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Use of Polystyrene-Supported DBU in the Synthesis and α-Selective Glycosylation Study of the Unstable Schmidt Donor of L-Kedarosamine

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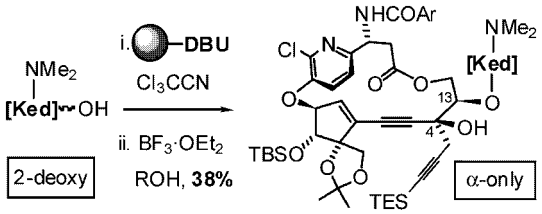
ABSTRACT



In the α-glycosylation study of the unusual, 2-deoxy amino sugar of kedarcidin, polystyrene-supported DBU (PDBU) was found to be invaluable to the clean preparation of the highly labile Schmidt donor of L-kedarosamine. By further recognition that the C4-alcohol should be left free for favorable acceptor reactivity, we could for the first time successfully assemble the C13-*O*-α-glycoside of the ansamacrolide substructure of the kedarcidin chromophore.

A central consideration in the total synthesis of the kedarcidin chromophore **1** resides in timing the construction of the fragile, nine-membered enediyne core with the attachment of the labile 2,6-dideoxy sugars, L-kedarosamine and L-mycarose (Figure 1).[1,2] Most conveniently, glycosylation events when performed at a late stage on unstable aglycon acceptors will ensure that a minimal number of reaction steps will be required in a total synthesis. This consideration demands for the glycosyl donor (cf. **2**) to be attached in a direct and exceptionally mild manner and thus demands that the amino group be left unprotected in its NMe_2 form.[3,4] As a consequence, synthetic difficulties are anticipated in the

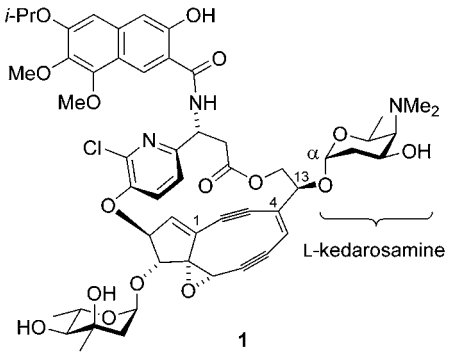


Figure 1. Structure of kedarcidin chromophore **1** featuring the unusual α-linked, 2,6-dideoxy sugar, L-kedarosamine.

(1) Isolation of kedarcidin and chromophore structure (**1**): (a) Lam, K. S.; Hesler, G. A.; Gustavson, D. R.; Crosswell, A. R.; Veitch, J. M.; Forenza, S.; Tomita, K. *J. Antibiot.* **1991**, *44*, 472−478. Hofstead, S. J.; Matson, J. A.; Malacko, A. R.; Marquardt, H. *J. Antibiot*. **1992**, *45*, 1250−1254. (b) 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*, 8432−8443. (c) Structure revision: Kawata, S.; Ashizawa, S.; Hirama, M. *J. Am. Chem. Soc*. **1997**, *119*, 12012−12013.

(2) For a very inspired and elegant synthesis of the aglycon of **1**, see: Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1062−1067.

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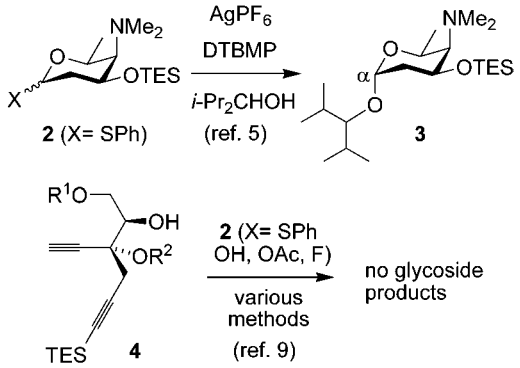
formation and handling of not only the activated sugar donor but also of the resulting 2,6-dideoxy-4-dimethylaminopyranoside. Not surprisingly, there are few reports describing direct glycosylation protocols for unprotected amino sugar donors, especially for 2,6-dideoxy systems.[5,6] Further challenges involve controlling the stereochemical outcome of the glycosylation event to be α-selective in a sugar that lacks a stereodirecting 2-substituent. Nevertheless, by extrapolating the stereochemistry of kedarosamine to *fuco*-like 2-deoxy systems that bear axially orientated 4-substituents, we anticipated that high α-selectivity would be inherently realized through substrate control.[3−5,7]

Our study began with the 2-deoxythioglycoside (**2**) of L-kedarosamine.[8] Encouraged by the successful α-selective glycosylation of **2** (X = SPh) with simple alcohols to give glycosides such as **3** using $AgPF_6$/2,6-di-*tert*-butyl-4-methylpyridine (DTBMP),[5] we investigated the glycosylation of the diyne alcohol **4** (Scheme 1). To our dismay, regardless

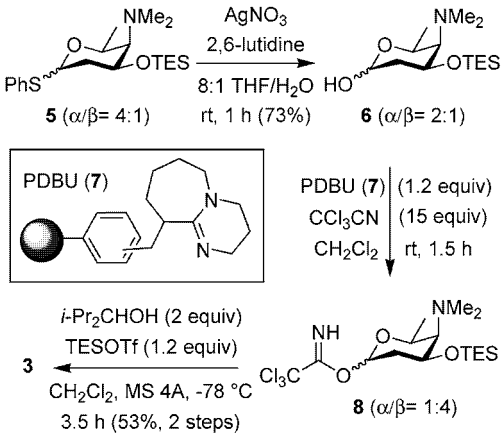
Scheme 1. Low Acceptor Reactivity of Diyne Fragment **4**



of the protective groups employed, the secondary alcohol in **4** (e.g., R^1 = Piv, R^2 = H, TES, MOM; or $R^1 = R^2 = CMe_2$) remained totally unreactive to these conditions or decomposed. It was therefore necessary to determine alternative glycosylation conditions. Yet, despite a multitude of reagent systems that were explored for donors derived from thioglycoside **2**, which worked well on simple alcohols such as *i*-Pr_2CHOH to give **3**, all efforts failed for the propargylic alcohol acceptor **4**.[9] Further efforts were plagued with a combination of the instability of the glycosyl donors derived from **2** (X = SPh) and reagent incompatibility to the free NMe_2 group. Specifically, under standard Schmidt conditions using DBU or K_2CO_3,[10] the isolation of the glycosyl trichloroacetimidate in pure form from **2** (X = OH) was unsuccessful and attempts to generate glycoside products of **4** could not be achieved or investigated in a reliable and systematic manner.

It became increasingly apparent that specific reagents and isolation conditions had to be judiciously chosen for the case at hand, especially since we favored the amino sugar (**5**) to bear a TES-ether as an easily removable protective group for the concluding stages to **1** (Scheme 2). First, we determined the best method to form the free sugar **6** from thioglycoside **5** and found $AgNO_3$/2,6-lutidine in wet THF to be aptly suited to the task, which allowed for a nonaqueous isolation procedure.[11] Next, we pursued the clean formation and isolation of the Schmidt donor **8** from **6**. Assessment of the most desirable preparative conditions led to the notion of using a polymer-supported base, which would necessitate a simple filtration and evaporation step at workup. Indeed,

Scheme 2. Reliable Route to Schmidt Donor **8**[a]



(3) Reviews on 2-deoxyglycoside formation: (a) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385−8417. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(4) For α-selective glycosylations using NH-protected kedarosamine donors, see: Vuljanic, T.; Kihlberg, J.; Somfai, P. *J. Org. Chem.* **1998**, *63*, 279−286.

(5) For a general α-selective method for both sugars of kedarcidin using $AgPF_6$ activation of 2-deoxythioglycosides, see: Lear, M. J.; Yoshimura, F.; Hirama, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 946−949.

(6) Glycosylation examples of sugar donors bearing unprotected amino-groups in total synthesis settings: Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975−3978. Paquette, L. A.; Collado, I.; Purdie, M. *J. Am. Chem. Soc.* **1998**, *120*, 2553−2562. Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Wu, Y.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 5319−5320. Toshima, K.; Maeda, Y.; Ouchi, H.; Asai, A.; Matsumura, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2163−2165. Kolar, C.; Dehmel, K.; Knoedler, U.; Paal, M.; Hermentin, P.; Gerken, M. *J. Carbohydr. Chem.* **1989**, *8*, 295−305.

(7) Instances of high α-selectivity with *fuco*-like 2-deoxypyranosyl donors: (a) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124−6125. (b) Kolar, C.; Kneissl, G. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 809−811. (c) Schene, H.; Waldmann, H. *Synthesis* **1999**, 1411−1422. (d) Florent, J.-C.; Gaudel, G.; Monneret, C.; Hoffmann, D.; Kraemer, H.-P. *J. Med. Chem.* **1993**, *36*, 1364−1368.

(8) **2** and **5** were prepared by thiolysis of protected, methyl L-kedarosaminides: Lear, M. J.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 4897−4900. Hanessian, S.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3−C6.

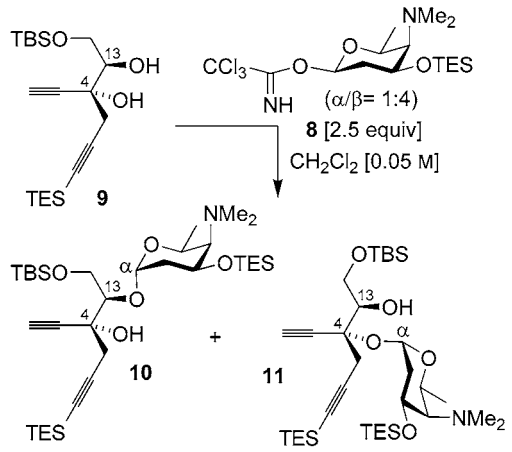
(9) Reagent systems explored include activation of **2** (X = SPh) with NIS, Selectfluor/BF_3·OEt_2 (via glycosyl fluoride), PhSeCl/$Mg(ClO_4)_2$ (unpublished findings), AgOAc/DTBMP and TBSOTf activation of resulting glycosyl acetate (unpublished work), Tf_2O activation of derived sulfoxide, and dehydrative glycosylations with **2** (X = OH): Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743−11746. Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766−1775. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436. Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.

(10) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731−732. Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257−1270.

(11) Method adapted from conditions to deprotect methylthiomethyl ethers: Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269−3270.

use of polystyrene-supported DBU (PDBU, **7**) developed by Tomoi and co-workers furnished the Schmidt donor **8** in a reproducible and clean manner.[12] After testing with *i*-Pr_2-CHOH, which gave **3** in a 53% yield under TESOTf activation (Scheme 2), reaction of the diyne fragment **9** with the imidate **8** generated the glycosylated adducts **10**/**11** for the first time, exclusively as α-anomers (Table 1).

Table 1. α-Selective Glycosylation of Diyne **9** with Imidate **8**[a]



entry	reagent (equiv)	temp (time)	yield (**10**:**11**)	**9**
1[b]	TBSOTf (2.2)	−78 °C (5.0 h)	38% (3.5:1)	31%
2	BF_3·OEt_2 (3.0)	−78 °C (3.0 h)	33% (2.0:1)	52%
3[c]	BF_3·OEt_2 (2.0)	−30 °C (3.0 h)	43% (1.8:1)	56%
4[d]	BF_3·OEt_2 (0.4)	0 °C (2.5 h)	85% (1.8:1)	3%
5[e]	Cp_2HfX_2 (0.2)	0 °C (2.5 h)	74% (1.0:1)	26%
6	$TiCl_4$ (0.2)	0 °C (4.5 h)	72% (1.3:1)	27%
7	$Hf(OTf)_4$ (0.6)	0 °C (3.0 h)	36% (3.9:1)	49%
8	HOTf (2.4)	0 °C (4.5 h)	20% (3.2:1)	79%

[a] See text and Scheme 2 for details. [b] Silylated products of **9** also recovered in 15% yield. [c] CH_3CN was used as solvent instead of CH_2Cl_2. [d] Similar results were obtained for C4-epimer of **9** in CH_2Cl_2, THF, CH_3CN, and $PhCH_3$. [e] Cp_2HfX_2 = Cp_2HfCl_2 (0.2 equiv)/$AgClO_4$ (0.4 equiv).

In the prospect that each acceptor would behave differently for any given glycosylation reaction with **8**, we focused upon optimizing the combined chemical yield of **10**/**11** (**10** being major) from the diyne alcohol **9** (Table 1). Besides minor amounts of **10**/**11**, TMSOTf and TESOTf mostly gave *O*-silylation-derived products of **9** due to the amino sugar acting as a base. As a more bulky and less reactive promoter, TBSOTf minimized, but never suppressed totally, this competing side-reaction and gave a 38% combined yield of **10**/**11** more cleanly (entry 1). Although no glycosides with 1.1−4.0 equiv of activators such as $LiB(C_6F_6)_4$, $LiPF_6$, $ZnBr_2$, $MgBr_2$·OEt_2, $Yb(OTf)_3$, CCl_3CHO, $Sc(OTf)_3$, and PPTS were observed (even at room temperature over 15 h), the use of BF_3·OEt_2 was found most successful and equally effective in either the presence of 4 Å molecular sieves (mildly basic) or Lewis acidic, AW-300 MS (entries 2−4).[3,7c] In these cases, the starting temperature was essential to optimizing the glycosylation yield, and 85% of **10**/**11** was attained at 0 °C by adding catalytic amounts of BF_3·OEt_2 to **9** in the presence of excess imidate **8** (entry 4). In comparison, at −78 °C, moderate yields and similar ratios were obtained regardless of reaction time, even by using excess BF_3·OEt_2 or by warming to −30 or to 0 °C (cf. entry 2).

As anticipated empirically,[3−5,7] we were pleased to discover that all reactions produced the 2-deoxy-α-glycosides of **10**/**11** exclusively. It was nevertheless surprising that acetonitrile had no effect on the stereochemical outcome and solvent effects in general were found to be rather negligible (cf. entry 3), which was confirmed more thoroughly for the C4-epimer of **9** (entry 4). These results are consistent with high substrate control and an unusually high preference for kinetically controlled, pseudoaxial attack onto an oxocarbenium intermediate like **12** (Figure 2).[13]

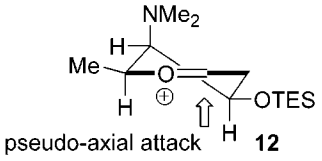


Figure 2. Proposed origin of high α-anomeric stereocontrol for L-kedarosamine.

In attempts to improve the reactivity and prolong the lifetime of sugar donors, various additives were added in combination with BF_3·OEt_2. However, all additives (for example, TMSOTf,[14] DTBMP, Bu_3SnCl, and TBAC) did not improve the combined yield of **10**/**11** but tended to destroy the starting material **9**. Although $Hf(OTf)_4$ and HOTf gave moderate to low conversions favoring the desired C13-*O*-glycoside **10** (entries 7 and 8), catalytic amounts of $TiCl_4$ or Cp_2HfCl_2/$AgClO_4$ were recognized as high-yielding reagent systems and were exceptionally clean (entries 5 and 6). Indeed, it should be noted that unreacted **9** was largely recovered for all the entries given in Table 1, and full recovery of precious starting material is clearly an important factor when determining viable glycosylation conditions in an advanced total synthesis setting of **1**.

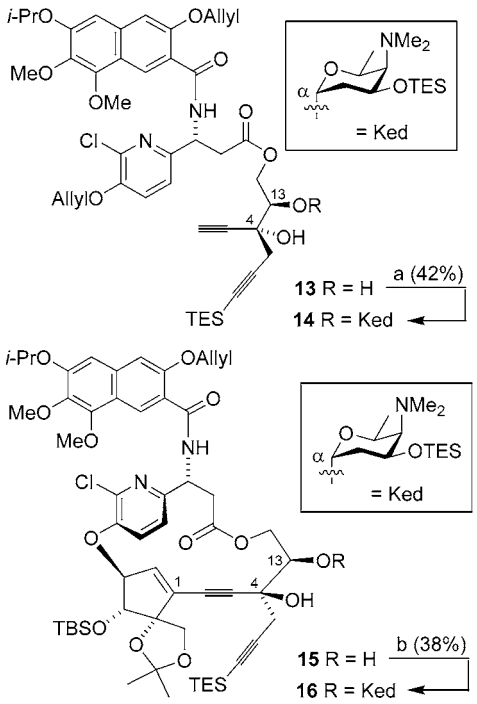
Armed with the experience described herein, we next focused on screening glycosylation conditions for various kedarcidin aglycon fragments (Scheme 3).[15] In short, leaving

(12) (a) Polystyrene-supported DBU (PDBU, **7**) can be prepared simply by adding Merrifield resin to *n*-BuLi/DBU in THF at −78 °C: Tomoi, M.; Kato, Y.; Kakiuchi, H. *Makromol. Chem.* **1984**, *185*, 2117−2124. Iijima, K.; Fukuda, W.; Tomoi, M. *J. Macromol. Sci., Pure Appl. Chem.* **1992**, *A29* (3), 249−261. (b) Cs_2CO_3 can be used to give imidate **8** (α/β = 1:2), which can also be removed by centrifugation or filtration (Urban, F. J.; Moore, B. S.; Breitenbach, R. *Tetrahedron Lett.* **1990**, *31*, 4421−4424), but the larger particle size of PDBU merited the most convenient, contaminant-free isolation procedure.

(13) Intramolecular participation of the 4-NMe_2 lone-pair, which transiently stabilizes the oxocarbenium species and directs pseudoaxial attack, is also conceivable; cf.: Jiao, H.; Hindsgaul, O. *Angew. Chem., Int. Ed.* **1999**, *38*, 346−348. Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.

(14) Nicolaou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rübsam, F.; Rodríguez, R. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1871−1874.

Scheme 3. Successful α-Glycosylation of the Kedarcidin Subunits **15** and **17** with L-Kedarosamine[a]



[a] Reagents and conditions: (a) **8** (15.0 equiv), $BF_3{\cdot}OEt_2$ (3.0 equiv), CH_2Cl_2/MeCN (1:1), 4 Å molecular sieves, rt, 12 h; (b) **8** (25.0 equiv), $BF_3{\cdot}OEt_2$ (13.0 equiv), $ClCH_2CH_2Cl$, 4 Å molecular sieves, 40 °C, 0.5 h.

the C4−OH free and intact was found to be vital to acceptor reactivity, since acceptors akin to **13** and **15**, which feature C4-*O*-protective groups or a C4−C5 olefin, were found to be virtually inert (see Supporting Information). Ultimately, $BF_3{\cdot}OEt_2$ with a large excess of the imidate **8** [15−25 equiv] proved to be most successful for the diols **13** and **15**. In the case of **13**, the use of 1:1 CH_3CN/CH_2Cl_2 at 0 °C moderated the reactivity of $BF_3{\cdot}OEt_2$, so that unreacted starting material could be completely recovered in 18% yield, giving a marginal preference for desired **14** in 42% yield and 40% of the C4-*O*-α-glycoside. For the ansamacrolide **15**, higher reaction temperatures were necessary, and employment of $ClCH_2CH_2Cl$ as the solvent at 40 °C gave a 38% yield of the desired C13-*O*-α-glycoside **16**, together with 27% recovery of **15** and about 10% impure C4-*O*-glycoside.

Notwithstanding the chemical challenges and inherent instabilities of nine-membered, epoxyenediyne aglycon units of **1**, this latter result holds promise toward finalizing current efforts to a most formidable target of contemporary organic synthesis.[2,5,15]

Acknowledgment. This work was supported under the CREST program from JST and a Grant-in-Aid for Scientific Research, Wakate B, by MEXT (to M.J.L.).

Supporting Information Available: Full experimental details and a general glycosylation procedure for the preparation of **6**, **8**, **10**, and **11** (and their C4-epimers) and **14** and **16**, including a representative scheme of glycosylation results with C4-*O*-protected and C4/C5-olefin counterparts of **13** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **13** and **15** were prepared by modification of our previous strategy: Yoshimura, F.; Kawata, S.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 8281−8285. Full details, including advanced studies of **1**, will be disclosed elsewhere.