higher than 95%.[19] Epoxidation, ethylation, oxidation, and acidic deprotection gave *exo*-brevicomin in 37% overall yield.

Acknowledgment. We thank the Ministry of Education, Japan, for a Grant-in-Aid for Scientific Research (No. 61470093) and Shin-etsu Chemical Industrial Co., Ltd. for a gift of organosilicon compounds.

(19) It has recently been reported that metalation of allyltrimethylsilane with the Schlosser's base and coupling with alkyl halides gave a high γ regioselectivity: Kumaglo, K.; Chan, T. H. *Tetrahedron Lett.* **1984**, *25*, 717. Chan, T. H.; Kumaglo, K. *J. Organomet. Chem.* **1985**, *285*, 109. This was the case also for our allylaminosilane which was used as the starting material in view of the compatibility with the highly reactive metalating agents. Details will be reported in due course.

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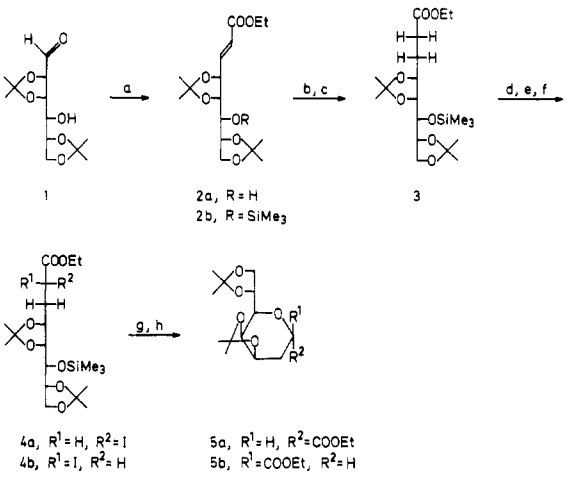
New Synthesis of a CMP-KDO Synthetase Inhibitor and of 2-Deoxy-KDO Derivatives Used in the Synthesis of Such Inhibitors

Summary: The deoxy-KDO derivatives **5a** and **5b**, which are useful in the synthesis of β-C-glycosides of KDO, were prepared in a stereospecific manner starting with a diacetonide of D-mannose (**1**). Deprotection of **5a** gives an acid that is a potent inhibitor of CMP-KDO synthetase.

Sir: During the course of work on design and synthesis of efficient inhibitors of the enzyme CMP-KDO synthetase[1,2] as potential, new antibacterial agents, we have found the diacetonides of ethyl (or methyl) 2,6-anhydro-3-deoxy-D-*glycero*-D-*talo*-(or *galacto*)octonates (**5a** and **5b**, respectively) to be particularly useful.[3,4] The first route chosen for the synthesis of **5** was via hydrogenolysis of the glycosyl chloride of KDO tetraacetate methyl ester which required KDO as a starting material.[4a] Although KDO can be prepared in practically useful yields (25–30%) by the Cornforth procedure,[2] the preparation is tedious and one of the starting materials is the rather expensive oxaloacetic acid.

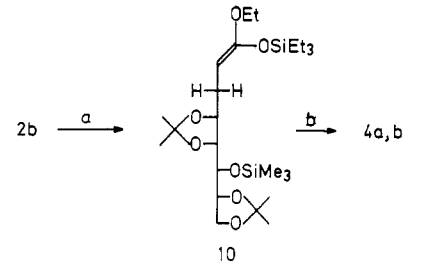
The presently reported method (Scheme I) for synthesis of **5**, which should be applicable to the syntheses of many other C-glycosides,[5] starts with 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (here depicted in the open-chain form **1**) which is available in ≥95% yield from D-mannose and acetone.[6] The reported conversion of this compound into the ester **2a** proceeds in practically quantitative yield.[7] Addition of a trace of benzoic acid,[8] which was not used in the earlier preparations of **2a**,[7] completely prevented it from cyclizing to the tetrahydrofurans **6**

Scheme I[a]



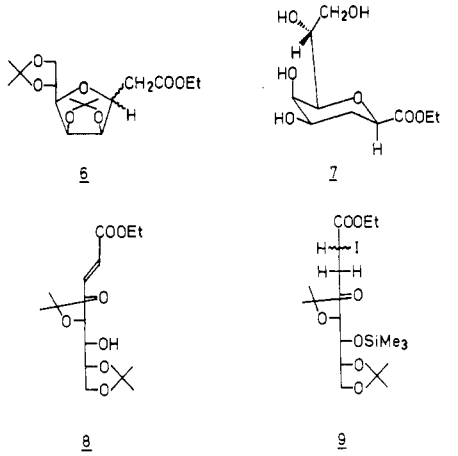
[a] (a) $Ph_3P{=}CHCOOEt$, toluene, 90 °C for ~5 h; (b) H_2 (Pd/C), EtOAc; (c) Me_3SiCl, pyridine–ether; (d) $LiN(i\text{-}C_3H_7)_2$, THF, −70 °C for 0.5 h; (e) $ZnCl_2$ (1 equiv) at −70 °C, then stirring for 1 h; (f) I_2 (1.2 equiv) in THF; (g) Bu_4NF (0.9 equiv), EtOAc–EtOH (9:1), room temperature for 5 min; (h) K_2CO_3 (3 equiv), stirring for 30 h.

Scheme II[a]



[a] (a) Et_3SiH, $(Ph_3P)_3RhCl$, toluene, 50 °C, 2 h; (b) ICl, pyridine, 0 °C.

Chart I



(1) KDO is an abbreviation for 3-deoxy-D-*manno*-2-octulosonic acid which links the *O*-antigen to lipid A in the lipopolysaccharide of gram-negative bacteria.[2]

(2) Review on the chemistry and biochemistry of KDO: Unger, F. M. *Adv. Carbohydr. Chem. Bichem.* **1981**, *38*, 323–388.

(3) The 2,6-anhydrooctonic acid obtained by complete removal of the protective groups from **5a** is the best inhibitor of CMP-KDO synthetase known so far; the corresponding acid from **5b** is inactive. Claesson, A; Luthman, K.; Gustafsson, K.; Bondesson, G. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 1063–1068. Luthman, K. Doctoral Thesis, Dec. 1986. *Acta Universitatis Upsaliensis. Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy. No 23*, Almquist & Wiksell International, Stockholm, 1986.

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0022-3263/87/1952-4414$01.50/0

(Chart I). This cyclization has been reported as a side reaction by Collins et al.[9a] Compound **3** [oil $[\alpha]^{20}_D$ +38.7° (*c* 1.04, $CHCl_3$)] was obtained by hydrogenation of **2a** followed by trimethylsilylation (90% after chromatography on silica gel, ether–pentane, 1:1).[10]

The lithium enolate of the ester **3** could be iodinated by adding a solution of it to a cold (−40 °C) solution of iodine in THF.[11a] This procedure was improved by converting the lithium enolate into the less reactive zinc enolate which permitted the direct introduction of iodine, as a solution in THF, into the reaction mixture.[11b] This modified procedure was convenient to use on a 30-mmol scale,[12] which gave a mixture (roughly 3:2) of the iodides 4a and 4b in 65–85% yields after short-path silica gel chromatography (ether–pentane, 1:1). Separation of the epimeric iodides could be achieved on silica gel (light petroleum–ether, 2:1, gave R_f values of 0.55 and 0.44), thus making possible structural determination by correlation with **5a** and **5b** (vide infra). It was thus shown that the faster moving iodide has structure **4a** and the other one structure **4b**.[13]

In order to simplify the synthesis of the iodides **4**, the unsaturated ester **2b** was first hydrosilylated[14] to give **10** (Scheme II) in 40–50% yield. Although performed under strictly anhydrous conditions, this reaction consistently afforded large amounts (30–50%) of the saturated ester **3** as a byproduct. The ketene acetal **10** was not purified, except for removal of the catalyst, but was treated with iodine monochloride to give the iodides **4** in excellent yield. Interestingly, this iodide synthesis does not appear to have been reported earlier;[15] it might prove useful for the synthesis of other types of α-iodo carbonyl compounds. In the present case, however, the concomitant formation during hydrosilylation of the saturated ester **3** made the overall procedure less attractive than the enolate iodination.

Another attractive way to obtain a silyl ketene acetal like **10** would be to use copper hydride for reduction and then trap the enolate with chlorotrimethylsilane (TMS-Cl) or, according to recent examples in organocuprate chemistry,[16] to use copper hydride in the presence of TMS-Cl. However, attempts using tributylphosphine for solubilization of CuH obtained from CuI and $LiAlH_4$ have not been successful so far.

After some experimentation it was found that compounds **4**, as a mixture or separately, could be converted directly to the C-glycosides **5** by treatment with tetrabutylammonium floride (TBAF) in EtOAc–EtOH (9:1) for 5 min followed by an excess of potassium carbonate (~3 equiv). In this way, the intermediate iodo alcohols, formed by desilylation, cyclized cleanly at room temperature without formation of byproducts and compounds **5** could be isolated in practically quantitative yields.[17] On the other hand, if only ethyl acetate or THF was used as a solvent, the basic nature of TBAF became apparent since varying amounts of compounds **6**[9], i.e., the cyclized form of compound **2a** (in this case the dehydroiodination product), were present among the products. It is apparent that ethanol efficiently masks the basic character of the fluoride anion.

Since iodide ions are released in the cyclization step, it was conceivable that either of the pure epimers **4a** or **4b** might undergo at least partial epimerization prior to stereospecific but slow cyclization. This fear proved unwarranted for all practical purposes since a sample of iodide **4a**, which was judged pure by TLC (UV detection), gave the products **5a** and **5b** in a 96:4 ratio (GLC on OV-17) when subjected to the cyclization conditions.

Assignment of configuration at C-2 to compounds **5a** and **5b** was greatly facilitated by the availability of the corresponding methyl esters that were prepared by an independent route starting from KDO.[4a,c] Furthermore, compound **5a** could be deprotected (10% CF_3COOH in EtOH in EtOH, room temperature, 1 h) to give compound **7**. This was compared spectroscopically with the corresponding methyl ester.[4a,18]

The epimers **5a** and **5b** separate readily on silica gel (R_f values 0.75 and 0.61 in ether–light petroleum 2:1). In order to obtain pure compounds **5a** and **5b**, one can thus effect the separation at this stage in the scheme or separate the iodides **4** prior to cyclization. This latter possibility is in fact of considerable interest;[3] by epimerization of the iodide **4b** (Bu_4NI, acetonitrile, room temperature overnight) to a 1:1 equilibrium mixture of **4a** and **4b**, followed by renewed separation and cyclization, it is possible to convert all iodide **4** to the more interesting epimer **5a**.

The sequence of reactions shown in Scheme I would appear to provide ready access to compounds **5**. Only one drawback has thus far been detected when applying the scheme on a routine basis. In some preparations of the mixture of iodides **4**, another product was detected by TLC and gave a spot between those of the iodides. The isolated product, sometimes constituting up to 10% by weight of the products, exhibited a ^1H NMR spectrum very similar to that of either of the iodides **4**. By comparison with authentic material, prepared analogously to Scheme I from the known D-*gluco*-octenoate 8,[9] the new products were shown to be the two inseparable iodo epimers **9** (~1:1 mixture) with the *gluco* configuration. This indicates that the *gluco*-octenoate **8** is an inseparable byproduct that arises in the formation of the Wittig product **2a**.[19]

Acknowledgment. I thank Miss K. Crona for skillful technical assistance and Miss A. M. Parnerud for per-

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(10) All new compounds were characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy.

(11) (a) Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995. (b) At the time of preparation of the present manuscript I realized that the enolate iodination in fact has been run by addition of iodine to the enolate (one example). Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544.

(12) The iodination on one occasion has been run on a 75-mmol scale which afforded 79% yield of epimers. Molin, H., private communication.

(13) ^{13}C NMR spectra ($CDCl_3$, TMS standard) **4a**: 171.0, 109.6, 107.6, 80.2, 77.0, 76.3, 72.0, 67.7, 61.3, 35.7, 28.0, 26.2, 25.8, 25.1, 19.9 (CHI), 13.5 ppm. **4b**: 170.8, 109.6, 107.9, 79.9, 76.8, 75.6, 71.7, 67.0, 61.4, 38.6, 28.0, 26.0, 25.8, 25.2, 14.7 (CHI) 13.6 ppm. MS (electron impact, 70 eV) gave M^+ 515 for both compounds. Optical rotations: **4a** $[\alpha]^{21}_D$ +61.9° (*c* 1.10, $CHCl_3$); **4b** $[\alpha]^{21}_D$ +16.2° (*c* 0.99, $CHCl_3$).

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(17) ^{13}C NMR ($CDCl_3$, TMS as standard). **5a**: 172.9, 109.4, 109.3, 73.7, 72.8 (C-6), 72.2, 70.0, 68.5, 67.2 (C-8), 60.9 (OCH_2), 27.0, 26.8, (C-3) 26.2, 25.1, 25.0, 14.2, **5b**: 170.5, 109.6, 109.2, 75.9, 74.4 (C-6), 72.5, 71.4, 71.3, 66.9 (C-8), 61.1 (-OCH_2-), 30.7 (C-3), 27.5, 27.0, 26.0, 25.5, 14.1. Optical rotations: **5a** $[\alpha]^{21}_D$ −43.8° (*c* 1.07, $CHCl_3$); **5b** $[\alpha]^{21}_D$ +28.9° (*c* 1.05, $CHCl_3$). Compound **5a** is semisolid at room temperature whereas **5b** is a solid, mp 104–106 °C.

(18) Unger, F. M.; Stix, D.; Schwarzinger, E.; Schulz, G. Communication at the 9th International Symposium on Carbohydrate Chemistry, London 1978. Abstract No. B49.

(19) By use of Knoevenagel–Doebner conditions it is possible to prepare the *gluco*-octenoate **8** as the major product from **1** and methyl hydrogen malonate.[9]

forming some initial experiments. Financial support was obtained from the National Swedish Board for Technical Development.

Registry No. 1, 40036-82-6; **2a**, 63753-76-4; **2b**, 109929-30-8; **3**, 109929-31-9; **4a**, 109929-32-0; **4b**, 109929-33-1; **5a**, 109150-98-3; **5b**, 109150-76-7; **7**, 109929-35-3; **10**, 109929-34-2; Ph_3P=CHCOOEt, 1099-45-2; CMP-KDO synthetase, 37278-28-7.

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A Facile Stereoselective Synthesis of Internal Conjugated (*E,E*)-Dienes Including 2,4-Alkadienylamines, -silanes, and -stannanes

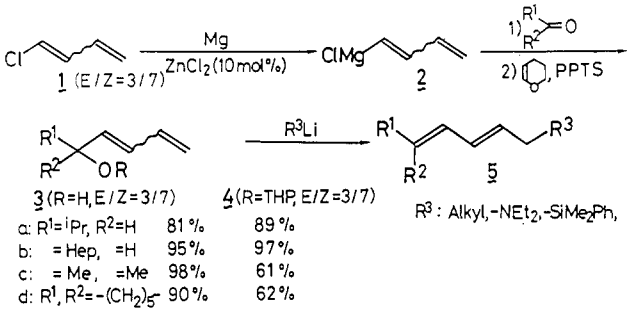
Summary: Tetrahydropyranyl ethers of 2,4-alkadien-1-ols, prepared by the reaction of 1,3-butadienylmagnesium chloride with carbonyl compounds, are regioselectively attacked on the C-5 position by various lithium reagents, such as RLi, R_2NLi, R_3SiLi, and R_3SnLi, under the elimination of lithium tetrahydropyranyl oxide, giving the corresponding (*E,E*)-dienes predominantly.

Sir: Regio- and stereoselective synthesis of conjugated dienes has received considerable attention for these decades because these dienes are important both for building blocks of natural products and for components of Diels–Alder reactions.[1,2] Although various reactions including Wittig reaction[2d] as well as transition-metal-catalyzed cross-coupling reaction between alkenylmetals and alkenyl halides have been commonly used,[3] more versatile method for synthesis of conjugated dienes bearing various types of substituents have been needed. This paper describes a novel highly stereoselective synthesis of internal conjugated (*E,E*)-dienes from easily accessible 1-chloro-1,3-butadiene,[4] a carbonyl compound, and a lithium reagent as shown in Scheme I.

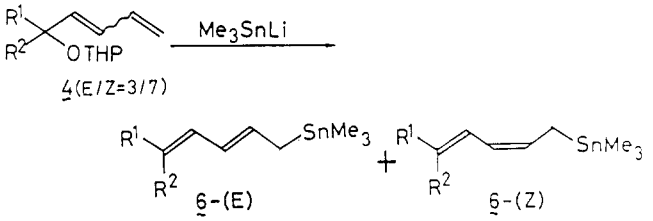
The Grignard reagent **2** was prepared from 1-chloro-1,3-butadiene (**1**) (*E*/*Z* = 3/7) and magnesium in the presence of zinc(II) chloride.[5] Treatment of a ketone or an aldehyde with **2** gave dienyl alcohol **3** in excellent yield which was converted into tetrahydropyranyl (THP) ether **4** by pyridinium *p*-toluensulfonate (PPTS) catalyst.[6] Among varioius organometallic reagents, alkyllithiums attacked regioselectively on the end of diene unit and afforded internal conjugated dienes **5**.[7] Lithium amide and silyllithium reacted also with **4**, affording 2,4-alkadienylamines[8] and 2,4-alkadienylsilanes,[9] respectively. Results are summarized in Table I.

Typical procedure for the formation of Grignard reagent **2** and successive transformation to conjugated dienes **5** is as follows. A mixture of magnesium (24 g, 1.0 mol) and zinc(II) chloride (6.8 g, 0.05 mol) were heated at 130 °C for 2 h under vacuum. Dried tetrahydrofuran (THF, 30 mL) and 1,2-dibromoethane (2.0 mL) were added, and the whole was stirred vigorously under an argon atmosphere.

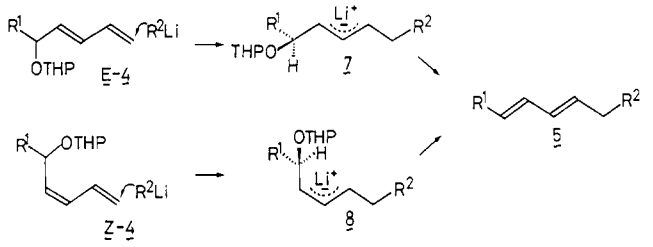
Scheme I



Scheme II



Scheme III



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