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De Novo Asymmetric Synthesis of Daumone via a Palladium-Catalyzed Glycosylation

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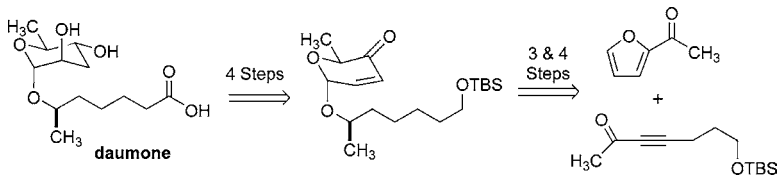
ABSTRACT



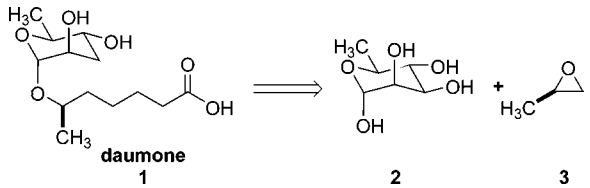
The enantioselective syntheses of daumone and two analogues have been achieved in seven to eight steps. This route relies upon a diasteroselective palladium-catalyzed glycosylation reaction for the formation of the anomeric bond. The asymmetry of the sugar and aglycone portion of daumone were introduced by Noyori reduction of an acylfuran and a propargyl ketone. A highly diastereoselective epoxidation and reductive ring opening established the desired C-2 and C-4 stereochemistry of daumone.

The recently purified pheromone daumone (**1**) has attracted significant attention for its ability to induce a dauer stage in *Caenorhabditis elegans*.[1] When *C. elegans* enter this dauer stage, they are capable of enduring various severe environmental conditions (e.g., overpopulation and starvation).[2] Because the *C. elegans* in the dauer stage appear not to age and experience extended lifetimes, there has been great interest in understanding the biochemical mechanism by which daumone regulates this process.[3] These studies have been significantly limited by the fact that neither pure daumone was available nor was the chemical structure of daumone known.[4] Recently, this problem has been alleviated by the extensive work of Jeong et al., who have isolated, characterized, and completed the total synthesis of daumone. Due to its fascinating biological activity, we desired access to synthetic samples of daumone, as well as several analogues.

In particular, we were also interested in preparing daumone via a de novo route that would take advantage of our recently developed palladium-catalyzed glycosylation reaction.[5,6] This route should allow for access not only to the desired natural product for biological study but also to analogues. Herein we report our successful endeavors toward the de novo synthesis of daumone, as well as a C-2 deoxy-analogue and a C-3 oxygenated analogue.

While in terms of overall efficiency the Jeong synthesis of daumone set quite a high standard (Scheme 1), it did not meet all of our requirements. In particular, we wanted a route that allowed for the late-stage introduction of a hydride.[7] The Jeong route to daumone derives the asymmetry from

Scheme 1. Jeong's Approach to Daumone (**1**)



(1) Viney, M. F.; Franks, N. R. *Naturwissenschaften* **2004**, *91*, 123−124.

(2) (a) Bargmann, C. I.; Horvitz, H. R. *Science* **1991**, *251*, 1243−1246. (b) Gordon, J. W.; Riddle *Dev. Biol.* **1984**, *102*, 368−378. (c) Cassada, R. C.; Russell, R. L. *Dev. Biol.* **1975**, *46*, 326−342.

(3) (a) Apfeld, J.; Kenyon, C. *Nature* **1999**, *402*, 804−809. (b) Bird, D. M.; Opperman, C. H. *J. Nematol.* **1998**, *30*, 299−308.

(4) Jeong, P.-Y.; Jung, M.; Yim, Y.-H.; Kim, H.; Kim, K.; Paik, Y.-K. *Nature* **2005**, *433*, 541−545.

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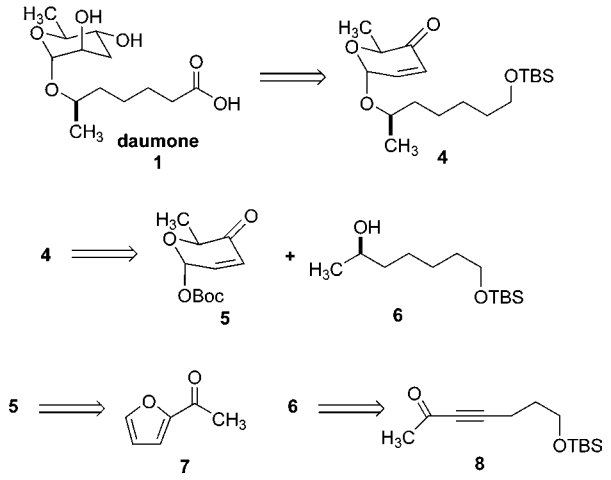
chiral fragments, these being L-rhamnose and (*R*)-propylene oxide. In contrast, we looked to prepare daumone from achiral starting materials using asymmetric catalysis to set the asymmetry without losing any overall efficiency.[8] Hence, this synthetic endeavor should serve as an excellent test to our de novo asymmetric approach to carbohydrate containing natural products.[5]

Retrosynthetically, we envisioned the 3-deoxy-L-rhamnose of daumone being derived from a diastereoselective alkene hydration and ketone reduction of the pyranone ring in **4** (Scheme 2). The glycosidic bond of pyranone **4** could be

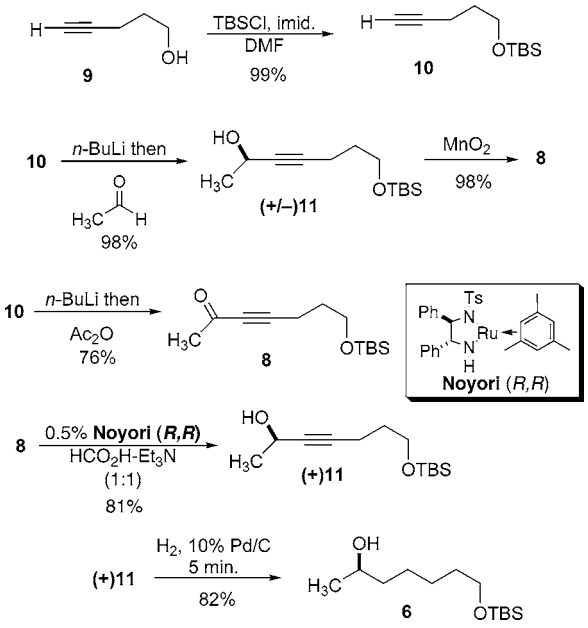
Scheme 2. Daumone (**1**) Retrosynthesis



stereoselectively installed by a palladium-catalyzed coupling of the pyranone **5** and alcohol **6**. Finally, it was envisioned that the absolute stereochemistry of both **5** and **6** could be established by applying two Noyori reductions of acylfuran **7** and propargyl ketone **8**, respectively.[9] Because this route couples two chiral subunits, it requires that both Noyori reactions occur with nearly complete enantiocontrol.

The synthesis of the aglycone precursor **6** begins with 4-pentynol **9** (Scheme 3), which was protected to give TBS-ether **10** with TBSCl/imidazole in DMF (99%). The terminal alkyne in **10** was converted into propargyl ketone **8** by two procedures. Either metalation of **10** with *n*-BuLi and then quenching with acetaldehyde followed by MnO_2 oxidation (98%) or in one step by quenching the

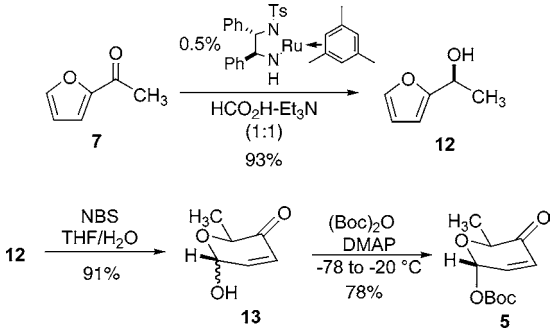
Scheme 3. Synthesis of Aglycone Precursor **6**



lithium acetylide of **10** with acetic anhydride (76%). Exposure of the propagyl ketone **10** to our modified Noyori conditions[10] provided excellent yield (81%) of propargyl alcohol **11** with high enantiomeric purity (>96% ee). Finally, the triple bond in **11** was cleanly reduced (H_2, 10% Pd/C) to give a good yield of **6** (82%, 63% overall yield from alkyne **9**).

With a reliable route to optically pure aglycone precursor **6** in hand, we next looked into the preparation of its pyranone coupling partner **5** (Scheme 4). This was quite

Scheme 4. Synthesisof α-Pyranone **5**



easily accomplished by use of an Achmatowicz reaction of furan alcohol **12**.[11] Once again employing the Noyori

(5) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407. (b) Babu, R. S.; M. Zhou; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428−3429. (c) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem.* **2005**, *24*, 169−177.

(6) For the work of others, see: (a) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714−8715. (b) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336−1337.

(7) We envisioned that by incorporating a late-stage ketone reduction the new route would be amenable to the incorporation of a tritium label. For similar examples of label incorporation, see: Weigel, T. M.; Liu, H.-W. *Tetrahedron Lett.* **1988**, *29*, 4221−4224.

(8) For alterative approaches to sugars, see: (a) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304−4309. (b) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979−3981.

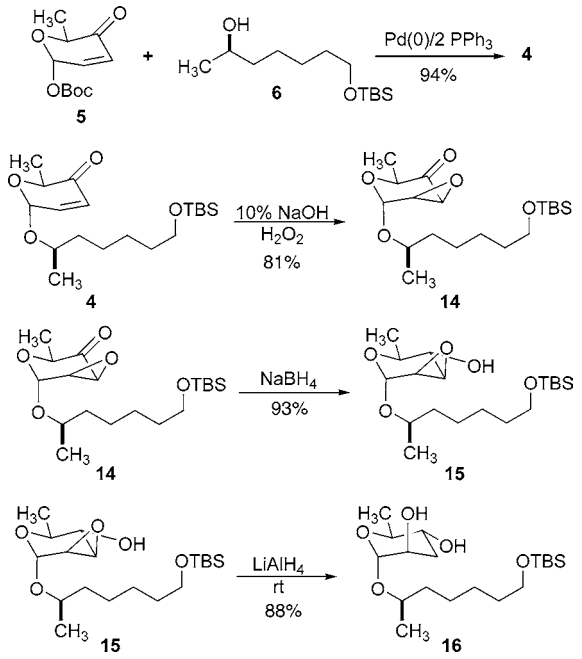
(9) (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73.

(10) Previously, we have shown that a lower ratio of HCO_2H/Et_3N (1:1 instead of 2:1) was required for the Noyori reduction of compounds with primary TBS groups; see: Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005−1009.

reduction, with the enantiomeric catalyst, the furan alcohol **12** can be prepared from acylfuran in very high enantiomeric excess (93% yield and >96% ee).[12] Treating furan alcohol **12** with typical Achmatowicz conditions (NBS in THF/H_2O) gave a good yield of the ring-expanded pyranone product **13** (91%). The hemiacetal of **13** was then diastereoselectively acylated with $(Boc)_2O$ to provide the Boc-protected pyranone **5** in excellent overall yield (66%) from acylfuran **7**.

As outlined in Scheme 5, we next investigated the glycosylation reaction of alcohol **6** with pyranone **5** followed

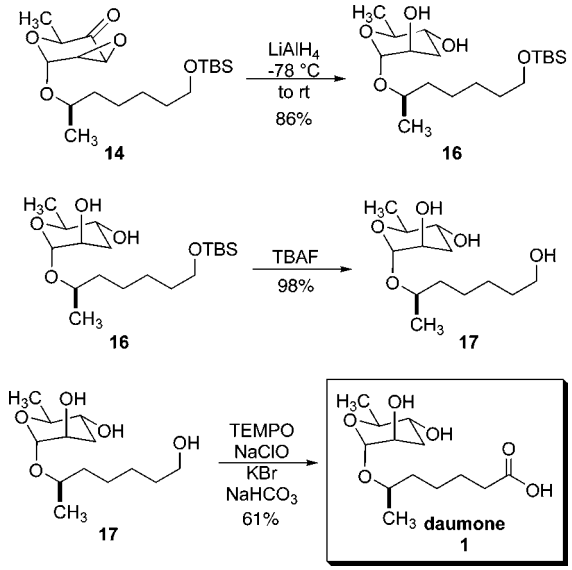
Scheme 5. Palladium-Catalyzed Glycosylation and Postglycosylation Transformation



by the subsequent conversion of the product enone **4** to the 3-deoxy-L-rhamnose **16**. Thus, exposing a CH_2Cl_2 solution of **5** and **6** to 5% palladium(0) and 10% triphenylphosphine provided an excellent yield (94%) of pyranone **4** as a single diastereomer.[5] Treating the glycosylated product **4** with hydrogen peroxide in the presence of a catalytic amount of base (10 mol % NaOH) diastereoselectively epoxidized the enone of **4**, producing epoxy-enone **14** in 81% yield.[13] In an equally diastereoselective fashion, the ketone of **14** was reduced with $NaBH_4$ (−78 to −20 °C) to form the equatorial alcohol **15** (93%). Taking advantage of an internal delivery of a hydride anion via chelation to the C-4 hydroxyl group, the epoxide **15** was regioselectivly opened with $LiAlH_4$ to form **16** in 88% yield.[14]

By combining the ketone reduction with the epoxide opening reaction, we achieved a one-step conversion of epoxy-enone **14** to diol **16** (Scheme 6). Thus, exposing **14**

Scheme 6. Conversion of **13** to Daumone (**1**)



to $LiAlH_4$ at −78 °C followed by warming to room temperature cleanly provided **16** in an 86% yield.[15] With the required stereochemistry of daumone installed in **16**, all that remained was the deprotection of the TBS-ether and the chemoselective oxidation of the primary alcohol to the carboxylic acid. This deprotection was most easily accomplished by exposing **16** to TBAF (98%). Finally, the triol **17** was cleanly oxidized to daumone (**1**) using a catalytic TEMPO procedure (61%).[16] We found that the spectral data for synthetic daumone (**1**) matched what was reported for the isolated natural product in terms of IR, ^1H and ^{13}C NMR, and optical rotation.[4,17]

This de novo approach to daumone, was also amenable for the preparation of sugar analogues (Scheme 7). Thus,

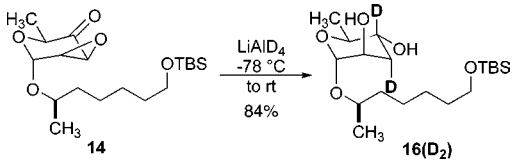
(11) An Achmatowicz reaction is the oxidative rearrangement of furfuryl alcohols to 2-substituted 6-hydroxy-2*H*-pyran-3(6*H*)-ones; see: (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165−176. For its use in carbohydrate synthesis, see: refs 5, 10, 12 and: (b) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863−866. (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033−4036.

(12) For other examples of the Noyori reduction of acylfurans, see ref 10 and: (a) Haukaas, M. H.; O'Doherty G. A. *Org. Lett.* **2001**, *3*, 3899−3992. (b) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407−6411.

(13) Jung, M. E.; Pontillo, J. *J. Org. Chem.* **2002**, *67*, 6848−6851.

(14) For other examples of epoxide-opening reactions with $LiAlH_4$, see ref 7 and: Mastihubova, M.; Biely, P. *Tetrahedron Lett.* **2001**, *42*, 9065−9067.

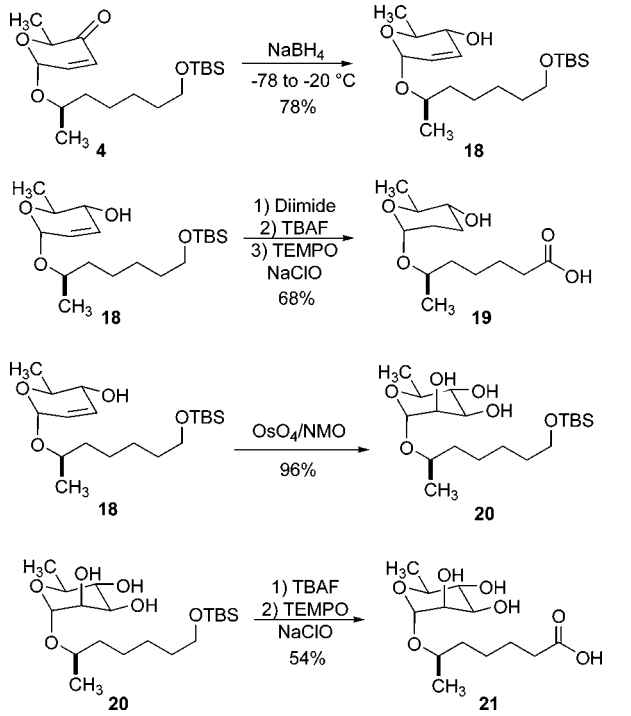
(15) As a prelude to our tritium labeling studies, epoxyketone **14** was treated with $LiAlD_4$, which cleanly afforded the bis-deuterated diol **16-(D_2)**.



(16) For other examples of a catalytic TEMPO oxidation to form carboxylic acids in unprotected carbohydrates see: a) Ying, L.; Gervay-Hague, J. *Carbohydrate Res.* **2003**, *338*, 835−841. (b) Bragd, P. L.; Besemer, A. C.; Bekkum, H. V. *Carbohydr. Polym.* **2002**, *49*, 397−406.

(17) Optical rotation for our synthetic daumone (**1**) was −85 (*c* 1.15), which was slightly higher than the previously reported $[\alpha]_D$ of −82 (*c* 0.1). Both values were measured in methanol.

Scheme 7. Syntheses of Daumone Analogues **18** and **19**



both the C-2 deoxy- and the C-3 hydroxy-daumone (**19** and **21**, respectively) were prepared from the palladium glycosylation product **4**. Simply reducing the enone with $NaBH_4$ provided allylic alcohol **18** as a single diasteromer and in 78% yield. The alcohol **18** was converted to the deoxy-analogue **19** by means of a diimide reduction of the pyran double bond followed by TBS-ether deprotection and oxidation to the carboxylic acid **19** (53% overall yield from enone **4**). Similarly, the pyran double bond of **18** was diastereoselectively oxidized to the rhamnose isomer **20** (96% yield), which as before was deprotected (98%) and oxidized (55%) to the C-3 hydroxy daumone analogue **21** in good overall yield (42% yield from enone **4**).

In conclusion, a short de novo asymmetric synthesis of daumone (**1**) has been developed. This highly enantio- and diastereocontrolled route illustrates the utility of a palladium-catalyzed glycosylation reaction for synthesis, as well as the Noyori reductions of two ketones. This approach provided both daumone (**1**) along with two analogues C-2 deoxy-daumone **19** and C-3 hydroxy-daumone **21** in 26, 33, and 26% overall yields from acylfuran **7**, respectively.[18] It is also worth noting that this route provided daumone in very comparable efficiency to the previous carbohydrate-based approach; however, this de novo approach started from achiral sources and required the use of only one protecting group. Further application of this approach to other members of this class of natural product synthesis and biological testing is ongoing.

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

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

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(18) These overall yields for **1**, **19**, and **21** are very similar from pentynol **9** (24, 31, and 25%, respectively).