catalyst control).[3] Catalytic RCM, albeit aimed to access a challenging 11-membered ring, would convert diene **III** to **II**, which would in turn serve as the precursor to unsaturated tricycle **I**. The most direct strategy to access cyclopentanone **III** would be through aldol addition of cyclic silyl enol ether **V** and aldehyde **IV**, both of which might be derived from a catalytic ACA.

We began by searching for an efficient and selective protocol to reach the intermediate represented by **V** (Scheme 1). We were cognizant from the outset that identifying an effective catalytic ACA to access **V** would be challenging. Only recently, a small number of disclosures regarding catalytic ACA of β-alkyl-substituted cyclic enones has appeared,[9] but such protocols almost exclusively deal with reactions of six- and seven-membered ring cyclic enones.[10] Our earlier studies involving chiral bidentate NHC·Cu complexes and dialkylzinc reagents had proven entirely ineffective with β-substituted cyclopentenones (<2% conv).[10b] Thus, we turned to the chiral Cu complex of NHC-sulfonate (*S*,*S*)-**1** (Table 1),[11] a recent and particularly active catalyst, and the more Lewis acidic Al-based alkylating agents (vs dialkylzinc reagents).[12] As depicted in entry 1 of Table 1, treatment of β-substituted cyclopentenone **4** and commercially available Me_3Al, in the presence of 2.5 mol % (*S*,*S*)-**1** and 5 mol % $Cu(OTf)_2$, gives rise to 75% conversion of **4** to *S*-**5** (36 h, −78 °C) in 73.5:26.5 er. We rationalized that increasing the freedom of rotation of the chiral NHC's N-aryl unit might enhance its effective size. Such considerations led us to prepare and examine complexes (*S*)-**2** and (*S*)-**3** which, as shown in entries 2−3 of Table 1, furnish the desired β,β-disubstituted

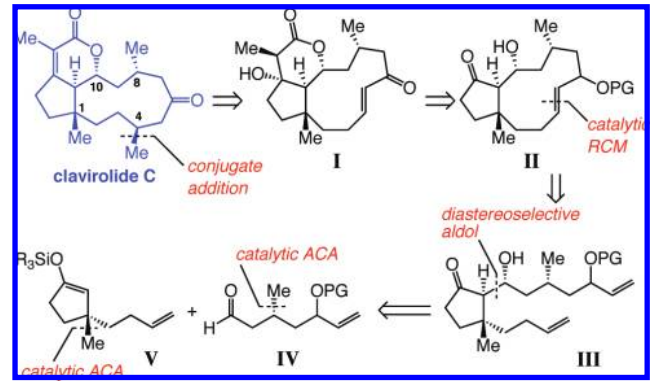
Table 1. Activity of NHC·Ag(I) Complexes for ACA of **4** with Me_3Al[a]



entry	NHC · Ag complex	product	conv (%);[b] yield (%)[c]	er[d]	ee (%)[d]
1	**1**	*S*-**5**	75; nd	73.5:26.5	47
2	**2**	*S*-**5**	97; nd	86:14	72
3	**3**	*S*-**5**	86; 80	93:7	86
4	**3**[e]	*S*-**6**	>98; 72	92:8	84

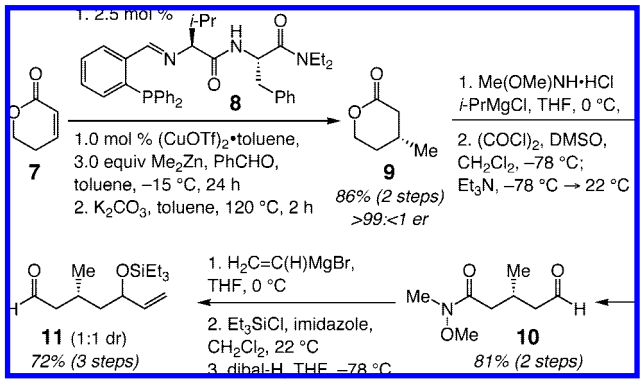
[a] Reactions performed under N_2 in THF. [b] Determined by analysis of ^{1}H NMR spectra of unpurified mixtures. [c] Yields of purified products. [d] Determined by chiral GLC analysis; see the Supporting Information for details. [e] Reaction was performed with 3.75 mol % **3** and 7.5 mol % $Cu(OTf)_2$; 4.0 equiv of Et_3SiOTf were added after 36 h (−78 °C, 4 h); see the Supporting Information for details. nd = not determined.

Scheme 1. A Retrosynthesis Analysis for Clavirolide C



10.1021/ja8058414 CCC: $40.75

Scheme 2. Enantioselective Synthesis of Aldehyde Fragment **11**



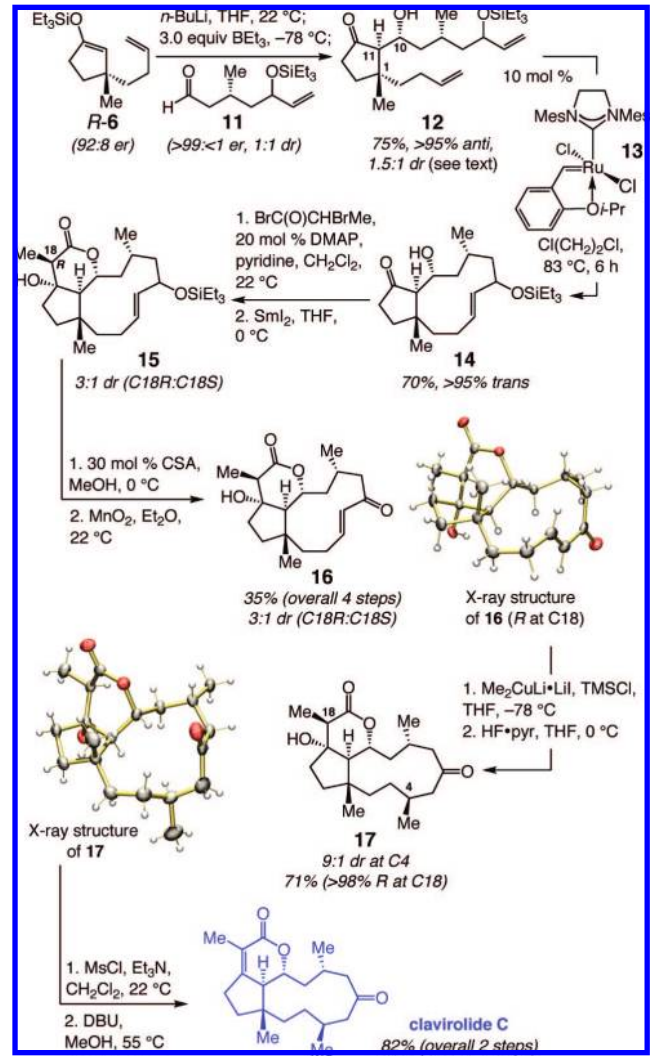
cyclopentanone *S*-**5** with improved selectivity (86:14 and 93:7 er, respectively). When the ACA, promoted by 3.75 mol % **3**, is quenched with Et_3SiOTf (−78 °C), enolsilane *S*-**6** is obtained in 92:8 er (84% ee) and 72% yield (entry 4, Table 1). To reach complete conversion, slightly higher catalyst loading is therefore required (3.75 mol % in entry 4 vs 2.5 mol % in entries 1−3).

Enantioselective synthesis of aldehyde **11** (Scheme 2) involves another class of chiral ACA catalysts developed in these laboratories.[13] The sequence illustrated in Scheme 2 begins with a two-step procedure involving reaction of unsaturated lactone **7** and Me_2Zn with $(CuOTf)_2$•toluene, all of which are commercially available, in the presence of chiral amino acid based ligand **8** and benzaldehyde (Zn-enolate must be trapped in situ for high yield).[13] The resulting Cu-catalyzed ACA/aldol product is converted to **9** in 86% overall yield and >99:<1 er. For the Cu-catalyzed transformation to proceed efficiently, ligand modification was required, since use of the previously reported chiral Schiff base, bearing an −N(H)*n*-Bu terminus (vs $-NEt_2$ in **8**), gives rise to an inefficient process (10 mol % catalyst, 48 h, 60% conv, 40% yield, >99:<1 er). Conversion to amide **10** (81% yield for two steps) is followed by a three-step sequence that delivers fragment **11** as an equal mixture of diastereomers (inconsequential to the total synthesis) in 72% overall yield.

With enantiomerically enriched cyclic enol silane *R*-**6** (92:8 er, obtained from ACA with *R*-**3**) and aldehyde **11** (>99:<1 er) in hand, we searched for an effective procedure for the union of the two fragments through a diastereoselective aldol addition (Scheme 3). After exploring a range of conditions, we established that treatment of the lithium enolate derived from **6** (*n*-BuLi, 22 °C) with BEt_3 at −78 °C, followed by the addition of aldehyde **11**, leads to the formation of aldol adduct **12** (75% total yield). The desired β-hydroxyketone is generated in >95% *anti*-aldol selectivity (C11−C10), a stereochemical preference that is due to the introduction of BEt_3 to the mixture.[14] Approach of the aldehyde *anti* to the slightly larger butenyl unit is, however, not significantly favored (C1−C11, 1.5:1 dr).[14]

Next, we addressed the problem of establishing conditions for efficient 11-membered ring closure through a catalytic RCM process. After extensive experimentation, we found that subjection of allylic ether **12** (4:1 dr)[15] to 10 mol % of Ru carbene **13**[16] under high dilution conditions ($ClCH_2CH_2Cl$, 10^{-3} M) with slow addition of the substrate to a solution of catalyst (83 °C, 6 h) results in clean formation of the desired ring structure;[17] cycloalkene **14** is obtained in 70% yield after purification and exclusively as the *trans* isomer (>95%). The present transformation represents a rare example of an efficient catalytic RCM that leads to the formation of an 11-membered ring.[18] Two additional points regarding catalytic RCM of **12** merit mention: (1) Use of the related second-generation

Scheme 3. Enantioselective Total Synthesis of Clavirolide C



Cy_3P-containing complex[19] under identical conditions leads to <10% conversion to the desired macrocycle **14** (>90% **12** recovered).[20] (2) Attempted RCM with the parent allylic alcohol results in the formation of a complex mixture of products; when the derived α,β-unsaturated ketone is used, the product mixture is contaminated with 30−35% of the homodimeric 22-membered ring.

Esterification of the secondary alcohol with 2-bromopropionyl bromide, followed by a SmI_2-mediated Reformatsky reaction, provides lactone **15**.[21] Removal of the silyl protecting group under acidic conditions (30 mol % CSA, 0 °C) and oxidation of the resulting secondary alcohol (MnO_2) furnishes enone **16**, the identity of which has been confirmed through X-ray crystal structure analysis. The four-step sequence, beginning with **14**, proceeds in 35% overall yield and 3:1 dr (*R* stereochemistry at C18 is major; inconsequential to the total synthesis).

Conjugate addition of Me_2CuLi•LiI to enone **16** in the presence of TMSCl,[22] and desilylation of the resulting enol silane with HF•pyr, leads to ketone **17** in 9:1 diastereoselectivity (at C4) in 71% yield (>98% *R* at C18).[23] As illustrated in Scheme 3, the identity of **17** has been established through X-ray crystal structure analysis. It is important to note that approach of the Cu-based reagent from the periphery[8] of the medium ring structure is expected to deliver the undesired stereochemistry at C4. Spectroscopic analysis (NOE measurement) indicates that, in equilibrium with the *s-trans* isomer, there exists a significant amount of the enone

s-cis conformer in solution.[24] It is plausible that the 11-membered enone's *s-cis* conformer reacts more readily to furnish the requisite stereoisomer as the major product.

Conversion of the tertiary alcohol in **17** to the derived mesylate is directly followed by subsequent elimination to afford the corresponding β,γ-unsaturated lactone (tetrasubstituted alkene). Direct treatment (without purification) of the unsaturated tricycle with DBU (in MeOH) delivers (−)-clavirolide C in 82% overall yield (two steps).[25]

The enantioselective synthesis of clavirolide C requires 17 steps (longest linear sequence) and affords the target molecule in 3.5% overall yield. These investigations confirm the stereochemical assignment for clavirolide C, which was originally based on an indirect correlation with products derived from catalytic hydrogenation of other members of this class of natural products (bearing olefins at C3−C4).[1a]

The total synthesis demonstrates the utility of Cu-catalyzed ACA reactions of unsaturated heterocycles with dialkylzinc reagents and provides another notable illustration of the special attributes of the thermally robust phosphine-free Ru-based olefin metathesis catalyst **13**.[20] Completion of the enantioselective synthesis required the development of an effective Cu-catalyzed protocol for generation of all-carbon quaternary stereogenic centers[5] by reactions of alkylaluminum reagents with one of the more difficult substrate classes in catalytic ACA.[26] Nonetheless, these investigations point to the yet unsolved problem of identifying a stereoselective method for aldol additions involving cyclic enol ethers adjacent to quaternary stereogenic centers, especially in cases where such neighboring substituents are similar in size (e.g., **6**).[27] Control of selectivity in these challenging transformations through an effective chiral catalyst is perhaps the most efficient and attractive option.[28] Studies along these lines are in progress.

Acknowledgment. The NIH (Grant GM-47480) and the NSF (Grant CHE-0715138) provided financial support. M.K.B. was a Bristol-Myers Squibb graduate fellow (2006−07). We thank Dr. Alexander W. Hird for early discussions, Adil R. Zhugralin for computational analyses, and Materia, Inc. for gifts of olefin metathesis catalysts. We are grateful to Dr. Bo Li for securing X-ray structures, Dr. John Boylan for NMR spectroscopy, and Marek Domin for obtaining mass spectra. Mass spectrometry facilities at Boston College are supported by the NSF (DBI-0619576).

Supporting Information Available: Experimental procedures and spectral, analytical data for all intermediates and synthetic clavirolide C. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Su, J.; Zhong, Y.; Zeng, L. *J. Nat. Prod.* **1991**, *54*, 380–385 For a review on dolabellane natural products, see: (b) Rodrígues, A. D.; González, E.; Ramírez, C. *Tetrahedron* **1998**, *54*, 11683–11729.

(2) Syntheses of various fragments of this class of molecules have been disclosed previously. See: (a) Zeng, Z.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 3459–3461. (b) Zhu, Q.; Qiao, L.; Wu, Y.; Wu, Y.-L. *J. Org. Chem.* **2001**, *66*, 2692–2699. (c) Sun, B.; Xu, X. *Tetrahedron Lett.* **2005**, *46*, 8431–8434. (d) Sun, B.; Xu, X. *Tetrahedron Lett.* **2006**, *47*, 299–302.

(3) For discussions regarding the role of asymmetric catalysis in target-oriented synthesis, see: (a) Hoveyda, A. H. In *Stimulating Concepts in Chemistry*; Stoddard, F. J., Shibasaki, M., Vogtle, F., Eds; Wiley−VCH: Weinheim, 2000; pp 145−160. (b) Taylor, M. S.; Jacobsen, E. N. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5368–5373.

(4) For recent enantioselective syntheses of related members of the dolabellane family of natural products, see: (a) Kingsbury, J. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 13813–13815. (b) Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740–742.

(5) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christophers, J., Baro, A., Eds; Wiley−VCH: Weinheim, 2006.

(6) For an overview regarding the use of amino acid based chiral catalysts for catalytic ACA reactions, see: Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779–1785.

(7) (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley−VCH: Weinheim: 2003. (b) Hoveyda, A. H.; Zhugralin, A. *Nature* **2007**, *450*, 243–251.

(8) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275–2281.

(9) Three cases of ACA of trialkylaluminum reagents to β-substituted cyclopentenones, catalyzed by chiral Cu-phosphoramidites, have been reported. High selectivity and efficiency are observed in only one instance involving a relatively reactive nucleophile (Et_3Al: 96.5:3.5 er, 93% ee). See: Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem.−Eur. J.* **2007**, *13*, 9647−9662, and references cited therein.

(10) (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. (b) Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184. (c) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417. (d) Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578–4581.

(11) (a) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew Chem., Int. Ed.* **2008**, *46*, 1097–1100. One application of catalytic ACA promoted by a chiral NHC·Cu complex (derived from **1**) to natural product synthesis has appeared. The transformation, however, involves a six-membered ring enone bearing an activating β-substituent. See: (b) Peese, K. M.; Gin, D. Y. *Chem.−Eur. J.* **2007**, *14*, 1654–1665.

(12) For asymmetric allylic alkylation reactions involving Al-based reagents promoted by chiral bidentate NHC·Cu complexes, see: (a) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864. (b) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446–447.

(13) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306–5310.

(14) For related diastereoselective aldol additions involving boron enolates, see: Yamamoto, Y.; Yatagai, H.; Maruyama, K. *Tetrahedron Lett.* **1982**, *23*, 2387–2390.

(15) The diastereomeric ratio can be increased from 1.5:1 to 4:1 (C1−C11) through partial separation of diastereomers by silica gel column chromatography. Silyl ether diastereomers (at C6) undergo Ru-catalyzed RCM with equal facility.

(16) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(17) Under rigorously anhydrous conditions, 5 mol % **13** can be used to obtain similar results. With 20 mol % **13**, yields exceed 80% without resorting to the use of strictly anhydrous conditions.

(18) For use of catalytic RCM to access 11-membered rings in syntheses of natural products or biologically active agents, see: (a) El Sukkari, H.; Gesson, J.-P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043–4046. (b) Winkler, J. D.; Holland, J. M.; Kasparec, J.; Axelsen, P. H. *Tetrahedron* **1999**, *55*, 8199–8214. (c) Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2003**, *68*, 1878–1885. (d) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888. (e) Fürstner, A.; Müller, C. *Chem. Commun.* **2005**, 5583–5585 For a brief overview of macrocyclization reactions through catalytic RCM, see: (f) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086–6101.

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

(20) Use of sterically and electronically modified versions of complex **13** leads to the formation of **14** with similar efficiency. For a discussion of the utility of such complexes and the attributes of phosphine-free Ru-based carbenes in catalytic olefin metathesis, see: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23.

(21) A similar sequence has been carried en route to the clavirolides; see ref 2a,b.

(22) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015–6018.

(23) After subjection to Me_2CuLi·LiI followed by aqueous workup, the 3:1 mixture at C18 is transformed to a single stereoisomer (*R*).

(24) See Supporting Information for additional details, including relevant X-ray data.

(25) See Supporting Information for complete spectral and physical data.

(26) For an account of the scope and limitation of this class of Cu-catalyzed ACA reactions, see: May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362.

(27) Due to the substantial difference in size of the substituents α to the enolsilane (e.g., H vs alkyl), this stereochemical issue is more easily addressed in the catalytic ACA/aldol sequence involving non-β-substituted cycloalkenones. For example, see: Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841–5842.

(28) Enantioselective aldol additions of five-membered ring enolsilanes to aryl-derived aldehydes have been reported. Reactions with alkyl-substituted aldehydes, however, are either inefficient or not included in such disclosures. See: (a) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron* **1998**, *54*, 10389–10402. (b) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319–9320. (c) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8331–8339.

JA8058414