The Journal of
Organic
Chemistry

VOLUME 55, NUMBER 9 APRIL 27, 1990

Communications

The Four-Carbon Elongation of *Aldehydo* Sugars Using 2-(Trimethylsiloxy)furan: A Butenolide Route to Higher Monosaccharides

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Received January 2, 1990

Summary: 2-(Trimethylsiloxy)furan is an available nucleophilic four-carbon synthon that reacts with sugar aldehydes and imines in the presence of BF_3 etherate, furnishing γ-C-glycosylated butenolides with very high diastereoselection. The title butenolides represent versatile homochiral candidates to be manipulated into higher carbon sugars.

The design of novel routes to higher sugars and related carbohydrate-like molecular assemblies remains a challenging problem, and central to this goal is controlling the stereochemical outcome of the overall reaction. Among the more viable approaches to these substances, the elongation of a sugar-derived template incorporating suitable stereogenic centers by means of *n*-carbon synthons has received extensive study,[1] often resulting in formation of multifunctional subunit precursors of the ultimate objective. Toward this end, chiral and achiral *n*-carbon nucleophiles have frequently been used in reactions with *aldehydo* sugars or dialdose progenitors.[2] We now report on the use of 2-(trimethylsiloxy)furan (TMSOF, 1)[3] as a four-carbon nucleophile which, on reaction with *aldehydo* derivatives **2a–d**, provide access to four-carbon elongated butenolide subunits **3a–d** with spectacular diastereoselectivity.[4]

3-*O*-Methyl-1,2,-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose (**2a**) smoothly reacted with TMSOF in CH_2Cl_2 at −80 °C in the presence of an equimolecular amount of BF_3 etherate to furnish, after processing with aqueous $NaHCO_3$ at −80 °C followed by treatment with a citric acid/methanol mixture,[5] the nine-carbon butenolide epimers **3a** and **4a**, with great preference (96:4) for the 4,5-*threo*:5,6-*erythro* compound **3a**.[6] Treatment of **3a** with triethylamine in CH_2Cl_2 at room temperature resulted in the formation of a 65:35 mixture of **3a** and **4a**, thus substantiating that **3a** and **4a** are epimers at C-4.[7]

Under the same reaction conditions, the TMSOF-based homologation of aldehydes **2b** and **2c** and imine **2d** proceeded effectively, producing the corresponding C-glycosylated butenolides **3b–d** in high yield and with high margin of diastereoselectivity, while the amount of epimers **4b–d** was less than 5% (Table I).

The configuration of the major butenolides shown in **3a–d** was determined by mechanistic analogies with closely related reactions as well as ^1H NMR spectroscopy and optical rotation considerations. The 5,6-*erythro* stereo-

(1) (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983. (b) Sinay, P.; Beau, J.-M.; Lancelin, J.-M. In *Organic Synthesis an Interdisciplinary Challenge*; Streith, J., Prinzbach, H., Schill, G., Eds.; Blackwell: Oxford, 1985; p 307. (c) Giese, B.; Hoch, M.; Lamberth, C.; Schmidt, R. R. *Tetrahedron Lett.* **1988**, *29*, 1375. (d) Dyer, U. C.; Kishi, Y. *J. Org. Chem.* **1988**, *53*, 3383. (e) Giese, B.; Linker, T.; Muhn, R. *Tetrahedron* **1989**, *45*, 935. (f) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1989**, *54*, 2034. (g) Dondoni, A. *Phosphorous, Sulfur and Silica* **1989**, *43*, 25; (h) Dondoni, A.; *Fantin*, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693.

(2) (a) Jarosz, S.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 4011. (b) Schmidt, R. R.; Preuss, R. *Tetrahedron Lett.* **1989**, *30*, 3409. (c) Preuss, R.; Schmidt, R. R. *Justus Liebigs Ann. Chem.* **1989**, 429. (d) Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1989**, *30*, 2359. (e) Yu, K.-L.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1442.

(3) Reactions of 2-(trimethylsiloxy)furan with simple chiral and achiral carbonyl compounds have been reported: Jefford, C., W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037. Brown, D. W.; Campbell, H. M; Taylor, A. P.; Zhang, X. *Tetrahedron Lett.* **1987**, *28*, 985. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *Tetrahedron Lett.* **1989**, *30*, 5325.

(4) For a review on the synthetic application of butenolide templates, see: Hanessian, S. *Aldrichimica Acta* **1989**, *22*, 3.

(5) Since some 5-O-silylated compounds survived $NaHCO_3$ quenching, the citric acid/methanol treatment ensured mild and quantitative deblocking.

(6) A uniform numbering system starting from the lactone carbon (C-1) was used for structures **3–5**.

(7) Vekemans, J. A. J. M.; Boerecamp, J.; Godefroi, E. F.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 266.

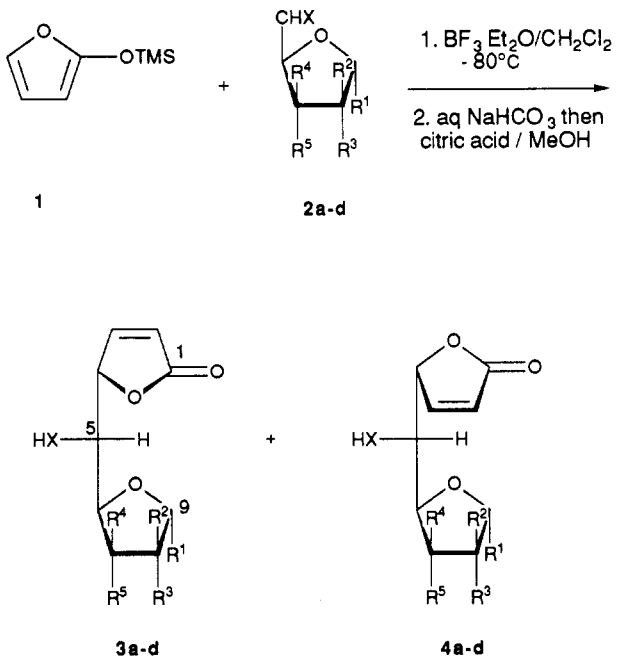
0022-3263/90/1955-2565$02.50/0

Table I. Synthesis of Butenolides 3 and 4 According to Scheme I

entry	reactant	products[a]	yield,[b] %	ratio of diastereoisomers[c]	mp, °C, or appearance	$[\alpha]^{20}_D$, deg (c)[d]
1	2a	3a	91	96:4	126–128	−80.0 (0.5)
		4a			oil	+38.3 (0.6)
2	2b	3b	86	95:5	137–139	−2.0 (2.0)
		4b			glass	+84.0 (0.7)
3	2c	3c	74	>98:<2	oil	−17.8 (0.7)
		4c[e]			oil	+34.3 (0.7)
4	2d	3d	90	>98:<2	glass	−25.5 (2.0)
		4d[e]			oil	−207.0 (1.8)

[a] All compounds have been characterized by ^{1}H NMR and elemental analyses. [b] Combined yield after chromatography. [c] HPLC from hydrolyzed reaction mixture. [d] For solutions in chloroform, 1-cm cell. [e] Obtained via Et_3N-promoted epimerization of the corresponding 4*S* butenolides **3c** or **3d**.

Scheme I



a : R1-R3 = OCMe2O ; R2 =R5= H ; R4 = OMe ; X = O

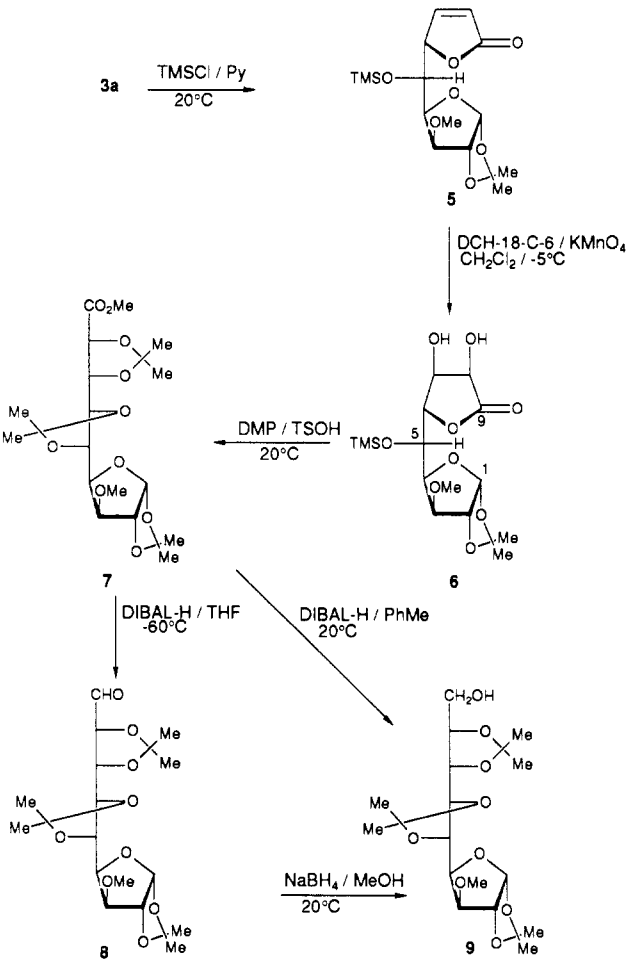
b : R1 = OTBS ; R2-R4 = OCMe2O ; R3 = R5 = H ; X = O

c : R1 = CH_2OBn ; R2 = R5 = OBn ; R3 = R4 = H ; X = O

d : R1-R3 = OCMe2O ; R2 = R5 = H ; R4 = OMe ; X = N-*p*-Anisyl

disposition in both **3** and **4** was expected as such assuming Felkin-selective approach of the nucleophile to unchelated **2**,[8] generating lactones having the 5*R* configuration, while the 4,5-*threo* relationship was mainly suggested by the levorotation of the major carbinols **3a–c** as compared with the dextrorotation of the minor epimers **4a–b**, according to an empirical, but reliable, rule recently suggested by us.[9] Thus, compounds **3** should have the 4*S* configuration and compounds **4** should have the 4*R* configuration. This assumption was further supported by the preferential

Scheme II



threo-selective behavior of Lewis acid promoted condensations of TMSOF with aldehydes.[3] In the instance of **3a**, the 4,5-*threo*:5,6-*erythro* relationship of the substituents was ultimately confirmed via single-crystal X-ray analysis.[10]

Butenolides **3**, as well as the corresponding stereoisomers **4** readily obtainable from **3** via Et_3N-promoted epimerization, represent appealing enantiomerically pure intermediates en route to higher carbohydrates, whose main feature lies in the inherent flexibility and functional diversity. Scheme II illustrates an example of the application of butenolide **3a** for the construction of a nine-carbon aldose.

(8) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* **1987**, *43*, 3533. Kim, K. S.; Sohng, J.-K.; Ha, S. B.; Cheong, C. S.; Jung, D. I.; Hahn, C. S. *Tetrahedron Lett.* **1988**, *29*, 2847. Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869.

(9) "4-Substituted 2,3-unsaturated γ-butyrolactones having the tail substituent *up* in the conventional Haworth's depiction [4*S* compounds **3a–c** in this paper] are levorotatory, while those having the substituent *down* [4*R* compounds **4a–c** in this paper] are dextrorotatory". Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gasparri Fava, G.; Ferrari Belicchi, M., submitted for publication in *Tetrahedron*. Due to the presence of the 4-methoxyphenylamine chromophore, the couple **3d**/**4d** deviates from this rule, however.

(10) Butenolide **3a** crystallized in the monoclinic $P2_1$ space group. The unit cell parameters were determined to be a = 13.231 (2) Å, β = 10.248 (2) Å, c = 5.348 (1) Å, and β = 94.66 (2)°; R = 0.055, R_w = 0.064. The X-ray crystallographic data were submitted to *J. Chem. Soc., Dalton Trans.*, for publication.

Thus, 5-*O*-trimethylsilyl derivative **5** (mp 147–148 °C, $[\alpha]^{20}_D$ = −93.6°, *c* 1, $CHCl_3$), readily obtainable either from **3a** (90%, TMSCl, pyridine), or directly from the condensation reaction between **2a** and **1** where the citric acid/MeOH treatment was avoided (51%), was transformed into β-L-*ribo*-D-*gluco*-nonuronolactone **6** (65%, mp 185–186 °C, $[\alpha]^{20}_D$ = −13.8°, *c* 0.85, EtOH) via anti-selective cis-dihydroxylation of the α,β-double bond using the $KMnO_4$/dicyclohexyl-18-crown-6/CH_2Cl_2 protocol developed by Mukaiyama.[11,12] Subsequent treatment of the diol **6** with dimethoxypropane (solvent) in the presence of a catalytic amount of TsOH at room temperature resulted in lactone ring opening, desilylation, and isopropylidene blocking of the four contiguous 5,6:7,8 OH groups, to generate crystalline nonofuranuronic acid methyl ester **7** in 60% yield (mp 96–97 °C, $[\alpha]^{20}_D$ = −31.5°, *c* 1.9, $CHCl_3$). The reduction of the ester moiety in **7** was achieved by using DIBAL-H either at −60 °C (THF), or at 25 °C (toluene), providing β-L-*ribo*-D-*gluco*-nonodialdofuranose **8** (73%, an oil, $[\alpha]^{20}_D$ = −44.5°, *c* 0.27, $CHCl_3$), or β-L-*ribo*-D-*gluco*-nonofuranose **9** (75%, an oil, $[\alpha]^{20}_D$ = −22.3°, *c* 0.13, $CHCl_3$), respectively. Alternatively, furanose **9** was quantitatively generated from **8** by $NaBH_4$ reduction of the C-9 aldehydo group (MeOH, 20 °C). Compounds **5–9** were obtained as single diastereoisomers (^{1}H NMR, HPLC), suggesting that no epimerization occurred during the overall sequence.

We will continue to evaluate the synthetic scope of the reaction and reiterate the elongation procedure outlined herein en route to higher sugar derivatives.

Acknowledgment. We thank the Consiglio Nazionale delle Ricerche, Progetto Finalizzato Chimica Fine II for the generous support of our programs and Prof. G. Gasparri Fava and Prof. M. Ferrari Belicchi (University of Parma) for performing the X-ray analysis.

Supplementary Material Available: Experimental procedures and ^{1}H NMR data for all new compounds (6 pages). Ordering information is given on any current masthead page.

(11) Mukaiyama, T.; Tabusa, F.; Suzuki, K. *Chem. Lett.* **1983**, 173.
(12) The stereochemistry of the diol **6** was assigned from ^{1}H NMR experiments, and shown to be 6,7-trans:7,8 cis, in accordance with a completely *erythro*-selective cis-hydroxylation process (see ref 11). Conventional IUPAC numbering system was adopted for structures **6–9**.

New Synthesis of Macrocyclic Dialkynyl Imines

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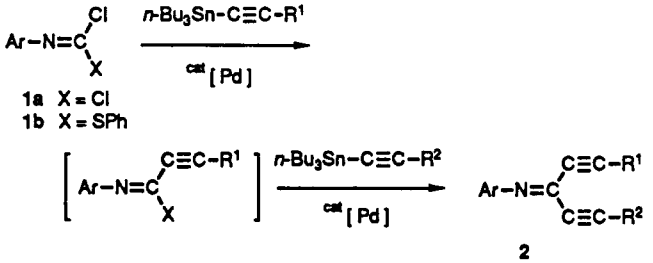
Received February 21, 1990

Summary: New macrocyclic N-substituted dialkynyl imines were successfully synthesized by the reaction of N-substituted isocyanide dichlorides with bifunctional alkynyltin compounds and were synthetically elaborated to novel bicyclic heteroatom-containing compounds.

During the last 2 decades, a variety of crown ethers have been prepared and attracted much attention from the view points of organic synthesis and bioorganic chemistry.[1] Various heteroatom analogues[2] of the crown ethers have also been designed and synthesized in efforts to develop new functional host molecules. Recently, we have reported palladium-catalyzed coupling reactions of N-substituted imidoyl chloride derivatives (**1**) with alkynyltins, giving symmetrical and unsymmetrical N-substituted dialkynyl imines (**2**).[3]



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We now report that new macrocyclic N-substituted dialkynyl imines (**4**)[4] may be successfully synthesized by the reaction of N-substituted isocyanide dichlorides (**1a**) with bifunctional alkynyltin compounds (**3**) and may be further elaborated to novel bicyclic heteroatom-containing compounds.

The reaction of N-substituted isocyanide dichloride (**1**) with bis(alkynyltin) compounds (1.2 molar equiv)[5] was carried out in the presence of bis(triphenylphosphine)-palladium(II) dichloride (0.05 molar equiv) and lithium perchlorate (1 molar equiv) at 50 °C under high dilution conditions (0.01 M), giving macrocyclic N-substituted dialkynyl imines (**4**) in satisfactory yields after column chromatography. Synthesis of macrocyclic dialkynyl imines of 12–20-membered rings are summarized in Table I.

The presence of lithium perchlorate in the cyclization reaction was significant and improved the product yields, although the role of lithium perchlorate remains to be clarified. Indeed, the yields of the products (**4**) in the absence of lithium perchlorate decreased to about half of the yields described in Table I. The cyclization might be favored by complexation of lithium perchlorate with bis(alkynyltin) compounds containing ether linkages.

Typical experimental procedure for the preparation of **4** was exemplified by the synthesis of **4h**: A solution of *N*-phenyl isocyanide dichloride (0.25 mmol), 1,13-bis(tributylstannyl)-4,7,10-trioxa-1,12-tridecadiyne (0.30 mmol), lithium perchlorate (0.25 mmol), and bis(triphenylphosphine)palladium(II) dichloride (0.0125 mmol) in

(1) For reviews: Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039. Lehn, J.-M. *Ibid.* **1988**, *27*, 89.
(2) Krakowiak, K. E.; Bradshaw, J. S.; Krakowiak, D. J. Z. *Chem. Rev.* **1989**, *89*, 929. Cooper, S. R. *Acc. Chem. Res.* **1988**, *21*, 141. Tsvetkov, E. N.; Borin, A. N.; Syundyukova, V. Kh. *Uspekhi Khimii* **1988**, *57*, 1353.
(3) Ito, Y.; Inouye, M.; Murakami, M. *Tetrahedron Lett.* **1988**, *29*, 5379; *Chem. Lett.* **1989**, 1261.
(4) Some macrocyclic dialkynyl ketones have been prepared: Sondheimer, F.; Pilling, G. M. *J. Am. Chem. Soc.* **1971**, *93*, 1977. Duckworth, V. F.; Hitchcock, P. B.; Mason, R. *J. Chem. Soc. D* **1971**, 963 and references cited therein.
(5) Bis(alkynyltin) compounds (**3**) were prepared by the following procedure: to a solution of diyne (3.0 mmol) in THF (6 mL) was added a hexane solution of butyllithium (6.0 mmol) dropwise at 0 °C. After 30 min, tributyltin chloride (6.0 mmol) was added, and then the reaction mixture was stirred at room temperature for 12 h. Extractive workup followed by evaporation of organic solvent afforded bis(alkynyltin) compound in >90% yield, which was used in the reaction with N-substituted isocyanide dichloride without further purification.

0022-3263/90/1955-2567$02.50/0