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Asymmetric Synthesis of Umuravumbolide[1]

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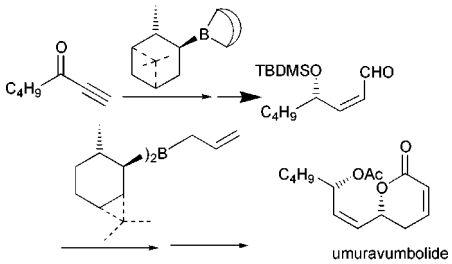
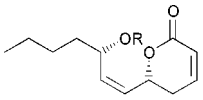
ABSTRACT



This first asymmetric synthesis of enantiopure desacetylumuravumbolide and umuravumbolide via asymmetric reduction, allylboration, and ring-closing metathesis confirms their revised structures and configurations. A convenient procedure to upgrade the enantiopurity of α,β-acetylenic alcohols is also described.

Several natural products containing 6-substituted 5,6-dihydro-α-pyrones isolated from various plant species have been established to be bioactive.[2] They offer a wide range of applications, such as plant growth inhibitors, pheromones, and antifeedal, antifungal, antibacterial, and antitumor agents.[2] Desacetylumuravumbolide (**1a**) and umuravumbolide (**1b**),[3] isolated from *Tetradenia riparia* Lamiaceae from central and southern Africa also belong to the above class of natural products. Although they have not been examined for their biological activity so far, several compounds from Lamiaceae family have been shown to be an emetic to treat loss of appetite.[4] Unfortunately, the exact structure and configuration of **1a** and **1b** were not known until recently.

On the basis of infrared studies, Van Puyvelde and co-workers erroneously reported that these compounds contain an *E*-double bond on the side chain of the pyranone moiety and also reported that they are optically inactive.[3] Achenbach and Witzke reported the synthesis of the racemic compounds containing the *E*-double bond.[5]



R = H: desacetylumuravumbolide, **1a**
R = Ac: umuravumbolide, **1b**

Recently, Davies-Coleman and Rivett reinvestigated and revised the structures of desacetylumuravumbolide and umuravumbolide as **1a** and **1b**, respectively.[6] They determined the absolute configurations on the basis of NMR and CD studies and also reported the optical rotations of these compounds.[6] However, there has been no chemical synthesis of these molecules to confirm their structure and/or stereo-

(1) Contribution 8 from the Herbert C. Brown Center for Borane Research.

(2) Davies-Coleman, M. T.; Rivett, D. E. A. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 1.

(3) Van Puyvelde, L.; Dube, S.; Uwimana, E.; Uwera, C.; Dommisse, R. A.; Esmans, E. L.; Van Schoor, O.; Vlietinck, A. J. *Phytochemistry* **1979**, *18*, 1215.

(4) Watt, J. M.; Brandwijk, M. G. *The Medicinal and Poisnous Plants of Southern and Eastern Africa*; Livingstone: Edinburgh, 1962.

(5) Achenbach, H.; Witzke, J. *Z. Naturforsch. B: Anorg. Chem. Org. Chem.* **1980**, *35*, 1459.

(6) Davies-Coleman, M. T.; Rivett, D. E. A. *Phytochemistry* **1995**, *38*, 791.

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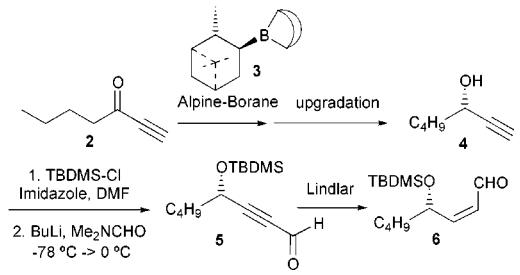
chemistry. Herein we report the first asymmetric synthesis of **1a** and **1b** involving two terpene-based borane reagents[7] for asymmetric induction.

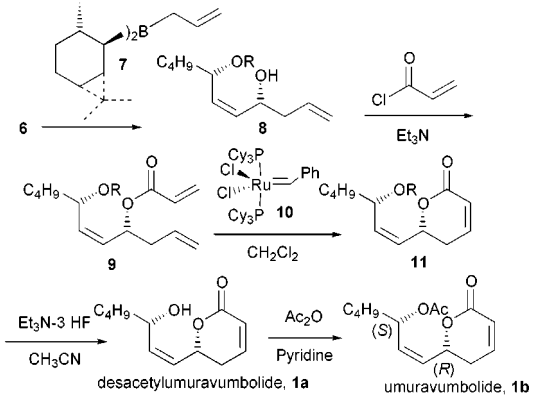
Our approach required optically pure (*S*)-1-heptyn-3-ol (**4**). Reduction of the corresponding acetylenic ketone **2**[8] with (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane)[9] (**3**) provided (*S*)-**4** in 75% yield and 74% ee.[10] Recrystallizing the 3,5-dintrobenzoate of **4** and recovering the alcohol by basic hydrolysis upgraded the enantiomeric purity to ⩾99% ee as determined by the HPLC analysis of the 3,5-dinitrobenzoate on a CHIRALCEL OD-H column.[11] Our successful synthetic strategy is outlined in Schemes 1

Scheme 1



and 2. TBDMS protection of **4**, followed by formylation, provided the acetylenic aldehyde **5** in 50% overall yield. This was converted to the required *Z*-olefinic aldehyde **6** in 65% yield by hydrogenation under Lindlar catalysis.

Scheme 2



Allylboration of **6** with *B*-allyldiiso-2-caranylborane (**7**)[12] provided enantiomerically pure **8** in 79% yield.[13] Esterification with acryloyl chloride, followed by ring-closing metathesis using Grubbs ruthenium catalyst (**10**),[14] provided the lactenone **11** in 65% overall yield (Scheme 2).[15]

Repeated attempts to deprotect the TBDMS group with Bu_4NF provided very low yields of **1a**, along with a mixture of products. We achieved the deprotection in 94% yield by utilizing triethylamine trihydrofluoride.[16] Acetylation provided 98% yield of **1b** (Scheme 2). The overall yield of **1b** starting with **4** is 15.4%.

The configurations as determined by analogy for Alpine-Borane reductions and allylborations with **7** and the signs of rotations matched with those reported by Coleman and Rivett.[6] While the rotation of $[\alpha]^{25}_D = -5.3$ (*c* 1.3, $CHCl_3$) for **1a** matched, the rotation of $[\alpha]^{25}_D = +35$ (*c* 1.8, $CDCl_3$) for **1b** is higher than that reported ($[\alpha]^{25}_D = +30$ (*c* 2.1, $CDCl_3$)).[6]

In conclusion, we have confirmed the structure and configuration of desacetylumuravumbolide and umuravumbolide by synthesis via asymmetric reduction, allylboration, and ring-closing metathesis as key steps. We have also reported a convenient procedure to upgrade the % ee of α,*β*-acetylenic alcohols.

Acknowledgment. Financial assistance from the Herbert C. Brown Center for Borane Research is gratefully acknowledged.

Supporting Information Available: Experimental procedures for the preparation of **1** and the spectroscopic data for compounds **1a**, **1b**, **5**, **6**, **8**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006583Z

(7) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1.

(8) Ketone **2** was prepared via Jones oxidation of commercially available 1-heptyn-3-ol.

(9) (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (*S*)-Alpine-Borane provides *S*-alcohol. (b) Alpine-Borane is the registered trademark of Aldrich Chemical Co.

(10) The reagent used was of 84% ee. Midland reported 92% ee with optically pure reagent for a similar alcohol on the basis of ^{1}H NMR analysis in the presence of $Eu(dcm)_3$.

(11) To confirm the efficacy of this upgradation procedure, we prepared 1-butyn-3-ol and 1-octyn-3-ol of 72% and 76% ee, respectively, by Alpine-Borane (84% ee) reduction of the corresponding ketone and upgraded them to 99% ee via the 3,5-dintrobenzoate.

(12) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *113*, 2389.

(13) We did not observe any of the diastereomers by ^{1}H NMR spectroscopy. The configuration is based on analogy for allylborations with **7**. This was confirmed by the rotation of the target molecule.

(14) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(15) The observed selectivity for the ring-closing metathesis reaction has precedence. Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211.

(16) Myers, A. G.; Gin, D. Y.; Rogers, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4697.