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# Convenient Route to Derivatives of the 2-Deoxysugar Subunits of the Kedarcidin Chromophore: L-Mycarose and L-Kedarosamine

Martin J. Lear and Masahiro Hirama*

*Department of Chemistry, Graduate School of Science, Tohoku University, and CREST, Japan Science and Technology Cooperation (JST), Sendai 980-8578, Japan*

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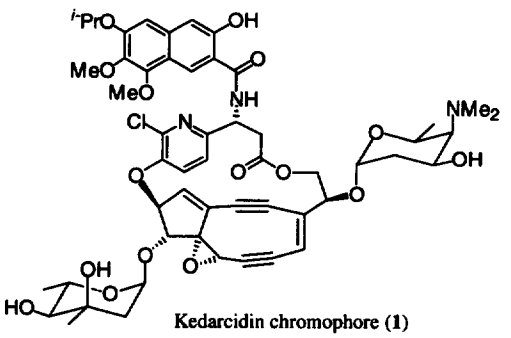
**Abstract**

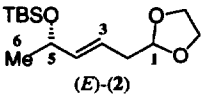
An efficient and practical synthesis of mycarose and kedarosamine derivatives has been devised from ethyl (*S*)-lactate *via* a versatile (*E*)-alkene intermediate. Noteworthy transformations include a highly *trans*-selective one-pot Julia olefination protocol and intramolecular cyclisation of a 2,3-epoxy carbamate.

*Keywords*: amino sugars; cyclisation; glycosides; olefination.

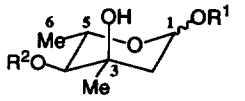
As a relatively new addition [1] to the family of cyclic enediynes, the kedarcidin chromophore (**1**) [2] belongs to an outstanding class of antitumour natural products [3] structurally predisposed toward DNA recognition and cleavage [4]. Encompassed within a research programme toward the total synthesis of **1** [2,5] is the necessity to use a practical route to derivatives of the 2-deoxysugars, L-mycarose (**3**) and L-kedarosamine (**6**). Although pathways to methyl L-mycaroside (**4**) [6] and methyl L-kedarosaminide (**7**) [7] have previously been devised, they collectively suffer from low yields and/or the need to prepare sugar precursors [8]. Starting from inexpensive ethyl (*S*)-lactate, this paper describes a convenient synthesis of both methyl 3-*O*-(triethylsilyl)-3-methyl-2,6-dideoxy-L-*ribo*-hexopyranoside (**5**) and methyl 4-(dimethylamino)-2,4,6-trideoxy-L-*lyxo*-hexopyranoside (**7**) *via* the versatile alkene intermediate (*E*)-(**2**).



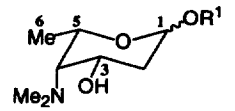
Kedarcidin chromophore (**1**)
- revised structure [2]



(*E*)-(**2**)



(**3**) $R^1$, $R^2$= H
(**4**) $R^1$= Me, $R^2$= H
(**5**) $R^1$= Me, $R^2$= $SiEt_3$



(**6**) $R^1$= H
(**7**) $R^1$= Me

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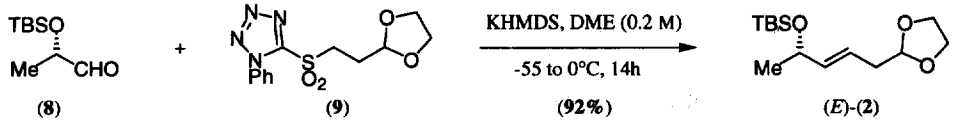
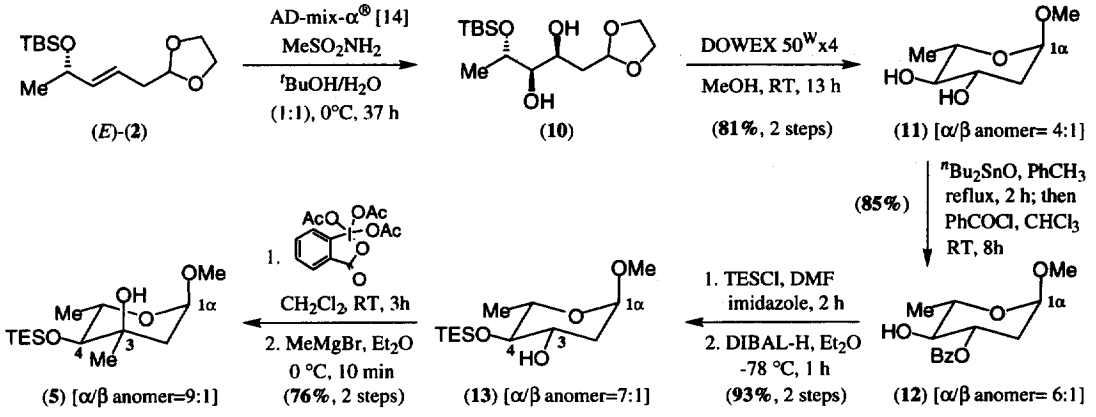
After some preliminary investigations, the alkene (*E*)-(**2**) was efficiently prepared following the *trans*-selective one-pot Julia olefination conditions recently reported by Kocienski *et al.* [9] (Scheme 1). Freshly prepared aldehyde (**8**) [10] (1.15 equivalents) was added to a preformed cooled anionic solution (KHMDS, DME) of the *N*-phenyltetrazolyl sulfone (**9**)[1] (10 g, 32 mmol scale) while maintaining the temperature close to –55 °C. After gradual warming to 0 °C over 14 h, the pure *trans*-alkene (*E*)-(**2**) was isolated in good yield[2] [(*E*):(*Z*)= 20:1 by 500 MHz $^1$H NMR spectroscopy on crude material]. Alternative methods of *trans*-alkene formation including Schlosser modification of the Wittig reaction [11], *cis-trans* isomerism, use of an oxaphospholane [12] or benzothiazole-based sulfone [13], gave inferior results.

**Scheme 1**




With pure (*E*)-**2** in hand, transformation to methyl 2,6-dideoxy-L-*arabino*-hexopyranoside (**11**) was accomplished *via* diastereoselective dihydroxylation with $(DHQ)_2PHAL$ [14] to give **10**[3] and DOWEX 50$^W$×4 assisted methanolysis of the silyl and dioxolane groups with concurrent cyclisation (Scheme 2). Stannylidene-directed regioselective 3-*O*-benzoylation [15] of diol (**11**) gave the monobenzoate (**12**) which was manipulated to the 4-*O*-TES protected sugar (**13**). After Dess-Martin periodinane oxidation [16], attack of methyl magnesium bromide on the derived ketone occurred exclusively from a less hindered trajectory[4] and the desired methyl L-mycaroside (**5**)[5] was isolated as a mixture of anomers [9:1 α/β ratio; $[\alpha]_D^{24}$ -92.9°(c 1.0, $CHCl_3$)].

**Scheme 2**

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[1] The sulfone (**9**) was formed by reaction of 1-phenyl-1*H*-tetrazole-5-thiol with 2-(2-bromoethyl)-1,3-dioxolane [NaH, DMF, RT, 12 h, 92 %] then oxidation with *m*CPBA [$NaHCO_3$, $CH_2Cl_2$, RT, 6 h, 89%].

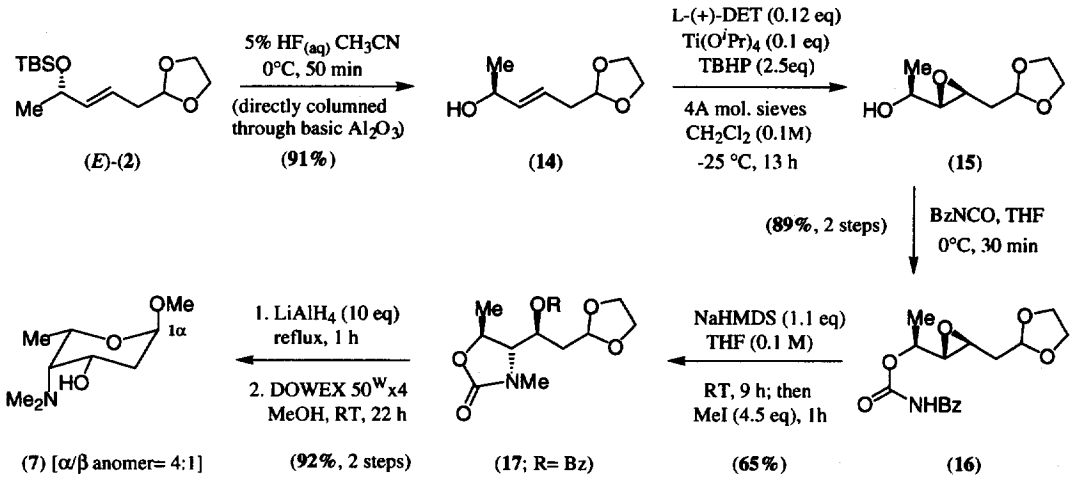
[2] Julia coupling has also been performed on a 40 g scale (0.13 mmol of **13**) affording pure (*E*)-**2** in 80% yield.

[3] The diol (**10**) was formed with good diastereoselectivity (*de* = 87%) as determined by 500 MHz $^1$H NMR spectroscopy on crude material and was subsequently used in pure form after column chromatography.

[4] The stereochemical outcome of the reaction is analogous to that described in ref. [6] and products epimeric at C-3 in **5** were not detected by 500MHz NMR spectroscopy on crude material.

[5] Methyl glycoside (**4**) [10:1 α/β anomer ratio; $[\alpha]_D^{27}$ –76.4° (c 0.6, $CHCl_3$)], derived from **5**, gave data in good agreement to ref. [6].

**Scheme 3**




Commencing from (*E*)-**2** once again, the 2,3-epoxy carbamate (**16**) was prepared from the silyl deprotected allylic alcohol (**14**) following an highly diastereoselective Sharpless epoxidation [17] with L-(+)-diethyltartrate to **15**[6] and carbamate formation with freshly prepared benzoyl isocyanate [18] (Scheme 3). Modifying the conditions of McCombie *et al.* [19], **16** was subjected to a base-induced intramolecular cyclisation with concomitant *N*- to *O*-benzoyl migration. The stabilised anion formed was quenched with excess methyl iodide to afford the *N*-methyloxazolidinone (**17**; R= Bz) in a reliable yield of *ca.* 65 % and, depending on the timing of work-up, a hydrolysis product (**17**; R= H or Me, 20-25 %). In contrast to the work of Roush *et al.* [20], formation of product (**17**; R= H) by the *direct* action of methyl isocyanate on the *trans*-2,3-epoxy alkoxide derived from **15** was complicated by *in situ* Payne rearrangement (yields of 10-30% could only be attained).

Completion of the synthesis of methyl L-kedarosaminide (**7**) entailed total $LiAlH_4$ reduction of the cyclic carbamate and benzoate groups in (**17**; R= Bz) directly followed by methanolysis. In this last step, the amino sugar was released from the acidic resin using 2% $Et_3N$ in $CH_2Cl_2$ after elution of side-products with methanol. Methyl kedarosaminide (**7**) was isolated as a mixture of anomers [4:1 α/β ratio; $[\alpha]_D^{28}$ –79.5°(c 0.7, $CHCl_3$)][7] and, due to its volatility, care should be taken in removing solvents *in vacuo*.

In summary, both 2-deoxypyranosides (**5**) and (**7**) corresponding to the sugar components of the kedarcidin chromophore have been synthesised in multi-gram quantity from the readily prepared alkene (*E*)-(**2**) in an overall yield of *ca.* 48%. Current efforts are being directed toward identifying α-selective glycosylation conditions and this work will be published in due course.

**Acknowledgements**

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[6] The epoxy alcohol (**15**) was formed exclusively as determined by 500 $^1$H MHz NMR spectroscopy on crude material and was subsequently used after column chromatography.

[7] Methyl glycoside (**7**) gave spectroscopic data in good agreement to those described in ref. [7].

## References


[1] Lam, K.S.; Hesler, G. A.; Gustavson, D. R.; Crosswell, A. R.; Veitch, J. M.; Forenza, S.; Tomita, K. *J. Antibiot.* **1991**, *44*, 472; 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; **1994**, *116*, 2233.

[2] Revised structure of 1: Kawata, S.; Ashizawa, S.; Hirama, M. *J. Am. Chem. Soc.* **1997**, *119*, 12012.

[3] Lhermitte, H.; Grierson, D. S. *Contemp. Org. Synth.*, **1996**, *3*, 41; **1996**, *3*, 97; Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.*, **1996**, *39*, 2103.

[4] Battigello, J.-M. A.; Zein, N. *DNA and RNA Cleavers and Chemotherapy of Cancer and Viral Diseases*, Meunier, B., Ed., Kluwer Academic Publishers: Netherlands, **1996**; *pp.* 53-63.

[5] Recent synthetic studies of 1: Kawata, S.; Hirama, M. *Tetrahedron Lett.*, **1998**, *39*, 8707; Myers, A. G.; Goldberg, S. D. *Tetrahedron Lett.* **1998**, *39*, 9633; Myers, A. G.; Horiguchi, Y. *Tetrahedron Lett.* **1997**, *38*, 4363; Caddick, S.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 2355; Kawata, S.; Yoshimura, F.; Irie, J.; Ehara, H.; Hirama, M. *Synlett* **1997**, 250; Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1995**, *117*, 8875; Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1994**, *116*, 10310.

[6] Synthesis of mycarose: Thiem, J.; Elvers, J. *Chem. Ber.* **1978**, *111*, 3514; Howarth, G. B.; Jones, J. K. N. *Can. J. Chem.* **1967**, *45*, 2253.

[7] Characterisation and synthesis of kedarosamine: Leet, J. E.; Golik, J.; Hofstead, S. J.; Matson, J. A. *Tetrahedron Lett.* **1992**, *33*, 6107; Vuljanic, T.; Kihlberg, J.; Hornyak, M.; Pelyvas, I. F.; Sztarieskai, F. J. *Tetrahedron Lett.* **1993**, *34*, 4087; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 6937; *J. Org. Chem.* **1998**, *63*, 279.

[8] Synthesis of sugar starting materials: Grethe, G.; Mitt, T.; Williams, T. H.; Uskokovic, J. *J. Org. Chem.* **1983**, *48*, 5309; Roth, W.; Pigman, W. *Meth. Carbohydr. Chem.* **1963**, *2*, 405.

[9] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

[10] Hirama, M.; Nishizaki, I.; Shigemoto, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1986**, 393.

[11] Schlosser, M. *Tetrahedron Lett.*, **1985**, *26*, 311.

[12] Hands A. R.; Mercer, A. J. H. *J. Chem. Soc. (C)* **1967**, 1099; Marynoff, B. *J. Am. Chem. Soc.* **1985**, *107*, 217.

[13] Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.

[14] AD-mix-α was freshly prepared: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

[15] David, S.; Hannessian, S. *Tetrahedron* **1985**, *41*, 643.

[16] Modified Dess-Martin conditions were used: Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

[17] Katsuki, T.; Martin, V. S. *Org. Reactions* **1996**, *48*, 1.

[18] Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 3742.

[19] McCombie, S. W.; Nagablhushan, T. L. *Tetrahedron Lett.*, **1987**, *28*, 5395.

[20] Roush, W.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752.