Intermolecular O-H Insertion Reactions of L-Tartrate Derived α-Diazo Ketones: Synthesis of Xylulose Derivatives

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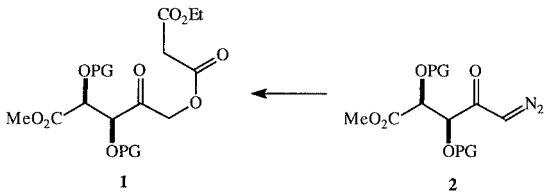
Received 1 July 1999; revised 22 November 1999

Abstract: BF_3•OEt_2 or Ru-catalyzed intermolecular O-H insertion reactions of L-tartrate derived α-diazo ketones have given rise to a new synthesis of xylulose derivatives.

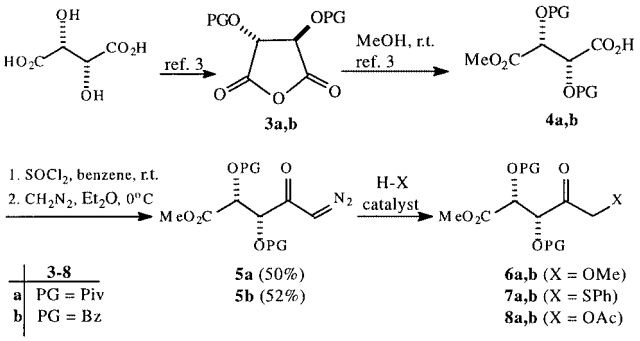
Key words: tartaric acid, α-diazo ketone, insertion reactions, xylulose

In a synthetic study towards syributins and secosyrins,[1] the major coproducts of syringolide elicitors isolated from *Pseudomonas syringae*, we required the xylulose derivative **1** as the key retrosynthetic precursor. Although **1** could be potentially available via O-acylation reaction of a suitably protected xylulonate derivative, the high cost of preparing such derivatives from xylulose forced us to seek for alternate cost-effective pathways. Towards this end and based on reports of O-H insertion reactions of a few carbohydrate derived α-diazo ketones to HOAc,[2] we now describe a facile synthetic strategy for **1** and other xylulose derivatives via intermolecular *O*-H insertion reaction of tartrate derived α-diazo ketones (e.g. **2**, Scheme 1).



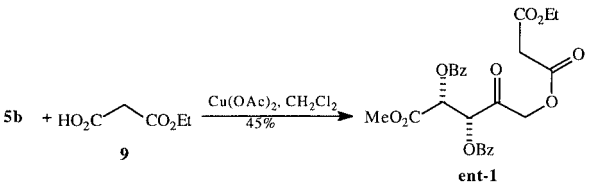
Scheme 1

While the absolute configurations in syributins and secosyrins required the D-tartrate derived α-diazo ketone **2**, in this work we used the cheaper L-tartrate derived α-diazo ketones **5a, b** as models. The latter were prepared in a few steps from L-tartaric acid. Thus, one-pot di-O-acylation and anhydride formation gave the anhydrides **3a** and **3b,** which upon ring opening with methanol produced the half esters **4a,** and **b**,[3] respectively, in near quantitative yields. Acid chloride formation ($SOCl_2$, benzene, room temperature) followed by treatment with excess diazo methane then gave the α-diazo ketones **5a, b** in 50−52% yields (Scheme 2). Intermolecular O-H insertion reactions to **5a, b** were first studied with methanol using $Rh_2(OAc)_4$ as the catalyst[4] which while giving rise to the desired xylulonates **6a, b** (25−30%), however, led to a number of side products which were difficult to separate from the desired adducts. In view of this, we searched for milder catalyst systems and found that $RuCl_2(PPh_3)_3$[5] or BF_3•OEt_2 are much better mediators for these reactions producing **6a, b** in 52−60% yields (Scheme 2, Table). $RuCl_2(PPh_3)_3$ and BF_3•OEt_2 were also found quite effective in catalyzing intermolecular S-H insertion reactions of **5a, b** with PhSH to give the thioxylulonate derivatives **7a, b** in 52−65% yields. On the other hand, O-H insertion reactions of **5a, b** to HOAc was best carried out with $Cu(OAc)_2$ as the catalyst to produce the *O*-acetyl xylulonates **8a, b** in 63−65% yields (Table). Unfortunately, intermolecular N-H insertion reactions of **5a, b** with H_2NCO_2Et or H_2NTos have so far failed under a variety of conditions.



Scheme 2

Having found the optimum conditions for intermolecular O-H insertion to **5**, we turned towards our original goal, i.e., to synthesize the syributin and secosyrin retrosynthetic precursor **1**. This was eventually achieved via $Cu(OAc)_2$-catalyzed insertion reaction of **5b** with the malonic acid half ester **9** in dichloromethane which produced *ent*-**1** (P = Bz) in 45% yield (Scheme 3).



Scheme 3

In conclusion, we have described a short chiral pool based synthesis of xylulose derivatives, en route syributins and secosyrins, via intermolecular O-H insertion reactions to tartrate derived α-diazo ketones. It also transpires from the

above study that milder catalysts like $RuCl_2(PPh_3)_3$ or $BF_3{\bullet}OEt_2$ may be better mediators over $Rh_2(OAc)_4$ for X-H insertion reactions with highly oxygenated α-diazo ketones.

All the mps are uncorrected. IR spectra were taken on a Perkin Elmer R-297 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on JEOL FX-100 (100MHz) and Bruker DPX200 (200MHz) instruments and are reported ppm scale. Optical rotations were measured on a JASCODIP-360 polarimeter. Column chromatography were performed on silica gel (60-120). Petroleum ether refers to the fraction boiling at 60-80 °C.

α−Diazo Ketones 5a, b; General Procedure

A mixture of $SOCl_2$ (8.35 g, 5.0 mL, 70 mmol) and *O*,*O*-diprotected tartaric acid monomethyl ester **4**[3] (10 mmol) was stirred for 1.5−2 h at r.t. All volatiles were then removed under reduced pressure and the acid chloride thus obtained was dissolved in CH_2Cl_2 (10 mL) and added to an ice cold ethereal solution of CH_2N_2, [CAUTION: Highly toxic; prepared from nitrosomethyl urea (5.5 g) and KOH (3.0 g) in H_2O (10 mL) and Et_2O (50 mL)],[6] over a period of 20 min. The mixture was then allowed to reach ambient temperatures and the excess CH_2N_2 was destroyed with a few drops of HOAc. Aq $NaHCO_3$ (10%, 20 mL) was then added, the Et_2O layer separated and the aqueous portion was extracted with Et_2O (2 × 20 mL). The combined organic layer was dried and evaporated under reduced pressure to give the crude α-diazo ketones **5a, b** which were purified by column chromatography over silica gel (10% EtOAc in petroleum ether).

(2*R*,3*R*)-Methyl 5-Diazo-4-oxo-2,3-dipivaloyloxypentanoate (5a)

Yield: 1.80 g (50%); oil

$[\alpha]_D^{20}$ +20.9 (*c* = 8, $CHCl_3$)

IR (neat): ν = 2986−2960 (br), 2880, 2120, 1750, 1730, 1635, 1450, 1360 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.30 (s, 9H), 1.32 (s, 9H), 3.72 (s, 3H), 5.48 (s, 1H), 5.54 (d, 1H, *J* = 3.3 Hz), 5.68 (d, 1H, *J* = 3.3 Hz)

Anal: $C_{16}H_{24}N_2O_7$ (356.42): Calc C, 53.94; H, 6.73; N, 7.89. Found: C, 53.31; H, 6.67; N, 8.12.

(2*R*,3*R*)-Methyl 2,3-Bis(benzoyloxy)-5-diazo-4-oxopentanoate (5b)

Yield: 2.10 g (52%); mp 107−108°C (EtOAc/ petroleum ether)

$[\alpha]_D^{20}$ −27.9 (*c* = 4.7, $CHCl_3$)

IR (Nujol): ν = 2960−2940 (br), 2120, 1720, 1625, 1450, 1370 cm^{-1}.

Table Xylulose Derivatives **6−8** Prepared via X−H Insertion Reactions of α-Diazo Ketones **5** (Scheme 2)

α-Diazo Ketone	X−H	Catalyst[a]	Product	Yield (%)	Mp[b] (°C)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular Formula[c]	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$ / TMS) δ, *J* (Hz)
5a	MeOH	A	**6a**	53	58−59	−18.5 (2.0)	$C_{17}H_{28}O_8$ (360.03)	3050, 2980, 1740, 1420	1.21 (s, 9 H), 1.24 (s, 9 H), 3.35 (s, 3 H), 3.75 (s, 3 H), 4.15 (AB q, 2 H, *J* = 17.4), 5.74 (d, 1 H, *J* = 2.7), 5.81 (d, 1 H, *J* = 2.7)
5a	MeOH	B	**6a**	57	−	−	−	−	−
5b	MeOH	A	**6b**	60	oil	−54.3 (0.9)	$C_{21}H_{20}O_8$ (400.38)	3060, 2980, 1735 (br), 1600, 1585, 1490, 1450	3.45 (s, 3 H), 3.77 (s, 3 H), 4.22 (s, 2 H), 6.15 (d, 1 H, *J* = 2.8), 6.18 (d, 1 H, *J* = 2.8), 7.45−7.60 (m, 6 H), 8.04−8.10 (m, 4 H)
5b	MeOH	B	**6b**	52	−	−	−	−	−
5a	PhSH	A	**7a**	57	oil	−17.2 (2.3)	$C_{22}H_{30}O_7S$ (438.45)	2950, 1750, 1730 (br), 1470, 1420	1.21 (s, 9 H), 1.25 (s, 9 H), 3.72 (s, 3 H), 3.81 (s, 2 H), 5.58 (d, 1 H, *J* = 1.6), 5.89 (d, 1 H, *J* = 1.6), 7.29−7.54 (m, 5 H)
5a	PhSH	B	**7a**	52	−	−	−	−	−
5b	PhSH	A	**7b**	65	oil	−46.4 (2.2)	$C_{26}H_{22}O_7S$ (478.42)	3060, 2980, 1730 (br), 1600, 1580	3.72 (s, 3 H), 3.90 (s, 2 H), 6.11 (d, 1 H, *J* = 2.7), 6.21 (d, 1 H, *J* = 2.7), 7.20−7.80 (m, 11 H), 8.10−8.40 (m, 4H)
5b	PhSH	B	**7b**	56	−	−	−	−	−
5a	HOAc	C	**8a**	63	oil	−19.2 (1.2)	$C_{18}H_{28}O_9$ (388.31)	3050, 2980, 1735 (br), 1450, 1420	1.24 (s, 9 H), 1.26 (s, 9 H), 2.16 (s, 3 H), 3.74 (s, 3 H), 4.83 (s, 2 H), 5.55 (d, 1 H, *J* = 2.5), 5.76 (d, 1H, *J* = 2.5)
5b	HOAc	C	**8b**	65	87−88	−33.4 (0.80)	$C_{22}H20O_9$ (428.29)	3050, 2980, 1730 (br), 1450, 1420	2.03 (s, 3 H), 3.69 (s, 3 H), 4.92 (m, 2 H), 5.96 (d, 1 H, *J* = 1.9), 6.10 (d, 1 H, *J* = 1.9), 7.30−7.48 (m, 6 H), 7.90−8.15 (m, 4 H)

[a] A = $RuCl_2(PPh_3)_3$; B = $BF_3{\cdot}OEt_2$; C = $Cu(OAc)_2$

[b] Recrystallization from EtOAc/petroleum ether.

[c] Satisfactory microanalyses obtained: C ±0.10, H ±0.37.

^{1}H NMR ($CDCl_3$): δ = 3.74 (s, 3H), 5.66 (s, 1H), 5.97 (d, 1H, *J* = 2.6 Hz), 6.04 (d, 1H, *J* = 2.6 Hz), 7.43−7.65 (m, 6H), 8.07−8.13 (m, 4H).

Anal: $C_{20}H_{16}N_2O_7$ (396.39): Calc C, 60.61; H, 4.04; N, 7.1. Found: C, 60.58; H, 4.01; N, 7.0.

$RuCl_2(PPh_3)_3$-Catalyzed O-H and S-H Insertion Reactions to α-Diazo Ketones 5a, b

A solution of the α-diazo ketones **5a, b** (1.0 mmol) in benzene (2 mL) was added dropwise over 2 h to a refluxing solution of MeOH (0.5 mL) or PhSH (0.5 mL) in benzene (5 mL) containing catalytic amounts of $RuCl_2(PPh_3)_3$ (0.02−0.05 g). After the addition was complete, the solution was refluxed for an additional 15 min. after which the solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (20 mL) and washed with H_2O. The organic layer was dried, evaporated under reduced pressure and the crude products purified by column chromatography over silica gel (5−10% EtOAc in petroleum ether) to give **6a, b** and **7a, b** (Table).

BF_3•OEt_2-Catalyzed O-H and S-H Insertion Reactions to α-Diazo Ketones 5a, b

BF_3•OEt_2 (7.0−14.0 mg) was added to a mixture of the diazoketones **5a** or **5b** (1.0 mmol) and MeOH (5 mL) [or PhSH (5 mL)] in CH_2Cl_2 (5 mL) at r.t. The mixture was then warmed at 40 °C for 2 h until evolution of N_2 had ceased. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with aq $NaHCO_3$ (10%, 10 mL) (10% aq NaOH for reaction with PhSH), dried and concentrated under reduced pressure. The crude products were purified by column chromatography over silica gel (5−10% EtOAc in petroleum ether) to give **6a, b** and **7a, b** (Table).

$Cu(OAc)_2$-Catalyzed Insertion Reactions of α-Diazo Ketones 5a, b with HOAc

To a solution of the α-diazo ketones **5a, b** (1.0 mmol) in HOAc (2 mL) was added $Cu(OAc)_2$ (2.0−3.0 mg) and the solution heated to 70−80 °C when rapid evolution of N_2 gas was observed. After N_2 evolution ceased (15 min), the mixture was poured into H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the organic layer washed with aq $NaHCO_3$ (10%, 2 × 10 mL), dried and concentrated to a syrup which was purified by silica gel chromatography (15−25% EtOAc in petroleum ether) to give **8a, b** (Table).

(2*R*,3*R*)-Methyl 2,3-Dibenzoyloxy-5-(1-ethoxycarbonylacetoxy)-4-oxopentanoate (*ent*-1)

$Cu(OAc)_2$ (3.0 mg) was added to a solution of the α-diazo ketone **5b** (0.20 g, 0.5 mmol) and malonic acid monoethyl ester (1.0 g, 7.5 mmol) in CH_2Cl_2 (1 mL). The solution was warmed to 40°C and after N_2 evolution had ceased, the mixture was poured into H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the organic layer washed with aq $NaHCO_3$ (10%, 2 × 10 mL), dried and concentrated to a syrup which was purified by silica gel column chromatography (15−25% EtOAc in petroleum ether) to give 0.11 g (45%) of *ent*-**1** (P = Bz) as an oil.

$[\alpha]_D^{20}$ −28.7 (*c* = 1.2, $CHCl_3$)

IR ($CHCl_3$): ν = 3050, 2920, 1740 (br), 1450 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.27 (t, 3H, *J* = 7.1 Hz), 3.47 (s, 2H), 3.78 (s, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 5.07 (AB q, 2H, *J* = 17.4 Hz), 5.99 (d, 1H, *J* = 2.8 Hz), 6.13 (d, 1H, *J* = 2.8 Hz), 7.46−7.66 (m, 6H), 8.08−8.13 (m, 4H).

^{13}C NMR ($CDCl_3$): δ = 13.9, 40.9, 53.1, 61.7, 67.3, 71.4, 75.6, 127.9, 128.4, 128.6, 130.0, 130.1, 133.6, 133.8, 134.2, 165.1, 165.4, 165.9, 166.5, 196.4.

Anal: $C_{25}H_{24}O_{11}$ (500.33): Calc C, 60.00; H, 4.80. Found: C, 59.95; H, 4.83.

Acknowledgement

DST (SP/S1/G-14/97) and JU (SRF to DD) are thanked for financial support.

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Article Identifier:
1437-210X,E;2000,0,03,0352,0354,ftx,en;H05799SS.pdf