ORGANIC LETTERS

2005
Vol. 7, No. 18
3969−3971

A Paternò–Büchi Approach to the Synthesis of Merrilactone A

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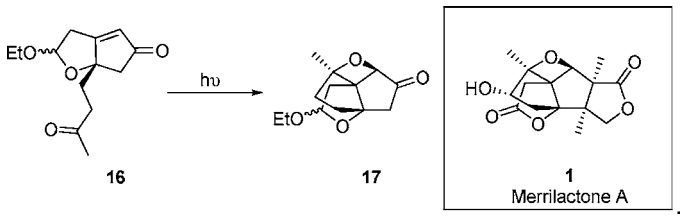
Received June 22, 2005

ABSTRACT



A six-step approach to the tetracyclic core of merrilactone A is described that uses an intramolecular Paternò–Büchi photoaddition to install the key oxetane ring. Irradiation of bicyclic enone 16, constructed through cyclopentenone alkylation followed by a domino oxy-/carbopalladation reaction, produces the tetracyclic oxetane 17 in excellent yield, having the core carbon skeleton of the target compound merrilactone A.

Merrilactone A was isolated from the pericarps of *Illicium merrillianum* A. C. Smith, a plant indigenous to Myanmar and southwest China, by Fukuyama in 2000.[1] The natural product was discovered as part of a screen for nonpeptide neurotrophic compounds, and subsequent biological assay showed it to significantly promote neurite outgrowth in cultures of fetal rat cortical neurons at low micromolar concentrations.[2] The structure of merrilactone A was determined using X-ray analysis combined with the modified Mosher method, characterizing the compound as the novel oxetane-containing sesquiterpene, **1**. The highly oxygenated, pentacyclic structure of the natural product featuring five contiguous fully substituted carbon centers combined with its promising neurotrophic activity make merrilactone A an excellent target for synthesis, and two groups have reported total syntheses to date: Danishefsky completed a racemic approach in 2002, followed by a more recent asymmetric variant, while Inoue and Hirama described a racemic route in 2003.[3,4]

Both successful syntheses utilize a homo-Payne rearrangement of the pentacyclic alcohol **2** as the final step,[1b] an elegant strategy that enables the installation of the oxetane to be saved until the very end of the synthetic sequence. We were interested in developing an alternative approach, whereby the central oxetane ring is introduced using an intramolecular [2+2] Paternò−Büchi photoaddition. Such a strategy aims to take advantage of the proven ability of photochemical [2 + 2] cyclizations to introduce quaternary stereocenters in sterically congested environments with high levels of stereocontrol[5] and could lead to an efficient route to the natural product. Our synthetic plan is shown in Scheme 1 and calls for the preparation of a bicyclic keto-olefin such

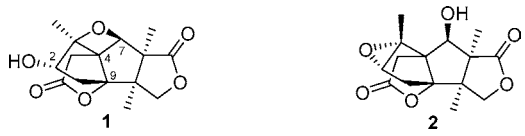


Figure 1. Merrilactone A, **1**, and homo-Payne precursor, **2**.

(1) (a) Huang, J.-M.; Yokoyama, R.; Yang, C.-S.; Fukuyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6111−6114. (b) Huang, J.-M.; Yang, C.-S.; Tanaka, M.; Fukuyama, Y. *Tetrahedron* **2001**, *57*, 4691−4698.

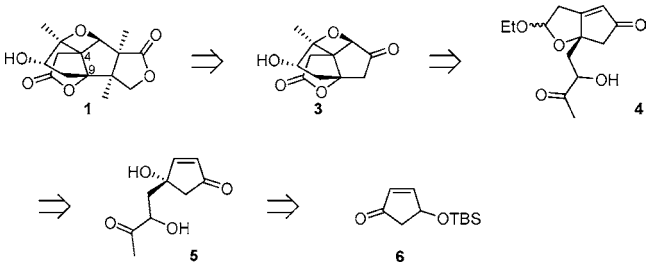
(2) Huang, J.-M.; Fukuyama, Y.; Yang, C.-S.; Minami, H.; Tanaka, M. *Chem. Pharm. Bull.* **2000**, *48*, 657−659.

(3) (a) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080−2081. (b) Inoue, M.; Sato, T.; Hirama, M. *J. Am. Chem. Soc.* **2003**, *125*, 10772−10773. (c) Meng, Z.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1511−1513.

(4) For a recent approach, see: Mehta, G.; Singh, S. R. *Tetrahedron Lett.* **2005**, *46*, 2079−2082.

10.1021/ol0514496 CCC: $30.25
Published on Web 08/11/2005

Scheme 1. Merrilactone A Synthetic Plan

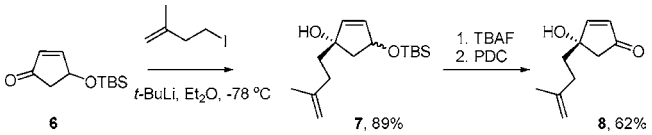


as **4** that can undergo [2 + 2] photocyclization to form the tetracyclic oxetane **3** having the characteristic oxa[3.3.3]-propellane structure around C4 and C9 of merrilactone A. The ketone would then provide a handle for annulation of the remaining lactone ring and completion of the synthesis. The keto-enone **4** would be available from a domino oxy-/carbopalladation reaction of the hydroxy-enone **5**, whereby the tertiary allylic alcohol undergoes oxy-palladation with ethyl vinyl ether followed by a Heck cyclization. Enone **5** arises from the alkylation of cyclopentenone **6**.

We wish to report our preliminary model studies on this synthetic sequence, in which we describe three of the four key carbon−carbon bond-forming steps, including the pivotal Paternò−Büchi photocyclization.

Our starting point is TBS-protected 3-hydroxycyclopentenone, available in multigram quantities from the Piancatelli rearrangement of furfuryl alcohol and subsequent protection.[6] Nucleophilic addition to the enone carbonyl group of **6** using organometallics prepared from 1-halo-3-methyl-but-3-enes was initially problematic, with Grignard and organocerium reagents producing low yields of the desired product **7**. Lithiation of 1-iodo-3-methyl-but-3-ene using Negishi's protocol,[7] followed by addition of enone **6** at −78 °C, eventually proved to be successful, affording alcohol **7** in 89% yield (Scheme 2). Desilylation and oxidation with PDC

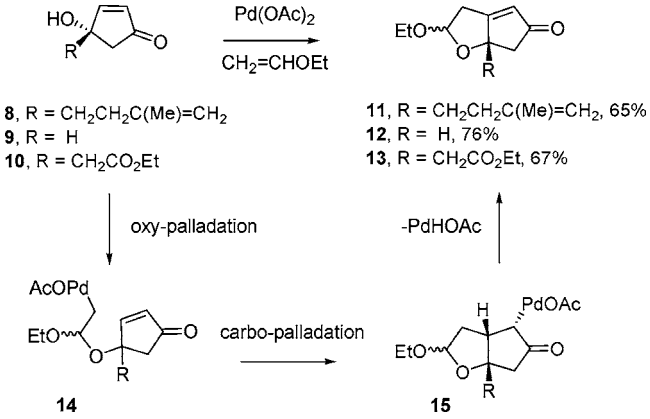
Scheme 2



gave the hydroxy-enone **8**, which is the substrate for the proposed domino oxy-/carbopalladation reaction.

We first examined the domino reaction using the simple hydroxy-enones **9** and **10** (Scheme 3).[8] Treatment with 1 equiv of $Pd(OAc)_2$ using ethyl vinyl ether as a solvent gave a clean transformation to the bicycles **12** and **13** in 76 and

Scheme 3. Domino Oxy-/Carbopalladation Reactions

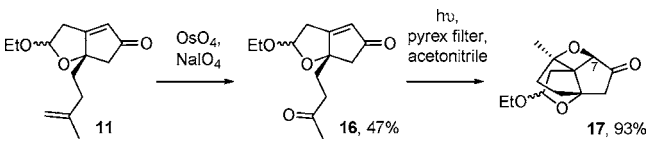


67% yield, respectively, as 1:1 acetal diastereoisomers. Our system differs from previous literature examples of domino oxy-/carbopalladations in that the double bond undergoing carbopalladation is part of a cyclic enone.[9] Consequently, the σ-palladium species **15** formed upon carbopalladation is unable to undergo the requisite *syn*-β-hydride elimination. The neighboring carbonyl group provides a possible solution to this problem, as rapid equilibration of palladium to the top face of the bicycle should be feasible through a η-3 oxy-π-allylpalladium species.[10] Subsequent elimination of PdHOAc then places the alkene at the ring junction.

Successful reaction of the relatively hindered tertiary alcohol **10** was encouraging, and we were pleased to see that exposure of hydroxy-enone **8** to the same oxy-/carbopalladation conditions produced the bicyclic acetal **11** in a similar 65% yield.

One-pot oxidative cleavage of alkene **11** gave the ketone **16**,[11] which is the substrate for the key [2 + 2] photoaddition. In the event, irradiation of a degassed acetonitrile solution of **16** (400 W medium-pressure mercury lamp, Pyrex filter) gave a clean cyclization to the tetracyclic oxetane **17** in very high yield (Scheme 4). The appearance of the C7 proton at

Scheme 4



δ = 4.60 and 4.66 for each acetal diastereoisomer in the ^{1}H NMR spectrum is diagnostic for the desired photoadduct and rules out the formation of any crossed adduct.[12] This is in accord with both the rule of five,[13] which describes the strong preference for five-membered ring formation in intramolecular [2 + 2] photocyclizations, and the known regio-

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(8) Enone **10** was prepared via the aldol reaction of cyclopenten-1,3-dione with the lithium enolate of ethyl acetate; see: Ciufolini, M. A.; Zhu, S. *J. Org. Chem.* **1998**, *63*, 1668−1675.

chemistry of Paternò−Büchi additions of ketones to electron-deficient alkenes.[12] The reaction sets three stereocenters and creates two rings simultaneously, forming tetracycle **17** having the oxa[3.3.3]propellane framework of merrilactone A.

In conclusion, we have developed a very short synthetic route that accesses the tetracyclic, oxetane core of merrilactone A in just six steps from TBS-protected 3-hydroxycyclopentenone. The route features a domino oxy-/carbopalladation reaction to create an angularly substituted oxa[3.3.0] system, followed by a highly efficient Paternò−Büchi photoaddition to install the central oxetane ring. Future work will examine the functionalization of the C2 position and the annulation of the remaining lactone ring from the ketone functionality present in **17**.

Acknowledgment. We thank the Government of the Basque Country for the award of a scholarship to J.I., the EPSRC for the award of a studentship to J.P., Astrazeneca and Pfizer for research support grants, and the EPSRC mass spectrometry service at the University of Swansea.

Supporting Information Available: Experimental procedures and characterization data for compounds **7**, **8**, **11**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0514496

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