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DIASTEREOSELECTION IN A DIRECTED CROSSED ALDOL REACTION BETWEEN TWO POLYOXYGENATED KETONES EMPLOYING TIN(II) ENOLATES. A FACILE STEREOSELECTIVE SYNTHESIS OF ETHYL 2-C-METHYL-DL-LYXOFURANOSIDE

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Tin(II) enolates of 1,3-dihydroxy-2-propanone derivatives react with a second ketone, methyl pyruvate, under mild conditions to afford the corresponding *anti*-crossed aldol products in moderate to excellent yields. Facile elaboration to the branched-chain sugar, ethyl 2-C-methyl-DL-lyxofuranoside, was demonstrated.

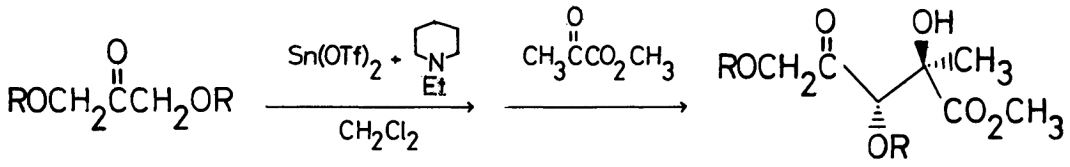
In recent years the total synthesis of carbohydrates has attracted much attention amongst organic chemists. In particular, with the rapidly growing interest in antibiotics research, branched-chain sugars have been demonstrated by their integral part as glycoside component to be worthy of concentrated investigation.[1] In this regard, chemical modification of naturally occurring carbohydrates has been almost solely employed, though laborious multi-step manipulation of the sugar framework is necessary for introduction of desired branched functionality. On the other hand, synthesis of branched-chain sugars from non-carbohydrate precursors facilitates a simple and versatile route into such units compared with the former method. However, in general, this latter approach suffers from overall poor stereoselectivity in the construction of branched center and consequently has received less attention as a general route into branched-chain sugars.

Recently, we have demonstrated that by employing tin(II) enolates, directed crossed aldol reaction between two different ketones with concomitant introduction of tertiary carbon center is facile.[2] Moreover, in the case of cross-coupling with aromatic ketone, predominant *anti*(threo)-selectivity was observed. Based on these preliminary findings, it was postulated that a directed aldol reaction between two suitably oxygenated carbonyl compounds should lead to branched-chain sugar backbone in a *one-step stereoselective* manner.

Saccharinic acid γ-lactones, known precursors to branched-chain sugar containing nucleosides,[3] appeared to be attractive synthetic intermediates since these γ-lactones have previously only been prepared by alkaline treatment of sugars or, in one case, by the treatment of 1-deoxy-L-*threo*-pentulose with hydrogen cyanide and subsequent acid hydrolysis.[4] Herein we wish to disclose our preliminary investigations on a facile *anti*-selective tin(II) enolate promoted crossed aldol reaction between 1,3-dihydroxy-2-propanone derivatives and methyl pyruvate, elaboration of

anti-product to the γ-lactone, 2-C-methyl-DL-lyxonolactone, and subsequent transformation to the corresponding ethyl furanoside.

In the first place, the tin(II) enolate of 1,3-dibenzyloxy-2-propanone (entry a) was treated with methyl pyruvate at 0°C for 3 h. Usual work-up of the reaction mixture afforded crossed aldol 1a in 63% yield and in an *anti* : *syn* ratio of 74 : 26. Since we had previously observed enhanced reactivity of the enolate of α-benzoyloxy acetophenone, we next focused our attention on ester functionalized 1,3-dihydroxy-2-propanone tin(II) enolates. And it was found that when the enolate of 1,3-dibenzoyloxy-2-propanone (entry b) was employed, aldol product 1b was obtained in 93% yield and with an *anti* : *syn* ratio of 85 : 15. Furthermore, this reaction could now be conducted even at -78°C, though essentially no change in aldol ratio was observed. Other examples are listed in the Table.



anti- 1a~g

TABLE: Diastereoselective Crossed Aldol Reaction[a)]

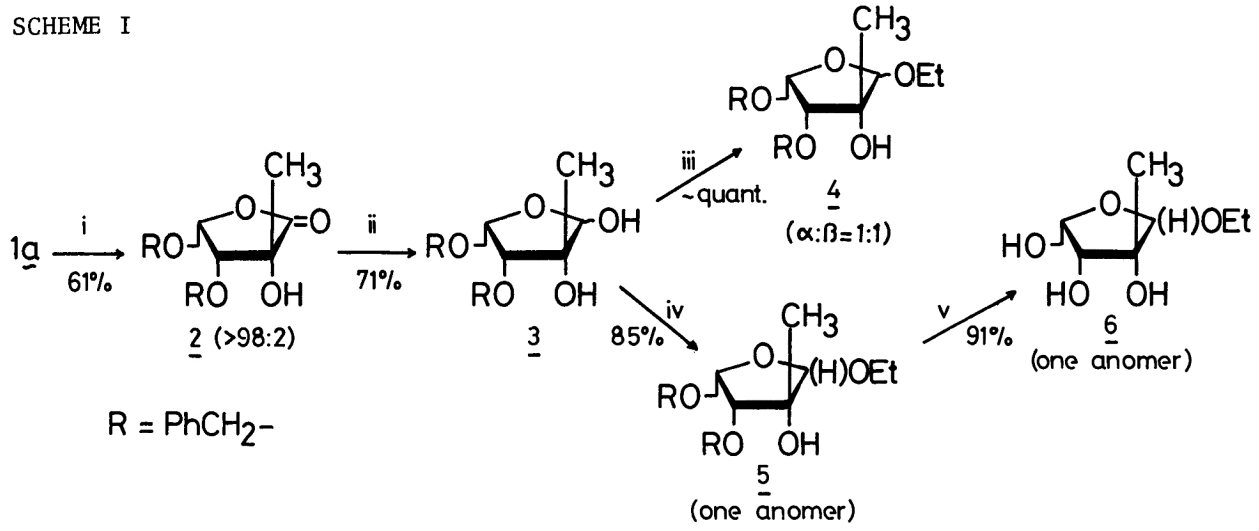
Entry	R	Enolization Conditions (°C, min)	Reaction Time (h)	Yield(%)[b)]	*anti* : *syn*[c)]
a	$PhCH_2$-	0, 15	3	63	74 : 26[d)]
b	PhC(O)-	"	1	93	85 : 15[e)]
c	"	-78, 30	4.5	53	85 : 15
d	*t*-BuC(O)-	0, 15	2	68	64 : 36[e)]
e	"	-78, 30	4.5	55	82 : 18
f	CH_3C(O)-	0, 15	2	45	85 : 15[e)]
g	"	-78, 30	4.5	37	71 : 29

a) Molar ratio of $Sn(OTf)_2$: N-ethylpiperidine : $(ROCH_2)_2CO$: methyl pyruvate = 1.1 : 1.2 : 1.0 : ∿1.3. For a typical experimental procedure see ref. 2.
b) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.
c) Diastereomeric ratio determined by 90 MHz ^1H NMR of crude product.
d) Diastereomeric ratio determined after silica gel separation of isomers.
e) Major isomer determined to be *anti*- by debenzylation of pure *anti*- 1a (5%Pd-C/H_2/10% HCOOH-MeOH, r.t., 2 h) followed by esterification (RCOCl/py, 0°C→r.t., 12 h).

Having established a facile diastereoselective procedure into acyclic branched-chain sugar backbone, we next proceeded to further elaborate this synthetic unit to saccharinic acid γ-lactone. This was achieved by acyclic stereoselective reduction of the *anti*-aldol 1 with concomitant ring closure to γ-lactone on work-up. Thus, after screening a wide variety of suitable reducing agents, it was found that reduction of the *anti*-aldol 1a with lithium tri-*sec*-butylborohydride (2.2 equiv., THF, -78°C, 2 h) gave 3,5-O-dibenzyl-2-C-methyl-DL-lyxonolactone (2) almost exclusively. (SCHEME I).

Having secured the lyxonolactone 2, elaboration to ethyl 2-C-methyl-DL-lyxofuranoside (6) was successfully achieved as illustrated in Scheme I. Thus, half-

SCHEME I



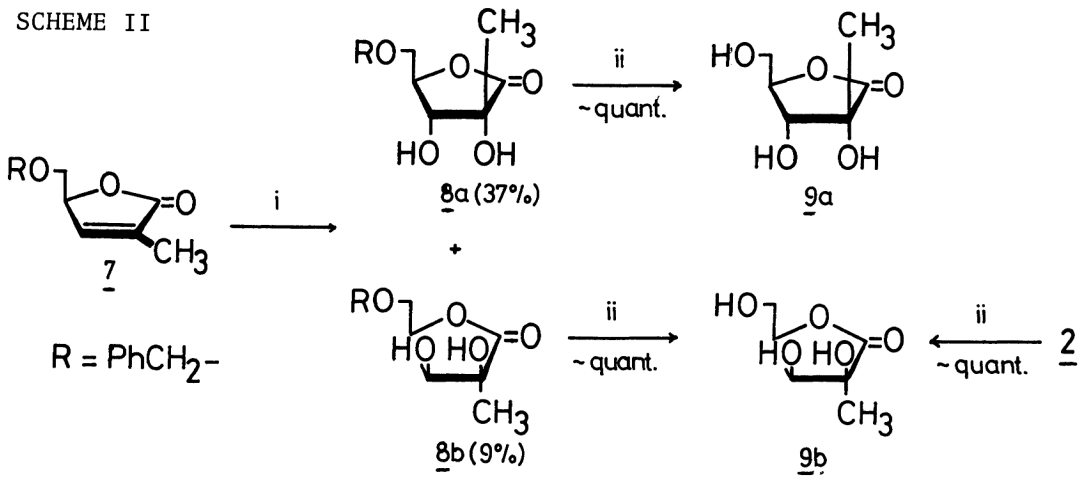
(i) Li(*s*-Bu)$_3$BH (ii) Dibal (iii) EtOH/H$^+$ (iv) KO^{t}Bu, excess EtI (v) H$_2$/5%Pd-C

reduction of 2 with diisobutylaluminum hydride (2.3 equiv., $PhCH_3$, -78°C, 1 h), followed by acid catalyzed glycosidation (1% HCl-EtOH, r.t., 12 h) gave ethyl 3,5-O-dibenzyl-2-C-methyl-DL-lyxofuranoside (4) as an anomeric mixture. Subjection of the lactol 3 to the Schmidt glycosidation conditions[5] (1.2 equiv. KO^{t}Bu, excess EtI, THF, r.t., 24 h) afforded ethyl furanoside 5 in 85% yield as one anomer only.[6] Catalytic hydrogenolysis (5% Pd-C/H$_2$/10% HCOOH-MeOH) of 5 gave the furanoside 6[7] in 91% yield.

Comparison of ^{1}H NMR and ^{13}C NMR spectral data of furanoside 6 with those of the known ethyl 2-C-methyl-D-arabino- and xylofuranosides[8] implied tentative assignment of *lyxo*-stereochemistry. For unambiguous verification of this assignment, and thus establishment of the relative stereochemical course of both the stereoselective aldol and acyclic reduction steps in the aforementioned synthesis, comparison with an authentic sample of 2-C-methyl lyxonolactone was desirable.

This was achieved, as illustrated in Scheme II, by *cis*-hydroxylation of

SCHEME II



(i) $KMnO_4$/10% DCH 18-C-6 (ii) H$_2$/5%Pd-C

γ-butenolide 7. Potassium permanganate-crown ether oxidation of 7 ($KMnO_4$/10% DCH 18-C-6, CH_2Cl_2, 0°C, 12 h) gave the 5-O-benzyl-2-C-methyl ribono- (8a) and lyxonolactone (8b) in 37% and 9% yields respectively.[9] Subsequent catalytic hydrogenolysis afforded the corresponding γ-lactones, 9a and 9b, of which the lyxonolactone 9b[10] displayed identical ^1H NMR and IR spectra with those of debenzylated γ-lactone 2, unambiguously confirming depicted relative stereochemistry as illustrated in Scheme I.

Thus, a facile *anti*-selective directed aldol reaction employing the tin(II) enolates of 1,3-dihydroxy-2-propanone derivatives with methyl pyruvate was achieved. Subsequent stereoselective reduction of this polyoxygenated unit provided a simple two-step route to the saccharinic acid γ-lactone, 2-C-methyl lyxonolactone, which was easily transformed to the corresponding 2-C-methyl furanoside.

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6) Assignment of anomeric center configuration was not made.

7) 6: ^1H NMR ($CDCl_3$) δ=1.24 (t, J=7 Hz, 3 H), 1.32 (s, 3 H), 2.8 - 4.0 (m, 8 H), 4.1 - 4.36 (m, 1 H), 4.57 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ=15.22, 22.73, 62.09, 64.55, 76.77, 77.26, 80.56, 105.95.

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10) 9b: viscous oil; ^1H NMR (CD_3OD) δ=1.4 (s, 3 H), 3.85 (d, J=6 Hz, 2 H), 4.05 (d, J=3 Hz, 1 H), 4.4 - 4.6 (m, 1 H), 4.8 (s, 3 H); IR (neat) 1785 cm^{-1}.

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