Pergamon

Tetrahedron Letters 40 (1999) 4897–4900

TETRAHEDRON LETTERS

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

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Received 30 March 1999; accepted 6 May 1999

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.

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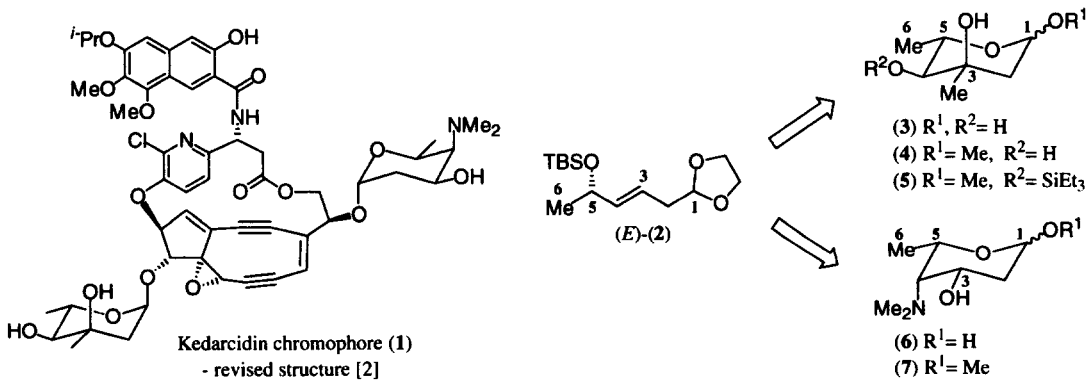
Keywords: amino sugars; cyclisation; glycosides; olefination.

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]

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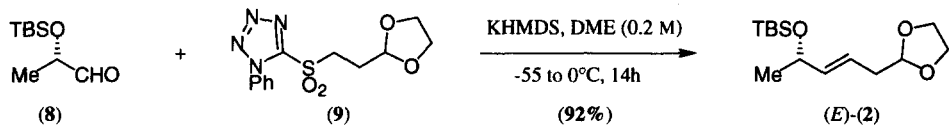
PII: S0040-4039(99)00906-5

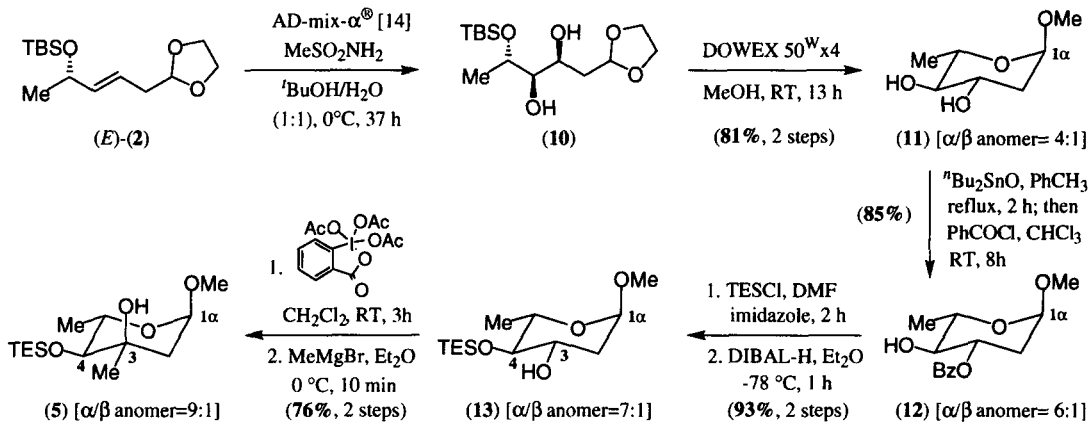
After some preliminary investigations, the alkene (*E*)-(**2**) was efficiently prepared following the *trans*-selective one-pot Julia olefination conditions recently reported by Kocienski *et al.* [9] (Scheme 1). Freshly prepared aldehyde (**8**) [10] (1.15 equivalents) was added to a preformed cooled 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}X4 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%].

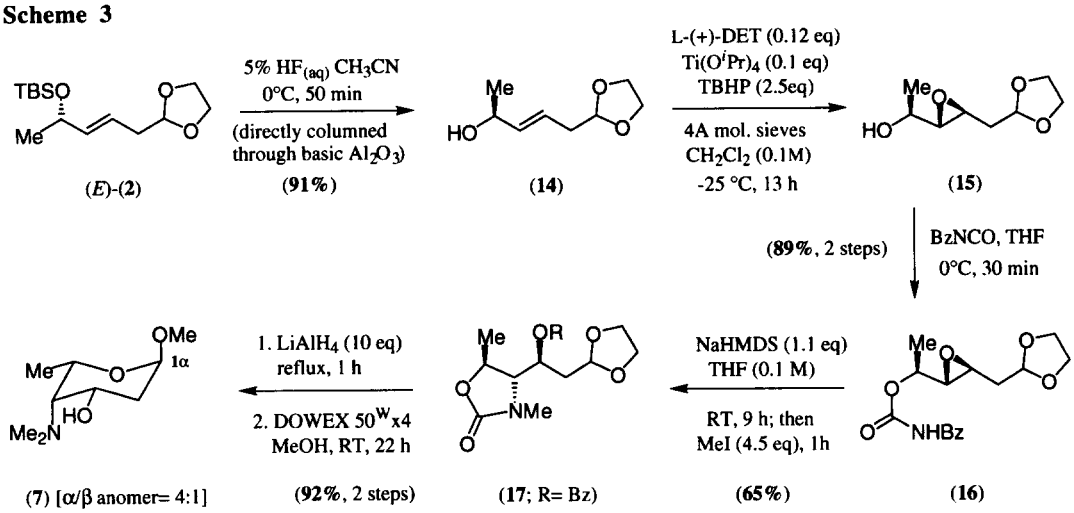
[2] Julia coupling has also been performed on a 40 g scale (0.13 mmol of **13**) affording pure (*E*)-**2** in 80% yield.

[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

A Japanese Society for the Promotion of Science Fellowship (to M. J. L.) is gratefully acknowledged.

[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].

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