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Synthesis of Methyl L-Kijanosides by Regio- and Stereoselective Ring Opening of 2-Oxazolidinone-Fused Aziridines

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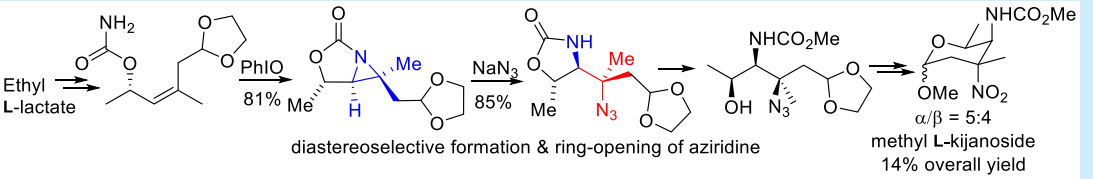


ABSTRACT: Kijanose is one of the most highly functionalized deoxysugars found in nature and a challenging synthetic target. We found that the ring opening of trisubstituted, 2-oxazolidinone-fused aziridines is regio- and stereoselective, and the azide adduct has the same stereochemistry as that of kijanose after converting the azido to a nitro group. Therefore, both α- and β-methyl L-kijanosides were prepared from ethyl L-lactate in 14% total yield.

Originally isolated from the acidic hydrolysis of an antibiotic kijanimicin (**2**),[1−3] D-methyl kijanosides (**1**) are one of the most highly functionalized sugars found in nature (Figure 1).[4] Kijanimicin and its related compounds,

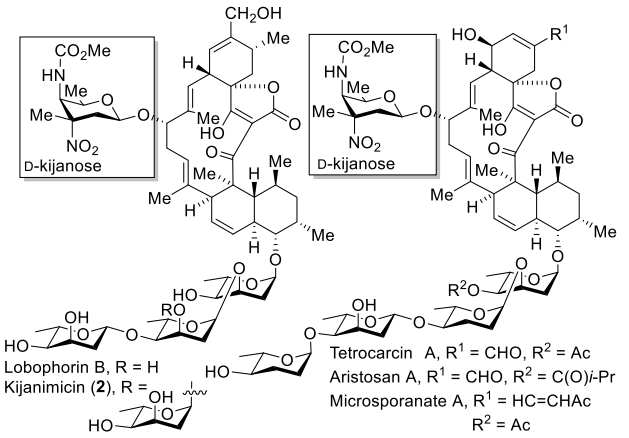
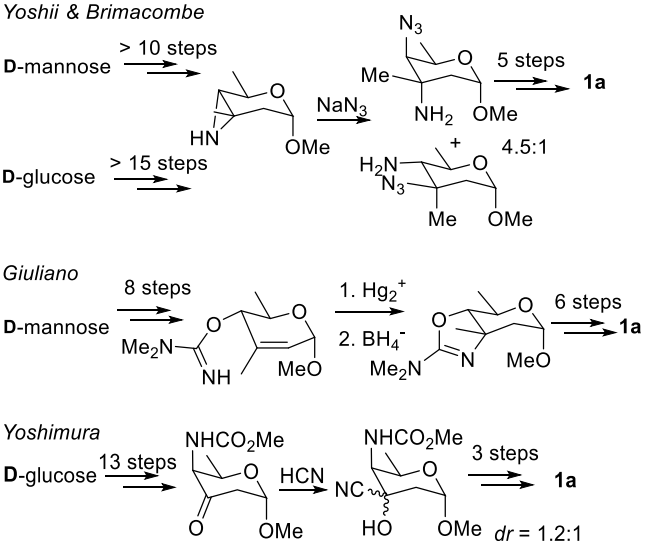


Figure 1. Methyl kijanosides and spirotetronate antibiotics.

including tetrocarcins,[5−9] arisostatins,[10,11] lobophorins,[12−18] and microsporanates,[19] belong to the family of spirotetronate antibiotics,[20−23] in which kijanose is the common nitrosugar linked to the polycyclic aglycone (tetronolide). More than 60 spirotetronate antibiotics have been isolated, and most of these compounds also exhibit antitumor or other biological activities that have therapeutic potential.[24−31] However, the synthesis or modifications of the spirotetronates rely heavily on enzymatic synthesis or semisynthesis, as the preparations and linkages of the aglycone and the deoxysugars remain a challenging task.[32−37] All of the reported chemical syntheses of methyl α-D-kijanoside start from monosaccharides, require more than 10 steps, and often encounter regio- or stereoselectivity issues (Scheme 1).[38−42] On the contrary, the identified gene cluster for the biosynthesis of kijanimicin suggests that 10 enzymes are

Scheme 1. Reported Syntheses of Methyl Kijanosides



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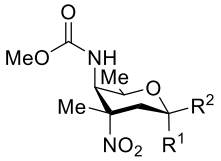
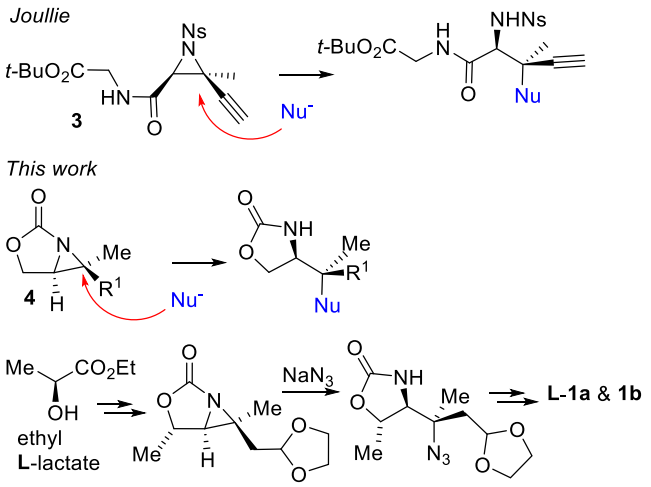
required for the production of kijanose, starting from glucose-1-phosphate.[4,43,44] A new and convenient synthesis to access kijanose and its derivatives should be beneficial for further studies on spirotetronate antibiotics.



Methyl α-D-kijanoside **(1a)**, R^1 = OMe, R^2 = H
Methyl β-D-kijanoside **(1b)**, R^1 = H, R^2 = OMe

To simplify the synthesis of kijanose, we felt that the issue of regioselectivity during the ring opening of aziridines could be resolved by using trisubstituted, 2-oxazolidinone-fused aziridines (**4**, Scheme 2). Joullié's group has developed a highly

Scheme 2. Regio- and Stereoselective Ring Opening of Trisubstituted Aziridines

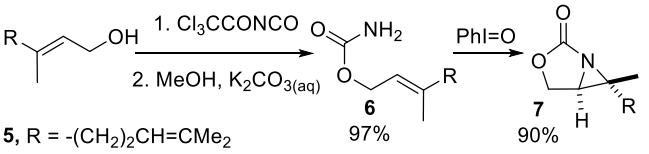


stereo- and regioselective ring opening of ethynyl aziridine **3**, in which nucleophiles prefer to attack the more substituted, propargylic carbon with inversion of configuration.[45−47] The calculation study indicated that the presence of an alkynyl group stabilizes the transition state and lowers the activation energy needed for this pathway.[48] We speculated that the beneficial effect of an alkynyl group in aziridine ring opening could also be implanted by the 2-oxazolidinone-moiety of **4**, as the ring strain is relieved when the ring opening occurs at the tertiary carbon. Indeed, ring-opening reactions of mono- and disubstituted, 2-oxazolidinone-fused aziridines have been studied[49,50] and nicely applied.[51] The corresponding trisubstituted aziridines have been prepared;[51−55] however, their ring-opening reactions and their stereochemistry have not been studied and utilized.

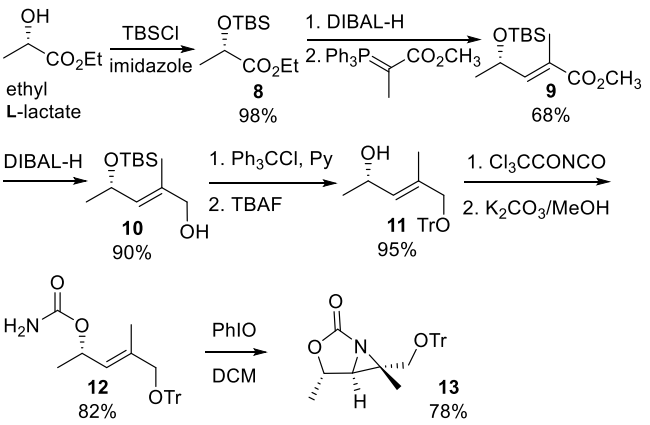
Starting with geraniol, 2-oxazolidinone-fused, trisubstituted aziridine **7** was prepared as a single diastereomer after the formation of carbamate **6** and further oxidation using iodosylbenzene (Scheme 3).[56] This sequence is more concise with a better yield of **7** than the previously reported methods.[50,55]

Optically active aziridines were prepared from ethyl L-lactate, which was first protected by a *tert*-butyldimethylsilyl (TBS) group as compound **8** (Scheme 4).[57,58] Reduction and a Wittig-type reaction with the stabilized ylide gave the (*E*)-α,β-unsaturated ester **9**, which was reduced by DIBAL-H to form

Scheme 3. Syntheses of Trisubstituted, 2-Oxazolidinone-Fused Aziridines



Scheme 4. Syntheses of Optically Active, Trisubstituted Aziridines Derived from an (*E*)-Alkene



allylic alcohol **10**. Protection of the terminal hydroxyl group and the removal of the TBS group provided chiral, secondary alcohol **11**, which yielded aziridine **13** after treatment with iodosylbenzene. The stereochemistry of carbamate **12**, that is, (*S*)-configuration and (*E*)-olefin, is conserved during the aziridination step, as shown in the X-ray crystallography of **13** (Figure 2).

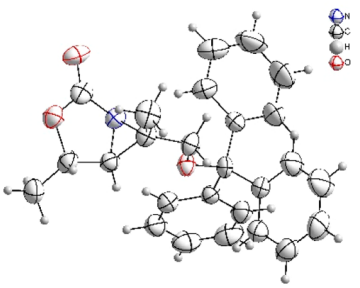


Figure 2. ORTEP of **13**

On the contrary, the Wittig reaction using the nonstabilized ylide derived from phosphonium salt **14** provided (Z)-majored alcohol **15** after the treatment of TBAF (Scheme 5).[59,60] The *Z*-alkene was assigned on the basis of the observed coupling between the olefinic proton and the allylic methyl group on ^{1}H NMR. Alcohol **15** was also converted to aziridine **17**.

The results for the ring-opening reactions of three trisubstituted and 2-oxazolidinone-fused aziridines **7**, **13**, and **17** are summarized in Table 1. N-nucleophiles, such as sodium azide and anilines, provided the corresponding single products with yields up to 98% (entries 1, 2, 6−8, 13, and 14). The X-ray crystallography of **18** is consistent with the expected ring opening of **7**, that is, occurring at the more substituted carbon with the stereocenter inverted (Figure 3a). C-nucleophiles, including cyanide and malononitrile, provided the products in moderate yield (entries 3, 4, 9, 10, and 15). Excellent yields

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Scheme 5. Syntheses of Optically Active, Trisubstituted Aziridines Derived from a (*Z*)-Alkene

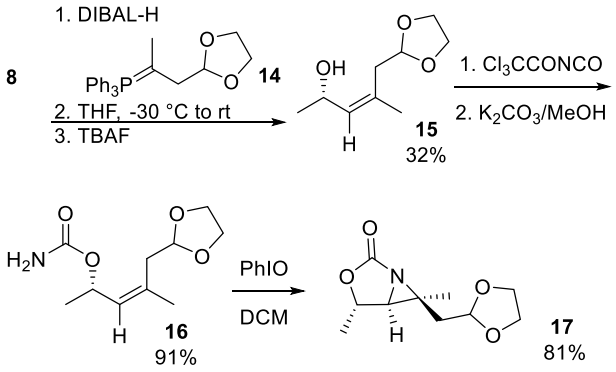
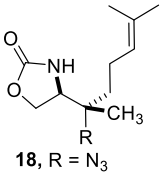
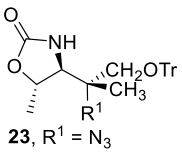
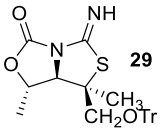
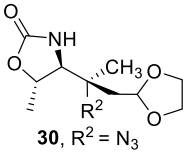


Table 1. Nucleophilic Ring Opening of Aziridines

entry	aziridine	nucleophile	product	yield (%)[a]
1	7	NaN_3	 **18**, R = N_3	88
2	7	aniline	**19**, R = NHPh	90
3	7	NaCN	**20**, R = CN	68
4	7	malononitrile	**21**, R = $CH(CN)_2$	80
5	7	thiophenol	**22**, R = SPh	82 (75)[b]
6	**13**	NaN_3	 **23**, R^1 = N_3	76
7	**13**	aniline	**24**, R^1 = NHPh	97
8	**13**	4-nitroaniline	**25**, R^1 = NH(*p*-NO_2-C_6H_4)	98
9	**13**	NaCN	**26**, R^1 = CN	81
10	**13**	malononitrile	**27**, R^1 = $CH(CN)_2$	62
11	**13**	thiophenol	**28**, R^1 = SPh	95
12	**13**	NaSCN	 **29**	90
13	**17**	NaN_3	 **30**, R^2 = N_3	85
14	**17**	aniline	**31**, R^2 = NHPh	75
15	**17**	NaCN	**32**, R^2 = CN	77
16	**17**	thiophenol	**33**, R^2 = SPh	98

[a]Isolated yields. [b]1 mmol scale.

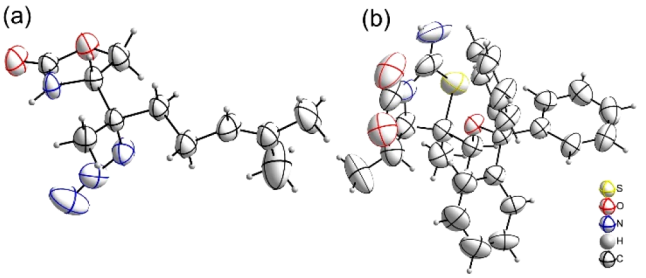
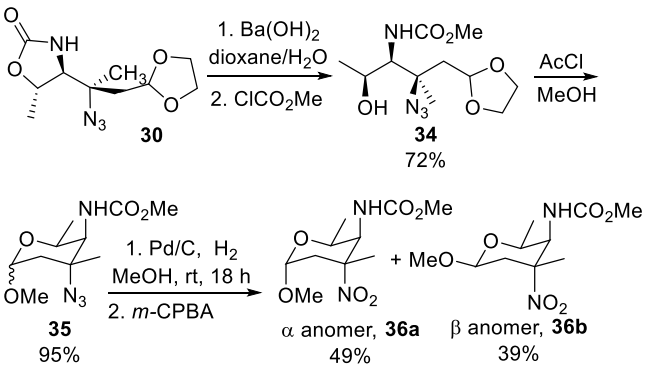


Figure 3. ORTEP of (a) **18** and (b) **29**.

were also obtained with thiophenol (entries 5, 11, and 16). The reaction of **13** and sodium thiocyanate gave the bicyclic compound **29**, which should derive from the addition of the carbamate group to the initial SCN adduct. The X-ray crystallography of **29** indicates that the stereochemistry of the aziridine ring opening of **13** is also in agreement with the expected pathway (Figure 3b).

Compound **30** has the required stereochemistry for L-kijanose. The 2-oxazolidinone was then hydrolyzed and converted to methyl chloroformate **34** (Scheme 6). Meth-

Scheme 6. Synthesis of Methyl L-Kijanosides



analysis of the 1,3-dioxolane yielded both α- and β-pyranose **35** (α/β = 5:4). The azido group was reduced, then oxidized to give the nitro group, and the aimed α- and β-methyl L-kijanoside, **36a** and **36b**, were isolated after column chromatography. Their NMR spectra were consistent with those of **1a** and **1b**.[2] Thus methyl L-kijanosides were synthesized for the first time from ethyl L-lactate in 14% overall yield. Because ethyl D-lactate is also commercially available, this synthesis could also be applied to prepare natural D-kijanose.

In summary, we have shown that the ring-opening reactions of trisubstituted, 2-oxazolidinone-fused aziridines, derived from both (*E*)- and (*Z*)-olefins, are highly regioselective and stereoselective. This method has been applied to prepare the deoxysugar kijanose efficiently and circumvent the shortcomings often encountered in the previous syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00443.

Experimental procedures and spectral data of compounds described herein (PDF)

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Accession Codes

CCDC 1570780, 1954130, and 1977159 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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