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Synthesis of a C(1)–C(14)-Containing Fragment of Callipeltoside A

Thomas R. Hoye* and Hongyu Zhao

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

hoye@chem.umn.edu

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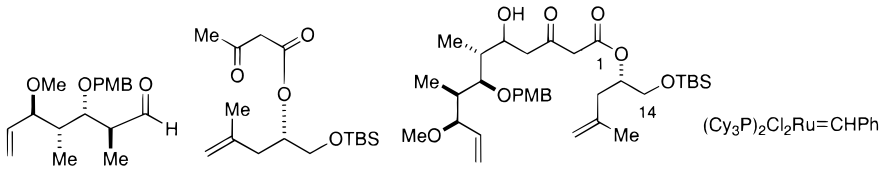
ABSTRACT



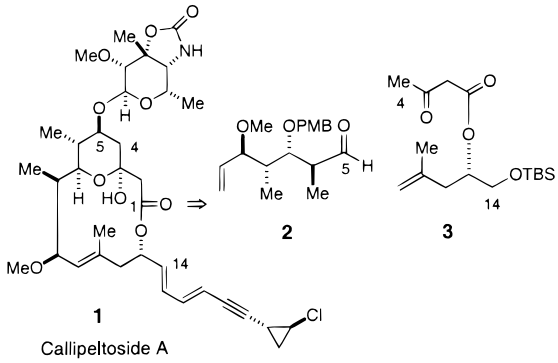
2 **3** **13** **15**

A C(1)–C(14)-containing fragment of callipeltoside A (1, Scheme 1) was synthesized efficiently via a dianion aldol coupling reaction between aldehyde 2 and ketoester 3. A surprising lack of reactivity between the alkenes in 13 and the Grubbs initiator 15 was encountered. An equally surprising rate acceleration of the reaction between 15 and allylic alcohols (alk-1-en-3-ols) as well as their subsequent cleavage to methyl ketones was discovered. In situ ^{1}H NMR analysis has proven to be a very useful tool for monitoring RCM reactions of complex substrates such as 13.

Callipeltoside A (**1**) was isolated from the shallow water sponge, *Callipelta* sp., in 1996 and was found to inhibit in vitro proliferation of KB and P388 cells and to protect cells infected with HIV virus.[1] A limited amount (3.5 mg) of callipeltoside A was obtained and its relative configuration was deduced by extensive NMR experiments. To determine the absolute configuration of callipeltoside A (**1**), to confirm the assigned relative configurations, and to provide material for further biological studies, we have undertaken its total synthesis. We report here our progress toward construction of the central macrolactone portion of **1**. Our efforts have resulted in the synthesis of a C(1)−C(14)-containing fragment having the assigned relative configuration. In one retrosynthetic plan (Scheme 1), we imagined the macrolactone in **1** to arise from precursors **2** and **3** by a dianion aldol-coupling and ring-closing metathesis strategy. While we have not yet successfully closed the macrocyclic ring, we have gained (surprising) insight into the reactivity of possible ring-closing metathesis substrates.

The synthesis of aldehyde **2** is outlined in Scheme 2. Exchange of the oxazolidinone auxiliary in the known *syn*-aldol adduct **4**[2] with *N*,*O*-dimethylhydroxylamine generated the Weinreb amide.[3,4] Protection of the secondary hydroxyl group as its trimethylsilyl ether followed by hydroboration/oxidation gave the primary alcohol **5** as essentially one diastereomer.[2] Protection of the new hydroxyl group as its *p*-methoxybenzyl ether **6** was followed by vinyllithium addition to give the terminal vinyl ketone.[5,6] PPTS/MeOH removal of the TMS ether quantitatively produced the β-hydroxyenone **7**. The 1,3-*anti*-diol **8** was then obtained as

Scheme 1



1 Callipeltoside A **2** **3**

(1) Zampella, A.; D'Auria, V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085−8.
(2) Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454−5.

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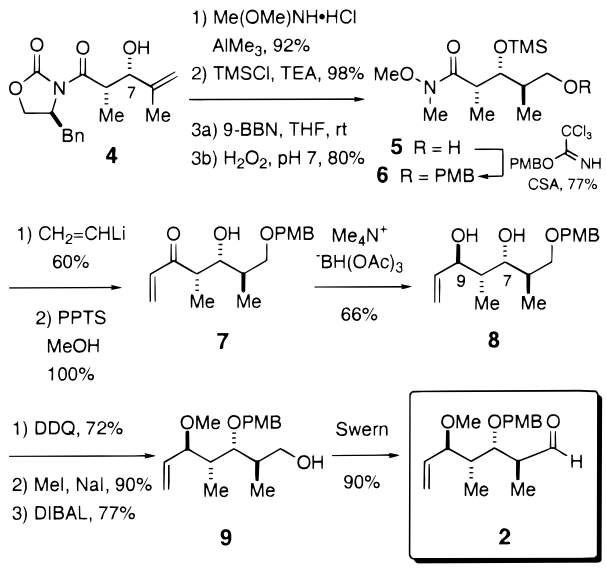
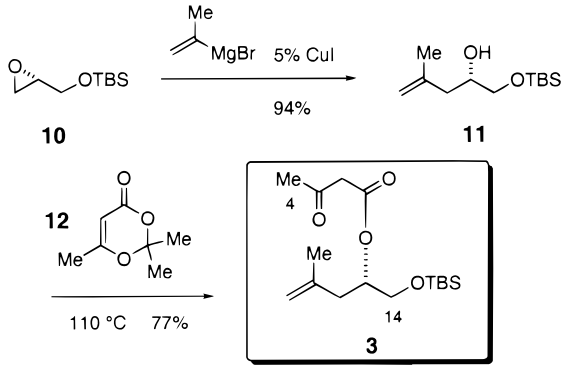
Scheme 2



the major isomer (9:1; *anti*:*syn*) by a hydroxyl-directed reduction with triacetoxyhydridoborate.[7] The configuration of the new center was determined by both acetonide[8a] and Mosher ester[7b] analyses. Migration of the PMB ether from the terminal C(5)-position to the more hindered C(7)-hydroxyl group and regioselective methyl ether formation was achieved by a three-step operation: (i) DDQ oxidation under anhydrous conditions,[9] accompanied by intramolecular trapping by the C(7)−OH, gave a cyclic *p*-methoxybenzylidene acetal; (ii) methylation of the C(9)−OH; and (iii) reductive opening of the acetal with DIBAL gave the primary alcohol **9** [a 10% yield of the regioisomeric primary PMB ether (i.e., the C(9)-methyl ether of **8**) was also formed].[10] Swern oxidation of **9** completed the synthesis of fragment **2**.

Preparation of the β-keto ester subunit **3** (Scheme 3) was achieved by copper-catalyzed addition of isopropenylmagnesium bromide to the TBS ether of (*R*)-glycidol (**10**). The resulting homoallylic alcohol **11** was converted to its acetoacetate derivative **3** by heating with dioxinone **12**.[11]

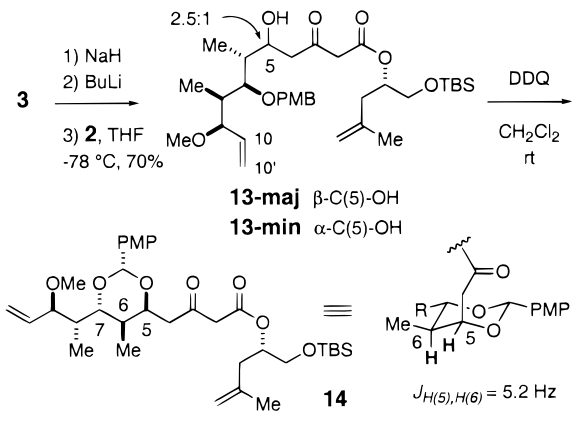
Scheme 3



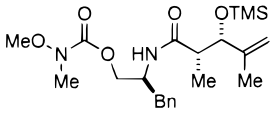
Subunits **2** and **3** were coupled via aldol reaction (Scheme 4). An excess of the dianion derived from the β-keto ester **3** with NaH/BuLi was added to aldehyde **2** at −78 °C to give a readily separable diastereomeric mixture of epimeric C(5)-alcohols **13** (2.5:1; 70% yield). To assign the configuration of the new stereocenter, the major diastereomer was oxidatively cyclized in a remarkably clean reaction to give the *p*-methoxybenzylidene acetal **14**.[12] The coupling constant between H(5) and H(6) in this derivative was 5.2 Hz, a value consistent with the C(5)/C7)-*anti* rather than -*syn* acetal.[13]

Attempts to form the macrocyclic lactone by ring-closing metathesis[14] of **13** have been unsuccessful. We routinely use

Scheme 4



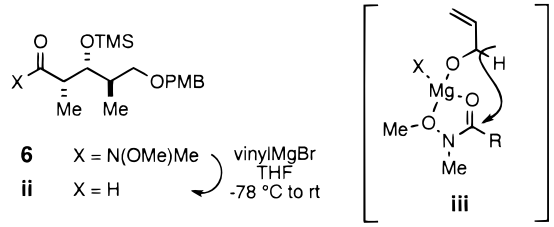
(3) Consistent with the report that the β-hydroxyl group is important for clean installation of the *N*,*O*-dimethylhydroxylamine moiety (Evans, D. A.; Gage, J. K.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−53), we observed that if the C(7)-hydroxyl group was first protected as its TMS ether prior to reaction with $Me_2AlN(Me)OMe$, the main product was **i**. An analogous byproduct was recently described (Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akheizer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237−54).



(4) New compounds **2**−**13** and the additional isolable Scheme 2 intermediates gave satisfactory ^1H and ^{13}C NMR, IR, and MS data.

(5) Linderman, R. J.; Cutshall, N. S.; Becicka, B. T. *Tetrahedron Lett.* **1994**, *35*, 6639−42.

(6) Initial attempts to add vinylmagnesium bromide (Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron*. **1995**, *51*, 10343−60) rather than CH_2═CHLi to **6** gave a complex mixture of products, which included the aldehyde **ii** as the major product (~20%). This reduction might proceed by way of complex **iii** between a molecule of **6** and the magnesium salt of allyl alcohol. Fragmentation of a Weinreb amide to formaldehyde has been recently reported (Seong, M. R.; Kim, J. N.; Kim, H. R.; Ryu, E. K. *Synth. Commun.* **1998**, *28*, 139−45).

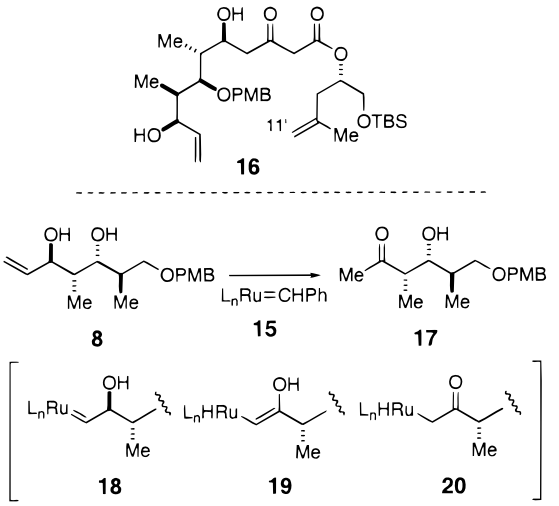


(7) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−78.

in situ monitoring of RCM reactions by ^{1}H NMR spectroscopy to follow their progress. In the case of substrate **13-maj** or **13-min** *no* styrene, the obligatory product from reaction of either alkene in **13** with $Cl_2(Cy_3P)_2Ru{=}CHPh$ (**15**), was detected.[15]

In a different study, we found that a terminal vinyl group with a free tertiary allylic hydroxyl group was much more reactive toward the Grubbs initiator than its methyl ether analogue.[16] We therefore hypothesized that the allylic alcohol **16** (Scheme 5), the C(9)−OH analogue of **13**, would be more

Scheme 5



reactive than **13** itself. Indeed, by monitoring the reaction between **15** and **16**[17] by ^{1}H NMR spectroscopy, we observed rapid disappearance of the terminal vinyl group and a comparable rate of appearance of styrene.[18] However, the desired RCM reaction did not occur; resonances for the methylene protons at C(11′) remained intact throughout. This prompted us to examine the reaction of a simpler secondary alk-1-en-3-ol (i.e., **8**, Scheme 5) with **15**. We observed rapid formation of the methyl ketone **17**.[19] Intermediates **18**−**20** can account for this stoichiometric cleavage reaction.[20] These observations suggest that secondary allylic alcohols represent a liability in RCM reactions when the desired transformation of intermediates such as **18** is slow.

In conclusion substrate **13**, which bears an allylic methyl ether [at C(9)] adjacent to its terminal vinyl group, is unreactive with either the ruthenium or molybdenum carbene complexes we have examined. However, since substrates containing secondary allylic ethers are known to engage in metathesis reactions,[21] we suspect that the additional remote branching in **13** further reduces its reaction rate. Strategies to circumvent this problem are now under study.

Acknowledgment. We thank the National Institutes of Health (CA-76497) for funding this project.

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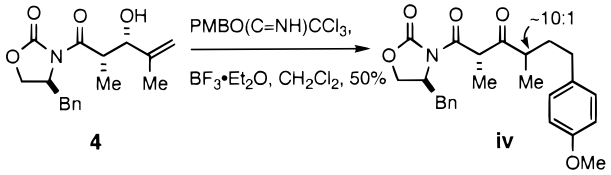
(8) (a) Diastereomeric acetonides were prepared from the major and minor diastereomeric diols **8** and **C(9)-epi-8**. Rychnovsky/Evans ^{13}C NMR analysis clearly indicated the 1,3-*anti* vs 1,3-*syn* nature of each: Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−8. Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−100. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−15. (b) Mosher ester analysis (Dale, J. A.; Mosher, H. A. *J. Am. Chem. Soc*. **1973**, *95*, 512−9) clearly supports the assignment of C(9)-*R* vs C(9)-*S* configuration in the major and minor diastereomers of **8**.

(9) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889−92. (b) Wang, Z. *Tetrahedron Lett.* **1989**, *30*, 6611−4.

(10) Initially, we tried a more direct sequence to prepare **9**, but attempts to protect the hindered hydroxyl in **4** with PMB were unsuccessful. Under acidic conditions (PMB-trichloromethylimidate/$BF_3{\cdot}OEt_2$) we isolated only the Friedel−Crafts product **iv** (in 50% yield) from the mixture of products. Under basic conditions (NaH, PMB−Cl, THF, 0 °C) retroaldol fragmentation predominated.



(11) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431−5.

(12) This cyclization was performed using 1 mg of pure **13-maj**. A second diastereomer of **14**, which we presume to be its anomeric epimer, was also observed (∼1:10 ratio).

(13) The reported value for the vicinal (*H*−*H*) coupling constant in a relevant 1,3-*syn*-acetal is much larger (J = 9.2 Hz; Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446−53) than that reported for a relevant 1,3-*anti*-acetal (J = 5.4 Hz; Roush, W. R.; Bannister, T. D.; Ermolendo, M. S.; Yashunsky, D. V.; Borodkin, V. S. *Tetrahedron Lett.* **1992**, *33*, 3587−90).

(14) (a) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1997**, *119*, 10302−16 and earlier refs therein. (b) For a recent review that includes known examples of macrocyclization reactions, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−50.

(15) Using the Schrock initiator $\{[(CF_3)_2(Me)CO]_2\}ArN{=}Mo{=}CH{-}C(Me)_2Ph$, we observed formation of $H_2C{=}CHC(Me)_2Ph$ at room temperature in C_6D_6 by NMR spectroscopy, which implies initial loading of the metal onto one of the olefins in **13**. However, the reaction is very slow and the overall conversion is low. We were unable to determine the fate of the resulting Mo−alkylidene.

(16) Linalool rapidly underwent RCM with **15** under conditions where linalool methyl ether was unreactive. We are continuing to study this phenomenon and report additional details elsewhere.

(17) Prepared from **8** by the sequence: (i) DDQ; (ii) TESOTf; (iii) DIBALH; (iv) Swern; (v) addition of dianion of **3**; and (vi) HF/MeOH.

(18) A major advantage of in situ NMR monitoring is that we can quickly assess with confidence whether a given substrate will engage in initial reaction with a given metal−carbene initiator (by the presence or absence of styrene and/or new M=C*H*R resonances). This in turn has permitted us to prepare only ∼1 mg of numerous complex substrates and confidently judge their reactivity.

(19) Alkenol **8** (2−3 mg) was exposed to ∼50 mol % of **15** in $CDCl_3$ at room temperature. Ketone **17** was the major product observed by direct NMR and GC/MS analysis of the reaction mixture and the only product (along with an approximately equal amount of starting **8**) isolated following HPLC purification.

(20) We speculate that an event similar to the **8** to **17** transformation converted **16** (∼1 mg)[18] to a methyl ketone, perhaps in the form of its hemiketal to the C(5)−OH.

(21) For example, see: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310−7318.