ORGANIC LETTERS

2004
Vol. 6, No. 16
2737−2740

Synthesis of the Sialic Acid (–)-KDN and Certain Epimers from (–)-3-Dehydroshikimic Acid or (–)-Quinic Acid

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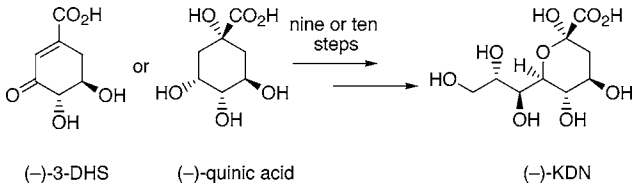
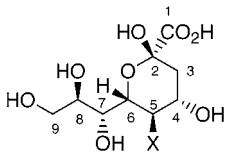
Received May 23, 2004

ABSTRACT



(–)-3-Dehydroshikimic acid (3-DHS, 4), a C_7-building block now available in large quantity from corn syrup, has been converted into the sialic acid (–)-KDN (3) as well as its C-7- and C-8-epimers. (–)-Quinic acid can be used for the same purpose.

Sialic acids, representative examples of which include Neu5Ac (**1**) and (+)-KDN (**2**), are abundant in nature and play pivotal roles in many significant biological events, including cell-to-cell recognition.[1,2] As such, these compounds have been the subject of intense scrutiny, and there has been an accompanying effort to develop effective syntheses of them[3,4] as well as certain analogues.[5]



1 X=NAc
2 X=OH

Various approaches have been described, including those employing non-carbohydrate-based starting materials.[3] Almost invariably a pivotal step used in constructing the full carbon framework of the target sialic acid involves formation of the C-1/C-2, C-2/C-3, or C-3/C-4 bond, with the last of these processes being biomimetic in nature and the most common variation. For example, Wong has shown[4d,f] that condensation of D- or L-mannose with sodium pyruvate in

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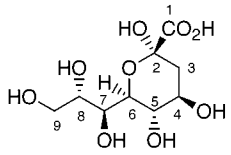
10.1021/ol049048y CCC: $27.50
Published on Web 07/14/2004

the presence of sialic acid aldolase (NeuAc aldolase) results in an aldol condensation with accompanying formation of KDN (**2**) or its enantiomer (**3**), respectively. Effective chemical variations on this approach,[3b,4g,j] which involve construction of the C-3/C-4 bond and the conjoining of a three- and a six-carbon building block (the so-called "3 + 6" approach), often employ a synthetic equivalent for the rather intractable pyruvate anion.

While being enormously useful, these approaches preclude ready construction of sialic acids that vary in the nature and stereochemistry of substituents at the C-7 and C-8 positions. Since these sites are now recognized as having significant potential in the development of sialic acid analogues with therapeutic[6] and/or diagnostic[7] utility, we detail herein new and relevant methodology. In particular, we report the first example of a "7 + 2" approach to sialic acids wherein the C-1 to C-7 fragment is obtained from the abundant chiron (−)-3-dehydroshikimic acid [(−)-3-DHS or **4**][8] and the remaining two carbons are derived from the commercially available ylide (triphenylphosphoranylidene)acetaldehyde [$Ph_3P{=}C(H)CHO$]. This approach results in the installation of a Δ^7-double bond within the sialic acid framework, which can be manipulated in various ways to construct, for example, stereochemically novel analogues of (−)-KDN (**3**) as detailed below. Furthermore, since we have recently demonstrated that (−)-3-DHS can be converted into appropriate derivatives of (+)-3-DHS,[9] the work detailed here allows for access to both the natural and non-natural enantiomeric forms of a wide-range of sialic acids.



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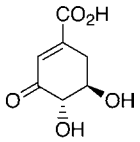
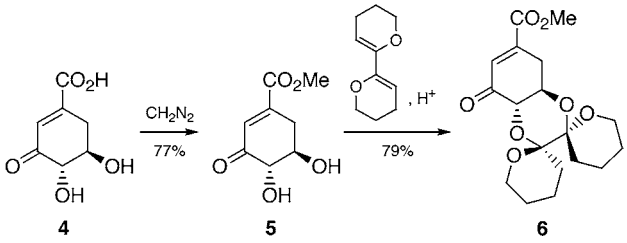


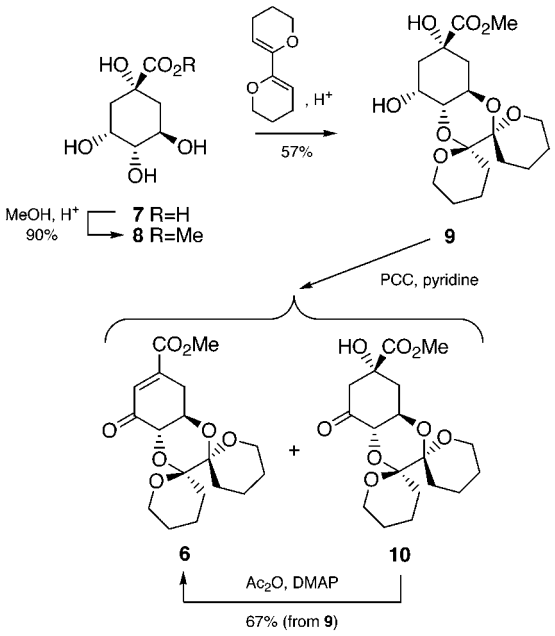
4

The opening stages of our approach are shown in Scheme 1, which outlines the first of two distinct and simple methods for the synthesis of a suitably protected form, **6**, of (−)-3-DHS. Thus, the *trans*-diol moiety associated with the readily derived methyl ester, **5**,[9] of (−)-3-DHS, was protected as the so-called "dispoke" acetal **6**[9] (79%) using the procedures developed by Ley and co-workers.[10] Alternately (Scheme 2), the readily derived methyl ester, **8**,[11] of commercially available (−)-quinic acid (**7**) was similarly protected as the "dispoke" acetal **9** (57%), which upon treatment with pyridinium chlorochromate (PCC) in the presence of 4 Å molecular sieves and pyridine afforded a mixture of the target enone **6** and the β-hydroxyketone precursor **10**. Reaction of this mixture with acetic anhydride in the presence of DMAP and Hünig's base then afforded enone **6** in 67% yield (from **9**).

Scheme 1



Scheme 2



Stereoselective 1,2-reduction of enone **6** was accomplished with K-selectride, and the resulting methyl shikimate derivative **11** (86%) (Scheme 3) was then subjected to the first pivotal step of the synthesis, namely, ozonolysis followed

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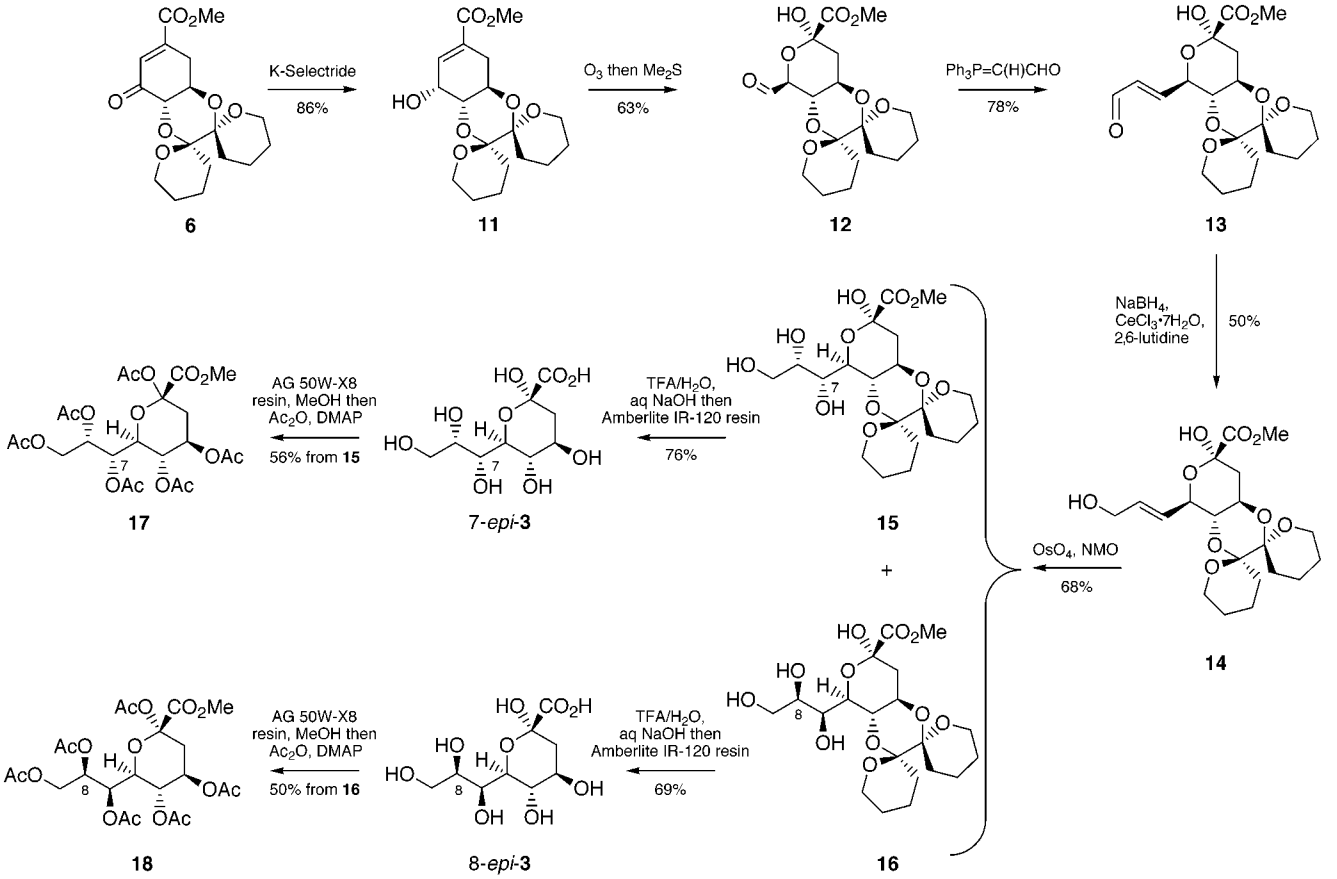
(11) Frank, M.; Miethchen, R. *Carbohydr. Res.* **1998**, *313*, 49.

Scheme 3



by reductive workup with dimethyl sulfide. Presumably, the corresponding keto-aldehyde is the first-formed product of this process but the highly electrophilic ketone carbonyl is trapped by the tethered C-6 hydroxyl to give the observed cyclic hemi-acetal **12** (63%), which was obtained as a single anomer. In the next and second pivotal step of the synthesis, the associated aldehyde was reacted, over 16 h at 18 °C, with (triphenylphosphoranylidene)acetaldehyde in a Wittig reaction to give the α,β-unsaturated aldehyde **13** (78%), incorporating the nine-carbon framework associated with most sialic acids, including those being targeted here.

1,2-Reduction of compound **13** was best effected using the Luche reagent,[12] viz. $NaBH_4/CeCl_3 \cdot 7H_2O$, with 2,6-lutidine present as a buffering agent. Buffering was necessary to ensure that the reaction medium did not become too acidic since, under such conditions, the substrate and/or product decompose rapidly. The resulting allylic alcohol **14** (50%) was subjected to *cis* dihydroxylation using the UpJohn procedure,[13] and a ca. 1:1 mixture of triols **15** and **16** (68% combined yield) was obtained. These products could be separated by careful flash chromatographic techniques, and the more mobile one (**15**) was subjected to global deprotection by sequential treatment with 95:5 v/v trifluoroacetic acid (TFA)/water (to cleave the bis-acetal unit) and then aqueous sodium hydroxide (to saponify the C-1 ester) thus affording, after treatment with an acidic resin, 7-*epi*-(−)-KDN (7-*epi*-**3**) (76%), the ^1H and ^{13}C NMR spectral data for which matched those reported[4d] for the enantiomer. Application of the same deprotection regime to isomer **16** afforded 8-*epi*-(−)-KDN (8-*epi*-**3**) (69%). These free sialic acids were independently subjected to sequential reaction with AG 50W-X8 cation ion-exchange resin in methanol and then acetic anhydride in the presence of DMAP and pyridine. In this manner the lipophilic derivatives **17** (56% from **15**) and **18** (50% from **16**) were obtained, each of which was subjected to full spectroscopic characterization.

(−)-KDN itself could be obtained (Scheme 4) by photoisomerization of enal **13** to its chromatographically separable (*Z*)-isomer **19** (100% at 42% conversion) followed by Luche reduction[12] to give the corresponding allylic alcohol (39%). In contrast to the observations of Kishi[14] and Danishefsky[15] concerning the stereoselectivity of osmium tetroxide-mediated oxidation of allylic alcohols and alkenylpyranosides,

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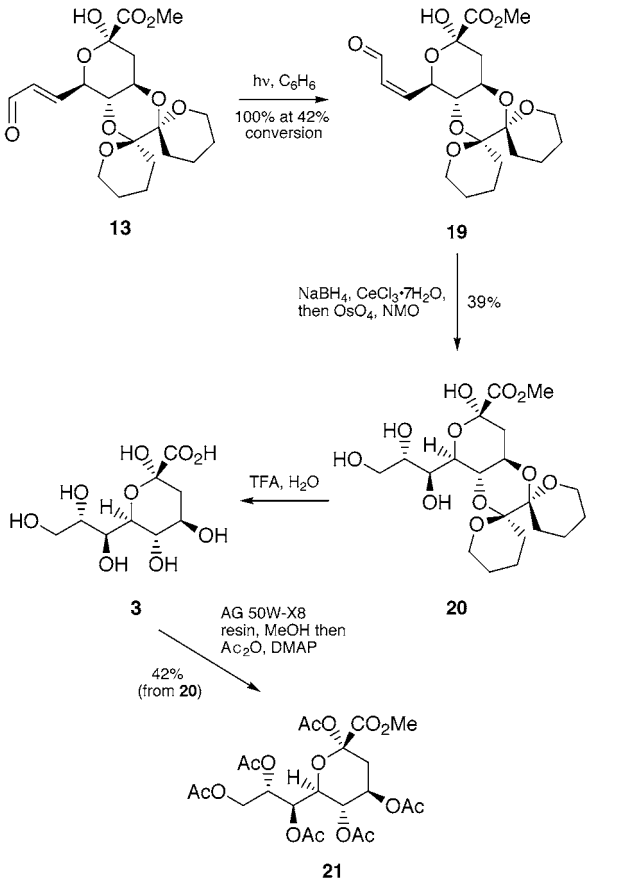
(15) DeNinno, M. P.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 3925.

Scheme 4



cis dihydroxylation of the latter compound using the previously employed UpJohn conditions[13] selectively afforded the illustrated triol **20** (42%), representing a protected form of (−)-KDN, as the major product of reaction. Stepwise deprotection of compound **20** then afforded (−)-KDN (**3**), which was fully characterized as the readily derived peracetylated methyl ester **21** {42% over three steps, mp 100−102 °C, $[\alpha]_D$ + 26.2 (*c* 0.18, $CHCl_3$), lit.[3b] mp 100−104 °C (for *ent*-**21**), lit.[4f] $[\alpha]_D$ + 26.3 (*c* 1.14, $CHCl_3$)}, the ^1H and ^{13}C NMR data for which matched those recorded[3b] for the (+)-enantiomer.

Acknowledgment. This work was generously supported by an Australian Research Council Discovery Grant, which provided a postdoctoral stipend to N.L.H. We also thank the Institute of Advanced Studies (IAS) for financial support, including the provision of an IAS postdoctoral Fellowship to K.A.J. Dr. Gregg Whited (Genencor International, Inc., Palo Alto, CA), is warmly acknowledged for providing us with generous quantities of (−)-3-DHS (**4**).

Supporting Information Available: Preparation and characterization of compounds 7-*epi*-**3**, 8-*epi*-**3**, **5**, **6**, **8**, and **9**−**21** as well as the ^1H and ^{13}C NMR spectra of compounds **6**, **8**, **9**, and **11**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049048Y