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Synthesis of L-Kedarosamine in Protected Form and Its Efficient Incorporation into an Advanced Intermediate to Kedarcidin Chromophore

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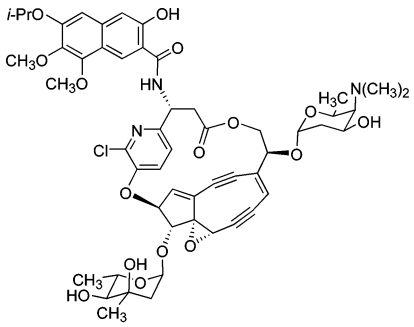
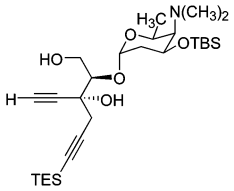
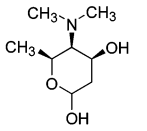
ABSTRACT



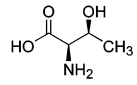
Kedarcidin Chromophore (**1**)



Synthetic Precursor (**2**)



L-Kedarosamine



D-Threonine

An efficient route to the complex L-kedarosamine α-glycosidic ether 2, a synthetic precursor to kedarcidin chromophore, is described. Central to the route, which is suitable for the preparation of multigram amounts of material, is a short synthetic sequence from D-threonine to protected L-kedarosamine derivatives and methodology for their α-selective coupling with appropriate hydroxyl acceptors.

Kedarcidin chromophore (**1**) is the nonprotein component of the natural product kedarcidin, one of a family of natural products with DNA-cleaving abilities that are thought to derive from the capacity of members of the family to form biradical intermediates.[1] Its proposed structure (**1**) contains many unusual structural features, including an ansa-bridge comprising a chloroazatyrosine β-amino acid derivative, and the rare amino sugar kedarosamine,[2] whose synthesis and incorporation into an advanced intermediate suitable for the synthesis of **1** (the precursor **2**) is the subject of this work.[3] Early incorporation of the kedarose residue represents one part of a broader strategy to assemble much of the structural complexity of kedarcidin chromophore prior to formation of its reactive epoxybicyclo[7.3.0]dodecadienediyne core.

Given the amounts of protected kedarosamine and the intermediate **2** that we were targeting (gram quantities), we felt that existing syntheses of kedarosamine were not suitable to our purpose.[2c−f] We therefore developed a new, more practical synthetic route, which begins with the known *N*,*N*-dimethyl derivative of D-threonine methyl ester (**3**, Scheme 1).[4] *O*-Acetylation of **3** (acetic anhydride, triethylamine,

(1) Isolation: (a) Lam, K. S.; Hesler, G. A.; Gustavson, D. R.; Crosswell, A. R.; Veitch, J. M.; Forenza, S.; Tomita, K. *J. Antibiot.* **1991**, *44*, 472. (b) Hofstead, S. J.; Matson, J. A.; Malacko, A. R.; Marquardt, H. *J. Antibiot.* **1992**, *45*, 1250. Characterization and structure proposal: (c) Leet, J. E.; Schroeder, D. R.; Hofstead, S. J.; Golik, J.; Colson, K. L.; Huang, S.; Klohr, S. E.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 7946. (d) Leet, J. E.; Schroeder, D. R.; Langley, D. R.; Colson, K. L.; Huang, S.; Klohr, S. E.; Lee, M. S.; Golik, J.; Hofstead, S. J.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8432. Structure revision: (e) Kawata, S.; Ashizawa, S.; Hirama, M. *J. Am. Chem. Soc.* **1997**, *119*, 12012. DNA-cleaving activity: (f) Zein, N.; Colson, K. L.; Leet, J. E.; Schroeder, D. R.; Solomon, W.; Doyle, T. W.; Casazza, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 2822. (g) Zein, N.; Casazza, A. M.; Doyle, T. W.; Leet, J. E.; Schroeder, D. R.; Solomon, W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8009.

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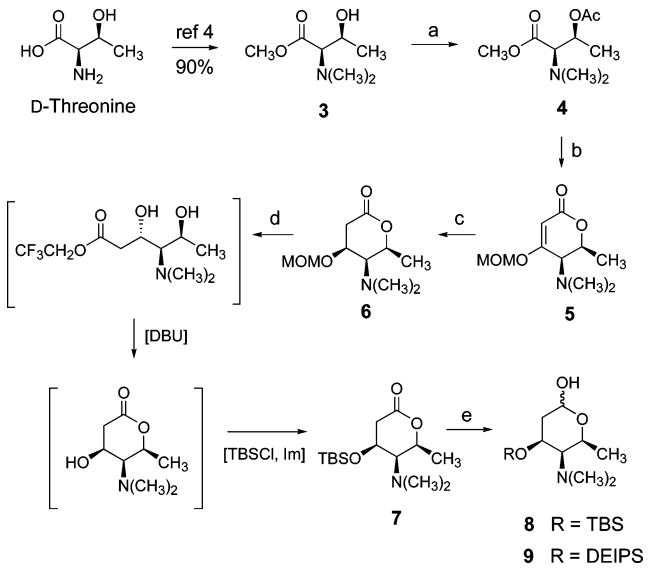
Scheme 1. Synthesis of Protected L-Kedarosamine Derivatives from D-Threonine[a]



[a] Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 23 °C, 93%; (b) LiHMDS, THF, −78 to −35 °C; MOMBr, −78 to 23 °C, 78%; (c) $Pd(OH)_2$, H_2, TFE, −20 °C, 82%; (d) AcCl, TFE, 23 °C; DBU, CH_2Cl_2, 23 °C; Im, TBSCl, 23 °C, 75%; (e) DIBAL, CH_2Cl_2, −78 °C, 96%.

4-*N*,*N*-dimethylaminopyridine) provided the diester **4** (93%). Addition of a solution of diester **4** in tetrahydrofuran (THF) over 40 min to a cold (−78 °C) solution of lithium bis(trimethylsilyl)amide (LHMDS, 2.3 equiv) in THF led to smooth Dieckmann cyclization; in situ alkylation of the resulting β-keto lactone enolate with methoxymethyl (MOM) bromide afforded the MOM enol ether lactone **5** in 78% yield (16.5 g of product) after purification by flash column chromatography. Hydrogenation of the enol ether double bond of the product (**5**) was accomplished by using a charcoal-supported palladium catalyst in 2,2,2-trifluoroethanol (TFE) as solvent at −20 °C, providing stereoselectively the MOM ether lactone **6** (82% yield, 9 g of product).

(2) Structure elucidation of L-kedarosamine: (a) Leet, J. E.; Golik, J.; Hofstead, S. J.; Matson, J. A.; Lee, A. Y.; Clardy, J. *Tetrahedron Lett.* **1992**, *33*, 6107. Another natural occurrence: (b) Kirst, H. A.; Larsen, S. H.; Paschal, J. W.; Occolowitz, J. L.; Creemer, L. C.; Steiner, J. L. R.; Lobkovsky, E.; Clardy, J. *J. Antibiot.* **1995**, *48*, 990. Syntheses of kedarosamine and derivatives: (c) Hornyak, M.; Pelyvas, I. F.; Sztaricskai, F. J. *Tetrahedron Lett.* **1993**, *34*, 4087. (d) Vuljanic, T.; Kihlberg, J.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 6937. (e) Vuljanic, T.; Kihlberg, J.; Somfai, P. *J. Org. Chem.* **1998**, *63*, 279. (f) Lear, M. J.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 4897.

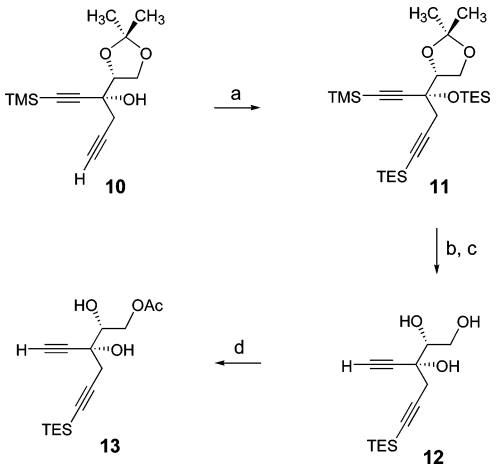
(3) For prior synthetic studies directed toward kedarcidin chromophore, see: (a) Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1994**, *116*, 10310. (b) Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1995**, *117*, 8875. (c) Sato, I.; Akahori, Y.; Iida, K.; Hirama, M. *Tetrahedron Lett.* **1996**, *37*, 5135. (d) Lhermitte, H.; Grierson, D. S. *Contemp. Org. Synth.* **1996**, *3*, 93. (e) Magnus, P.; Carter, R.; Davis, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283. (f) Kawata, S.; Yoshimura, F.; Irie, J.; Ehara, H.; Hirama, M. *Synlett* **1997**, 250. (g) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732. (h) Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1062. (i) Myers, A. G.; Hurd, A. R.; Hogan, P. C. *J. Am. Chem. Soc.* **2002**, *124*, 4583. (j) Koyama, Y.; Lear, M. J.; Yoshimura, F.; Ohashi, I.; Mashimo, T.; Hirama, M. *Org. Lett.* **2005**, *7*, 267.

(4) Cohen, A.; Bergmann, E. D. *Tetrahedron* **1966**, *22*, 3545.

Both the choice of the solvent and the catalyst were critical to the success of this transformation. In other protic solvents reductive cleavage of the MOM ether occurred as the major reaction pathway and in nonprotic solvents reaction was slow to proceed. Different catalysts (Raney-Ni, PtO_2) promoted reductive cleavage of the MOM ether. Although a charcoal-supported rhodium catalyst did provide the desired MOM ether (**6**) as the major product, the yield was lower than that with the charcoal-supported palladium catalyst. Acidic cleavage of the MOM ether group of the lactone **6** was achieved in a mixture of acetyl chloride in trifluoroethanol as solvent, conditions which, interestingly, also promoted ring-opening of the δ-lactone by the solvent. As part of the same operation, after concentration, a solution of DBU in dichloromethane was added to the reaction mixture, leading to re-closure of the δ-lactone; addition of *tert*-butyldimethylsilyl (TBS) chloride and imidazole then formed the crystalline TBS-protected lactone **7** (75% yield overall). Reduction of the lactone with diisobutylaluminum hydride then afforded kedarosamine 3-TBS ether (**8**) as a 1.5:1 mixture of α- and β-anomers, respectively (96%, 1-g scale; 39% over 7 steps from D-threonine). On a somewhat larger scale (8−9 g) and with nearly identical efficiency, we also synthesized the corresponding 3-diethylisopropylsilyl (DEIPS) ether derivative (**9**) (substituting DEIPSCl for TBSCl, see the Supporting Information).

The dialkynyl diol **13**, the acceptor for glycosylation studies, was prepared in a 4-step sequence from the known intermediate **10**[3a] (Scheme 2). Treatment of **10** with LHMDS

Scheme 2. Synthesis of the Dialkynyl Diol **13**[a]



[a] Reagents and conditions: (a) LHMDS, TESCl, THF, −78 °C, 97%; (b) HF, CH_3CN, 23 °C; (c) K_2CO_3, MeOH, −10 °C, 93% (two steps); (d) AcCl, pyridine, 0 °C, 82%.

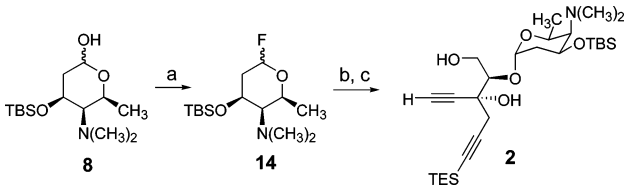
(2.2 equiv) and quenching of the resulting dianion with TESCl formed the bis-triethylsilylated product **11** in 97% yield (18-g scale). The acetonide and *O*-triethylsilyl groups within the product were cleaved in the presence of hydrofluoric acid in acetonitrile at 23 °C; stirring of the crude product with potassium carbonate in methanol at −10 °C

then selectively removed the *C*-trimethylsilyl group, affording the triol **12**. Selective acetylation of the primary hydroxyl group of the triol **12** occurred upon exposure to acetyl chloride (1.05 equiv) in pyridine, affording the glycosylation substrate **13** as a colorless oil after purification by flash-column chromatography (82% yield, 9-g scale).

Having developed efficient routes to the kedarosamine derivative **8** and the dialkynyl diol **13**, our efforts were then focused on finding an appropriate means of activation of **8** for an α-selective glycosidic coupling. Several standard methods of glycosidic activation were explored, including the Schmidt trichloroacetimidate method,[5] as well as procedures involving glycosyl phenylthioglycoside,[6] acetate,[7] and fluoride derivatives.[8] The glycosyl fluorides **14** were found to be the most effective donors among the aforementioned derivatives, and were prepared by treatment of lactol **8** with (diethylamino)sulfur trifluoride (DAST) in THF, affording a 2:1 mixture of α- and *β*-anomers **14**, respectively (Scheme 3).[9] The glycosyl fluorides **14** were not stable to chromatography on silica gel, and were therefore used directly for coupling, without purification. Coupling of the mixture of fluorides **14** with the acceptor **13** (2.5 equiv) was performed by using the Suzuki protocol (Cp_2HfCl_2, $AgClO_4$)[10] and gave rise to a 4:1 mixture of regioisomeric α-glycosidation products, favoring α-glycosidation of the secondary hydroxyl group of **13** (unreacted **13** was readily recovered). The product mixture was most conveniently purified (chromatographically) after cleavage of the acetate esters (K_2CO_3, MeOH). The kedarcidin chromophore precursor **2** was obtained in pure form in 60% yield (from **8**, three steps, 1.2-g scale). The regioisomeric product of α-glycosidation of the tertiary hydroxyl group was isolated separately, in 14% yield (see the Supporting Information).[11] Other promoters of glycosidation ($Cp_2ZrCl_2-AgClO_4$,[10a] $SnCl_2-AgClO_4$,[12] TiF_4,[13] SiF_4,[14] Tf_2O,[15] TMSOTf,[14] and $BF_3\cdot Et_2O$[16]) were less effective in terms of the degree of conversion and/or the regioselectivity of the glycosidation reaction. For example, use of titanium(IV) fluoride as a promoter afforded a 1:1 mixture of regioisomeric glycosidation products.

We have also applied the protocols of Scheme 3 to synthesize the DEIPS-protected kedarcidin precursor corresponding to **2** (using the DEIPS-protected kedarosamine precursor **9**, Scheme 1, 3-g scale, and only 1.5 equiv of **13**, see the Supporting Information), in 50% yield. The latter compound has been successfully transformed into the proposed structure of kedarcidin chromophore.[17]

Scheme 3. Synthesis of the Kedarcidin Chromophore Precursor **2** from the Kedarosamine Derivative **8**[a]



[a] Reagents and conditions: (a) DAST, THF, −45 °C; (b) Cp_2HfCl_2, $AgClO_4$, **13**, CH_2Cl_2, 0 °C; (c) K_2CO_3, MeOH, 23 °C, 60% (three steps).

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

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(11) The Hirama group has reported a similarly regioselective glycosidation reaction employing an anomeric trichloroacetimidate derivative of L-kedarosamine (15−25 equiv) and a complex diol substrate in their preparation of an advanced kedarcidin chromophore intermediate, obtaining a regioselectivity of ∼4:1 in favor of α-glycosidation of the secondary hydroxyl group; see: Osahi, I.; Lear, M. J.; Yoshimura, F.; Hirama, M. *Org. Lett.* **2004**, *6*, 719.
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