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C-ARYL-GLYCOSIDES AND 3-DEOXY-2-GLYCULOSONATES VIA INVERSE TYPE HETERO-DIELS-ALDER REACTION [1)]

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Abstract: The functionally substituted α,ß-unsaturated carbonyl compounds 1a,b provide with styrenes and with methyl α-methoxyacrylate in regiospecific and endo-and site-selective inverse type hetero-Diels-Alder reactions the dihydropyrans 2-4 and 9, respectively, which are readily transformed into C-aryl-ß-glucopyranosides and into methyl (methyl 3-deoxy-ß-arabino-2-heptulopyranosid)onates. Thus, from achiral precursors up to five new centers of chirality are generated in a three step procedure.

C-Aryl-glycosides and 3-deoxy-2-glyculosonates are wide-spread in Nature [2-4)]. The biological importance of these compounds prompted development of several synthetic approaches. C-Aryl-glycosides were mainly obtained from glycosyl donors and activated benzene derivatives in Friedel-Crafts type reactions [4)]; however, many difficulties were encountered in these reactions. 3-Deoxy-2-glyculosonate syntheses were mainly developed for KDO [3,6)] and NeuNAc [4,7)] and derivatives thereof; from the different routes some are rather lengthy. We now devised a de novo-synthesis approach to this class of compounds based on the successful synthesis of carbohydrates and related natural products via inverse type hetero-Diels-Alder reactions [8-10)]. In this strategy the readily available functionally substituted α,ß-unsaturated carbonyl compounds 1a,b [9,11)] serve as 1-oxa-1,3-dienes and the required heterodienophiles are styrenes and alkyl α-alkoxy-acrylates, respectively (Scheme).

The reaction of compound 1a with α-methoxystyrene afforded under normal pressure only very minor amounts of the desired dihydropyran 2a (70°C, 65 h →5 %). Therefore the reaction was carried out under higher pressure providing then regio- and endo-specifically compound 3a in reasonable yield (5.2 kbar, 60°C, 30 h →57 %). Similarly from 3,4-dimethoxystyrene the dihydropyran 3b was obtained in 81 % yield. The structural assignment was confirmed by the subsequent transformations of compound 3b. Deacetylation with potassium carbonate in methanol (71 %), O-benzyla-

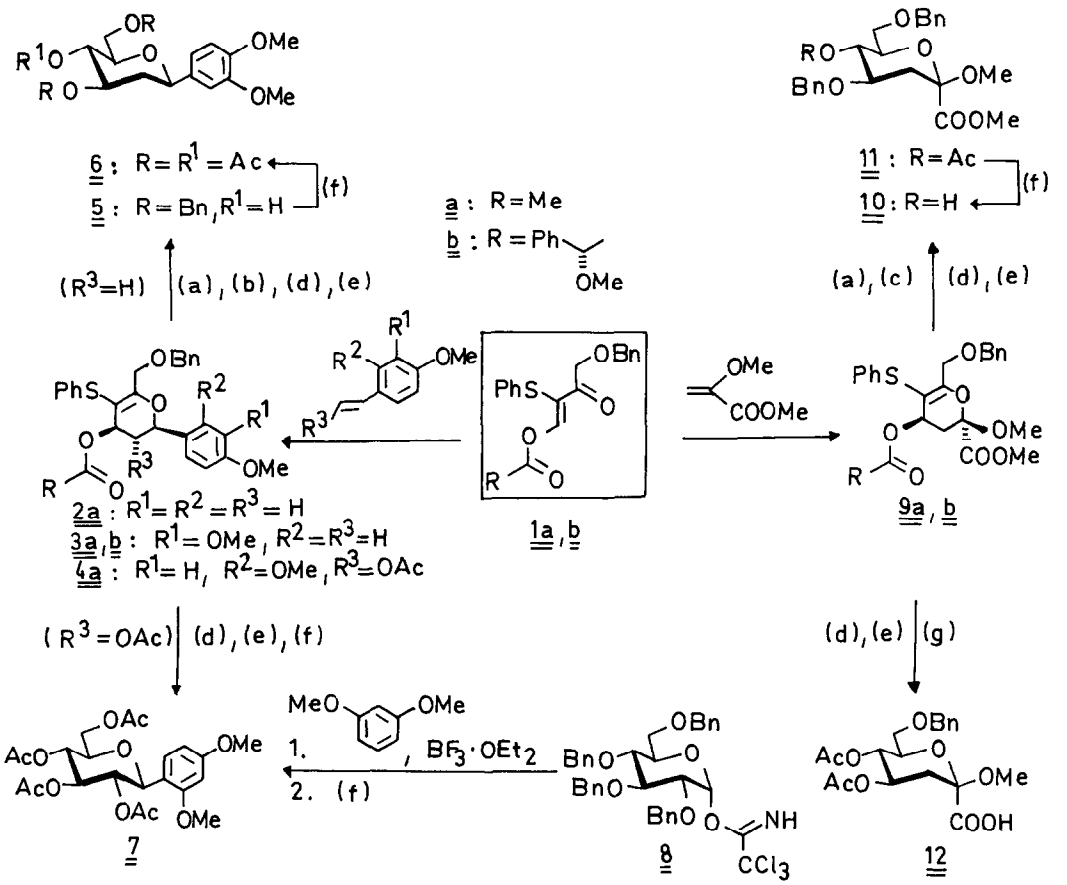
tion with sodium hydride/benzyl bromide (62 %), removal of the phenylthio group with Raney-nickel treatment in THF (70 %), and treatment with the borane dimethylsulfide complex and oxidative work up with hydrogen peroxide (30 % solution in water)/NaOH afforded diastereospecifically the 4-O-unprotected (2-deoxy-ß-D,L-glucopyranosyl)benzene derivative 5. Hydrogenolytic debenzylation and subsequent O-acetylation provided derivative 6 in accordance with the ^{1}H-NMR data.

Asymmetric induction of these reactions with the O-methylmandeloyl group as chiral auxiliary in 1-oxa-1,3-diene 1b was also possible. For instance, with the 3,4-dimethoxystyrene again only the endo-products 3b were obtained; the site-selectivity being 3:1, thus providing convenient entries into the D- or L-series. Removal of the mandeloyl group with potassium carbonate/methanol furnished as expected material identical by ^{1}H-NMR to that obtained from compound 3a after deacetylation.

The successful synthesis of C-aryl-2-deoxy-ß-glucopyranosides 5 and 6 encouraged to explore this strategy also for the synthesis of the more important C-aryl-ß-glucopyranosides. For this aim ß-oxy-substituted styrenes were required. However, due to their enol character the unwanted regioisomer was obtained, when an O-alkyl protective group was used [12]. With an O-acetyl group instead, and with 1a as heterodiene exclusively the desired regioisomer 4a (endo-product) was obtained. Removal of the phenylthio group with Raney-nickel, diastereospecific 4-hydroxy and 5-hydrogen transfer with borane dimethyl sulfide/hydrogen peroxide, hydrogenolytic debenzylation, and O-acetylation afforded the ß-glucopyranosyl benzene derivative 7 in 41 % overall yield. Thus a short and versatile C-aryl-glucopyranoside synthesis could be developed which should prove valuable in the regio- and stereo-controlled synthesis of more complicated target molecules.

The structure of compound 7 was confirmed independently via the trichloroacetimidate approach [13]. The glucosyl donor 8 [14] and resorcin dimethylether afforded under $BF_3 \cdot OEt_2$ catalysis the corresponding ß-D-glucopyranosylbenzene derivative which after hydrogenolytic debenzylation and O-acetylation had ^{1}H-NMR data identical with compound 7.

The finding that styrenes serve as heterodienophiles with the 1-oxa-1,3-dienes 1a,b was reason to also apply the less electron rich methyl α-methoxyacrylate as heterodienophile in this reaction. However, compound 1a did not react under normal pressure. Therefore the reaction was carried out under higher pressure, thus providing regiospecifically the desired dihydropyran 9a as an endo/exo-mixture (5.5 kbar, 60°C, 48 h 9a-endo: 9a-exo = 3:1, 60 % yield). Separation of the endo-isomer by flash chromatography, deacetylation with potassium carbonate/methanol (93 %), and O-benzylation with benzylbromide/Ag_2O (90 %), subsequent removal of the phenylthio group with Raney-nickel in THF (qu) and diastereospe-



Scheme: (a) K_2CO_3, MeOH; (b) Bn-Br, NaH; (c) Bn-Br, Ag_2O; (d) Raney-Ni, THF; (e) $BH_3 \cdot SMe_2$; H_2O_2, NaOH; (f) Pd/C, H_2; Ac_2O, pyridine, (g) A_2O, pyridine

cific 5-hydroxy- and 6-hydrogen-transfer (carbohydrate numbering) with the $BH_3 \cdot SMe_2/H_2O_2$, NaOH system [7] provided the desired partly O-protected 3-deoxy-arabino-2-heptulosonate 10 as ß-glycopyranoside (96 %). For the final structural assignment (see below) this compound was transformed into the 5-O-acetyl derivative 11 (91 %). Even a convenient two-step transformation of cycloadduct 9a-endo via direct phenylthio group removal with Raney-nickel in THF (qu) and subsequent diastereospecific 5-hydroxy- and 6-hydrogen-transfer with the $BH_3 \cdot SMe_2/H_2O_2$, NaOH system in presence of the 4-O-acetyl group was possible providing directly a 5-O-unprotected 3-deoxy-arabino-2-heptulosonate with different protective groups at O-4 and O-7. Treatment with acetic anhydride/pyridine gave compound 12.

Preliminary investigations towards asymmetric induction of the cycloaddition reaction with 1b and methyl α-methoxy acrylate gave an increased endo-preference (5.5:1; 43 %), however, the site-selectivity in the endo-product 9b was only 3:2. After removal of the O-acyl group of this mixture with potassium carbonate/methanol the compound obtained had identical ^{1}H-NMR data with that similarly obtained from dihydropyran 9a-endo.

The structural assignment of these compounds was possible via their ^{1}H-NMR data. The relative configuration at C-4 to C-6 of compounds 11 and 12 was deduced from the coupling constants ($J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 9.7 Hz). The ß-configuration could be assigned by the chemical shift difference between protons H-3 and H-3' of $>$0.6 ppm which is according to structural investigations of related KDO-derivatives [3,15] found from 0.26-0.64 ppm for ß-anomers and from (0-0.27 ppm) for the α-anomers.

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