Enantioselective Alkylation of 2,2-Dimethyl-1,3-dioxan-5-one Using the SAMP-/RAMP-Hydrazone Method

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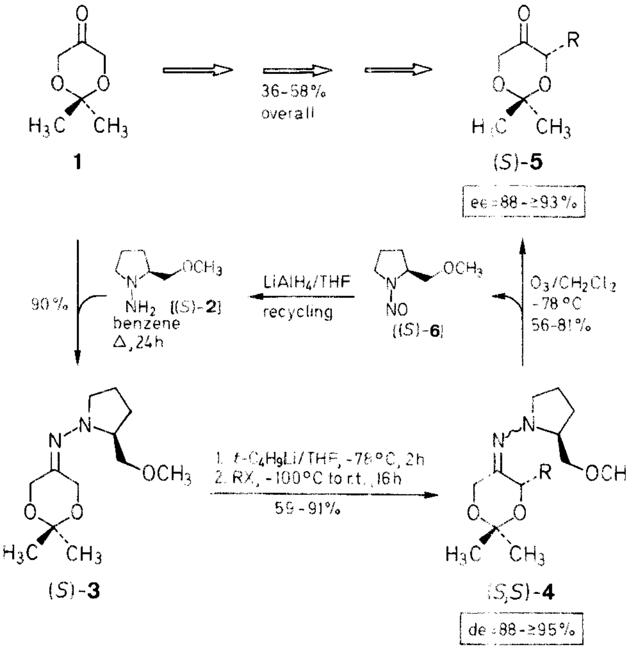
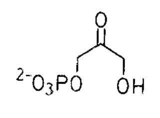
The lithiated SAMP-hydrazone (*S*)-**3** [(*S*)-1-(2,2-dimethyl-1,3-dioxan-5-ylideneamino)-2-methoxymethylpyrrolidine] is used as a chiral 1,3-dihydroxyacetone-enolate equivalent **C** in overall enantioselective α-alkylations leading to 4-alkyl-2,2-dimethyl-1,3-dioxan-5-ones (*S*)-**5a–i** in good overall chemical yields and of high enantiomeric purity (ee = 88 – ≥ 93 %).

Dihydroxyacetonephosphate **A** (DHAP) is used in nature to build 2-ketoses by way of enzyme catalyzed aldol reactions. Several groups have reported the syntheses of natural and unnatural carbohydrates and analogues from reactions of **A** with various aldehydes using aldolases as catalyst.[1-10] Direct reactions of 1,3-dihydroxyacetone and aldehydes lead to mixtures of ketoses and aldoses.[11] So far, only a few examples, under stoichiometric organic reaction conditions, have been reported that resemble the dihydroxyacetone-d^2-synthon **C**, namely enamine acylations[12] and metal enolate aldol reactions.[13-15] Therefore, suitable dihydroxyacetone-enolate equivalents are desirable.

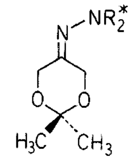
We now report a new type of chiral DHAP-enolate equivalent **B** using our SAMP-/RAMP-hydrazone methodology[16,17] and its application in an efficient 3-step process resulting in overall enantioselective α-alkylations.



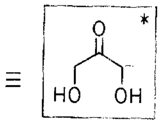
4, 5	R	X	4, 5	R	X
a	CH_3	I	**f**	CH_2Ph	Br
b	C_2H_5	I	**g**	CH_2OCH_2Ph	Cl
c	n-C_6H_{13}	Br	**h**	$(CH_2)_2OCH_2Ph$	I
d	$CH(CH_3)_2$	Br	**i**	$CH_2CO_2CH_3$	Br
e	$CH_2CH{=}CH_2$	Br			



A



B



C

As is illustrated in the scheme, 2,2-dimethyl-1,3-dioxan-5-one (**1**)[18-22] is transformed to the corresponding SAMP-hydrazone (*S*)-**3** by reaction with (*S*)-1-amino-2-methoxymethylpyrrolidine [(*S*)-**2**; SAMP].[17,23] The chiral hydrazone is obtained as a pale yellow oil and can be stored for several months at −25 °C under argon. Optimum metalation of hydrazone (*S*)-**3** is accomplished by addition of *tert*-butyllithium to a tetrahydrofuran solution of (*S*)-**3** at −78 °C. Alkylation of the metalated hydrazone by addition of a slight excess of alkyl halide at −100 °C produces the hydrazones (*S*,*S*)-**4** with high asymmetric inductions (de = 88 – ≥ 95 %) (Table 1). Careful work-up at room temperature leads to hydrazones **4** of mainly *Z*-configuration. However, determination of the diastereomeric excess using ^{13}C-NMR spectroscopy requires the *E* isomer (Table 2). The isomerization can be accomplished by short heating to about 50 °C (TLC control). Chromatographic purification gives (*E*,*S*,*S*)-**4** as colorless or pale yellow oils, or as a colorless solid in the case of (*E*,*S*,*S*)-**4d**.

The alkylated ketones (*S*)-**5** are obtained from (*S*,*S*)-**4** following ozonolysis in CH_2Cl_2 at −78 °C and chromatographic purification (Table 3). The oxidative cleavage of the C=N double bond with ozone is mild, fast, and non-destructive towards the ketal functionality. It also permits the recycling of the chiral auxiliary by reduction of the nitrosamine (*S*)-**6** with lithium aluminum hydride.[16,17,23] Only in the presence of additional double bonds larger amounts of by-products such as ozonides are produced [(*S*)-**5e**, R = $CH_2CH{=}CH_2$, overall yield 23 %].

In the case of (*S*)-**5a** (R = CH_3), the enantiomeric excess could be determined by ^1H-NMR lanthanide-induced-shift (LIS) experiments, which showed that the ozonolysis is free of racemization. In all other cases the ee values of the ketones (*S*)-**5** given in Table 3 are based on the corresponding de values of (*S*,*S*)-**4**. All enantiomers, diastereoisomers, and racemates required for the aforementioned correlation are accessible by changing the chiral auxiliary (RAMP instead of SAMP) or by racemization of **5** with basic alumina and regeneration of resulting 1 : 1 mixture of epimeric hydrazones.

The absolute configurations shown in the scheme and listed in the Tables are in accordance with the postulated mechanism for SAMP/RAMP alkylations.[24] Supportive evidence is provided in

Table 1. Hydrazones **4** Prepared by Diastereoselective α-Alkylation of (*S*)-**3**

Product[a]	Yield[b] (%)	$[\alpha]_D^{23}$ (neat)	de[c] (%)	Molecular Formula[d]	IR (NaCl) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	MS m/z (%)
(*S*,*S*)-**4a**	81	+138°	≥95	$C_{13}H_{24}N_2O_3$ (256.3)	1470, 1385, 1240, 1180, 1130, 1080, 860	1.33 (d, 3H, J = 6.5, CH_3); 1.40, 1.42 (2s, 6H, 2CH_3); 1.57–2.08 (m, 4H, 2βNCH_2); 2.42 (m, 1H, $NC\underline{H}H$); 3.35 (s, 3H, OCH_3); 2.99–3.52 (m, 4H, OCH_2, NCH, $NCH\underline{H}$); 4.15 (dd, 1H, J = 15.5, 2.0, $CNC\underline{H}H$); 4.47 (qd, 1H, J = 6.5, 2.0, CNCH); 4.49 (d, 1H, J = 15.5, $CNCH\underline{H}$)	256 (M^+,10); 98 (97); 70 (100)
(*R*,*R*)-**4a**[f]	82	−151°	≥95				
(*S*,*S*)-**4b**	91	+160°	≥95	$C_{14}H_{26}N_2O_3$ (270.4)	1460, 1380, 1225, 1170, 1120, 1075, 875	0.97 (t, 3H, J = 7, CH_3); 1.39 (s, 6H, 2CH_3); 1.50–2.08 (m, 6H, 2βNCH_2, CH_2); 2.40 (m, 1H, $NC\underline{H}H$); 3.34 (s, 3H, OCH_3); 2.98–3.47 (m, 4H, OCH_2, NCH, $NCH\underline{H}$); 4.12 (dd, 1H, J = 15.5, 2.0, $CNC\underline{H}H$); 4.25 (m, 1H, CNCH); 4.50 (d, 1H, J = 15.5, $CNCH\underline{H}$)	270 (M^+,0.4); 98 (100); 70 (90)
(*S*,*S*)-**4c**	59	+109°	≥95	$C_{18}H_{34}N_2O_3$ (326.5)	1460, 1380, 1230, 1130, 1105, 1065	0.88 (t, 3H, J = 7, CH_3); 1.39 (s, 6H, 2CH_3); 1.23–2.05 (m, 14H, 5CH_2, 2βNCH_2); 2.39 (m, 1H, $NC\underline{H}H$); 3.33 (s, 3H, OCH_3); 2.98–3.45 (m, 4H, OCH_2, NCH, $NC\underline{H}H$); 4.12 (dd, 1H, J = 15.5, 2.0, $CNC\underline{H}H$); 4.32 (m, 1H, CNCH); 4.51 (d, 1H, J = 15.5, $CNCH\underline{H}$)	326 (M^+,5); 98 (100); 70 (90)
(*S*,*S*)-**4d**	75	+127°[g]	≥95	$C_{15}H_{28}N_2O_3$ (284.4)	1470, 1390, 1230, 1140, 1115, 1065, 1030	0.91, 1.00 (2d, 6H, J = 6.8, 2CH_3); 1.37, 1.38 (2s, 6H, 2CH_3); 1.58–2.08 (m, 4H, 2βNCH_2); 2.22 (sept d, 1H, J = 6.8, 3.8, CH); 2.41 (m, 1H, $NC\underline{H}H$); 3.35 (s, 3H, OCH_3); 2.98–3.45 (m, 4H, OCH_2, NCH, $NCH\underline{H}$); 4.06 (dd, 1H, J = 15.3, 1.8, $CNC\underline{H}H$); 4.17 (dd, 1H, J = 3.8, 1.8 CNCH); 4.55 (d, 1H, 15.3, $CNC\underline{H}H$)	284 (M^+,9); 98 (100); 70 (86)
(*S*,*S*)-**4e**	91	+ 94°	≥95	$C_{15}H_{26}N_2O_3$ (282.4)	1645, 1460, 1380, 1220, 1120, 1070	1.40 (s, 6H, 2CH_3); 1.58–2.05 (m, 4H, 2βNCH_2); 2.30 (m, 1H, $C\underline{H}H_{allyl}$); 2.40 (m, 1H, $NC\underline{H}H$); 2.68 (m, 1H, $CH\underline{H}_{allyl}$); 3.33 (s, 3H, OCH_3); 2.98–3.45 (m, 4H, OCH_2, NCH, $NCH\underline{H}$); 4.12 (dd, 1H, J = 15.8, 2.0, $CNC\underline{H}H$); 4.40 (m, 1H, CNCH); 4.44 (d, 1H, J = 15.8, $CNCH\underline{H}$); 5.04 (m, 1H, $C\underline{H}H_{olef}$); 5.12 (m, 1H, $CH\underline{H}_{olef}$)	282 (M^+,2); 98 (90); 70 (100)
(*S*,*S*)-**4f**	60	−144°	≥95	$C_{19}H_{28}N_2O_3$ (332.4)	1500, 1455, 1380, 1230, 1110, 1070	1.24, 1.36 (2s, 6H, 2CH_3); 1.58–2.08 (m, 4H, 2βNCH_2); 2.37 (m, 1H, $NC\underline{H}H$); 3.34 (s, 3H, OCH_3); 2.74–3.49 (m, 6H, OCH_2, NCH, $NCH\underline{H}$, $C\underline{H}HPh$, $CH\underline{H}Ph$); 4.11 (dd, 1H, J = 15.5, 1.9, $CNC\underline{H}H$); 4.48 (d, 1H, J = 15.5, $CNCH\underline{H}$); 4.59 (m, 1H, CNCH); 7.13–7.32 (m, 5H_{arom})	332 (M^+,3); 183 (100); 98 (46); 70 (46)
(*S*,*R*)-**4g**	68	+ 78°	≥95	$C_{20}H_{30}N_2O_3$ (362.5)	1460, 1380, 1230, 1110 (br)	1.42 (s, 6H, 2CH_3); 1.50–2.03 (m, 4H, 2βNCH_2); 2.38 (m, 1H, $NC\underline{H}H$); 3.32 (s, 3H, OCH_3); 2.98–3.45 (m, 4H, OCH_2, NCH, $NCH\underline{H}$); 3.60–4.80 (m, 7H, CNCH, $CNC\underline{H}H$, $CNCH\underline{H}$, OCH_2, OCH_2Ph); 7.20–7.35 (m, 5H_{arom})	362 (M^+,7); 183 (98); 98 (62); 91 (100); 70 (95)
(*S*,*S*)-**4h**	86	+ 65°	88	$C_{21}H_{32}N_2O_4$ (376.5)	1460, 1380, 1230, 1120 (br)	1.37 (s, 6H, 2CH_3); 1.55–2.07 (m, 5H, 2$\beta NCH_2OCH_2C\underline{H}H$); 2.30–2.73 (m, 2H, $NCH\underline{H}$, $OCH_2CH\underline{H}$); 3.33 (s, 3H, OCH_3); 2.60–3.70 (m, 6H, OCH_2NCH, $NCH\underline{H}$, $OC\underline{H}_2CH_2$); 3.90–4.75 (m, 5H, CNCH, $CNC\underline{H}H$, $CNCH\underline{H}$, OCH_2Ph); 7.25–7.35 (m, 5H_{arom})	376 (M^+,4); 98 (98); 91 (78); 70 (100)
(*S*,*S*)-**4i**	62	+ 85°	89	$C_{15}H_{26}N_2O_5$ (314.4)	1745, 1445, 1385, 1230, 1175, 1120, 1075	1.38, 1.43 (2s, 6H, 2CH_3); 1.58–2.05 (m, 4H, 2βNCH_2); 2.43 (m, 1H, $NC\underline{H}H$); 2.50 (dd, 1H, J = 16.5, 8.5, $COC\underline{H}H$); 2.97 (dd, 1H, J = 16.5, 4.0, $COCH\underline{H}$); 3.33 (s, 3H, OCH_3); 3.02–3.45 (m, 4H, OCH_2, NCH, $NCH\underline{H}$); 3.69 (s, 3H, CO_2CH_3); 4.18 (dd, 1H, J = 16.0, 2.0, $CNC\underline{H}H$); 4.46 (d, 1H, J = 16.0, $CNCH\underline{H}$); 4.86 (m, 1H, CNCH)	314 (M^+,9); 269 (100); 98 (79); 70 (99)

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[a] Absolute configuration of major isomer.

[b] Yield of isolated product **4** based on **3**.

[c] Determined by ^{13}C-NMR spectroscopy, see Table 2.

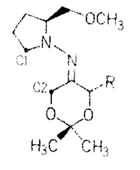
[d] Satisfactory microanalyses obtained: C ±0.36, H ±0.30, N ±0.38.

[e] Data of the major isomer with *E* configuration at the C=N double bond are given.

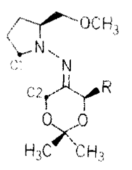
[f] The RAMP-hydrazone (*R*)-**3** was methylated.

[g] Obtained at 45°C.

form of the hydroxymethylated 2,2-dimethyl-1,3-dioxan-5-one derivative, which is obtained by hydrogenolysis of (*S*)-**5g** and also via aldol reaction of (*S*)-**3** with paraformaldehyde and subsequent ozonolysis. Both reactions lead to the same configuration at the new stereogenic center. In such aldol reactions the absolute configuration has been proven in the case of several free ketoses by comparison of rotation values or ^{13}C-NMR studies.[25] The enantiomeric products (*R*)-**5** are available by using RAMP as chiral auxiliary (see Table 1,3).



(*E,S,S*)-**4**



(*E,S,R*)-**4**

Table 2. ^{13}C-NMR Data ($CDCl_3$/TMS) of Product Hydrazones **4** Used for Calculation of de-Values

4	δ C1[a] (*E,S,S*)-**4**	(*E,S,R*)-**4**	δ C2[a] (*E,S,S*)-**4**	(*E,S,R*)-**4**
a	55.34	54.72	59.65	60.43
b	55.58	54.75	59.79	60.40
c	55.56	54.72	59.79	60.45
d	55.70	54.81	60.19	60.56
e	55.64	54.75	59.83	60.45
f	55.69	54.97	59.88	60.53
g[b]	55.78	[c]	59.75	[c]
h	55.36	54.72	59.84	60.54
i	55.40	54.72	59.16	59.12

[a] See formulas (*E,S,S*)-**4** and (*E,S,R*)-**4**.

[b] Absolute configuration at the new stereogenic center reversed due to priority rules.

[c] Not detectable.

Table 3. Highly enantiomerically enriched 4-alkyl-2,2-dimethyl-1,3-dioxan-5-ones (*S*)-**5** Prepared

Product	Yield[a] (%)	$[\alpha]_D^{23}$ (neat)	ee[b] (%)	Molecular Formula[c]	IR (NaCl) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)	MS *m/z* (%)
(*S*)-**5a**	56 (41)	−292°	93	$C_7H_{12}O_3$ (144.2)	1750, 1380, 1230, 1170, 1110	1.32 (d, 3H, *J* = 6.6, CH_3); 1.42, 1.44 (2s, 6H, 2CH_3); 3.98 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.32 (d, 1H, *J* = 17, COCH$\underline{H}$); 4.38 (q, 1H, *J* = 6.6, COCH)	144 (M^+, 5); 72 (61); 43 (100)
(*R*)-**5a**[d]	66 (49)	+295°	93	$C_7H_{12}O_3$ (144.2)			
(*S*)-**5b**	70 (58)	−274°	≥95	$C_8H_{14}O_3$ (158.2)	1750, 1380, 1225, 1080, 1010	0.95 (t, 3H, *J* = 7.5, CH_3); 1.42 (s, 6H, 2CH_3); 1.30–2.05 (m, 2H, CH_2); 3.92 (d, 1H, *J* = 17, COCH$\underline{H}$); 4.12 (m, 1H, COCH); 4.24 (d, 1H, *J* = 17, COCH$\underline{H}$)	158 (M^+, 4); 72 (100); 43 (78)
(*S*)-**5c**	81 (43)	−196°	≥95	$C_{12}H_{22}O_3$ (214.3)	1755, 1380, 1230, 1105	0.88 (t, 3H, *J* = 6, CH_3); 1.42 (s, 6H, 2CH_3); 1.10–1.90 (m, 10H, 5CH_2); 3.93 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.20 (m, 1H, COCH); 4.28 (d, 1H, *J* = 17, COCH$\underline{H}$)	214 (M^+, 0.6); 72 (100); 43 (57)
(*S*)-**5d**	80 (54)	−242°	≥95	$C_9H_{16}O_3$ (172.2)	1750, 1385, 1230, 1095, 1080, 1035	0.90, 1.02 (2d, 6H, *J* = 6.6, 2CH_3); 1.42 (s, 6H, 2CH_3): 2.23 (m, 1H, CH): 3.90 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.04 (m, 1H, COCH); 4.20 (dd, 1H, *J* = 17, 1.5, COCH$\underline{H}$)	172 (M^+, 3); 72 (100); 43 (55)
(*S*)-**5e**	27[e] (22)	−241°	≥95	$C_9H_{14}O_3$ (170.2)	1750, 1380, 1230, 1110	1.44, 1.46 (2s, 6H, 2CH_3); 2.33 (m, 1H, C$\underline{H}$$H_{allyl}$); 2.64 (m, 1H, CH$\underline{H}_{allyl}$); 4.00 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.26 ((dd, 1H, *J* = 17, 1.5, COCH$\underline{H}$); 4.30 (m, 1H, COCH); 5.09 (m, 1H, C$\underline{H}$$H_{olef}$); 5.15 (m, 1H, CH$\underline{H}_{olef}$); 5.84 (m, 1H, CH_{olef})	170 (M^+, 5); 72 (100); 43 (73)
(*S*)-**5f**	66 (36)	−228°	≥95	$C_{13}H_{16}O_3$ (220.3)	1750, 1385, 1230, 1180, 1110	1.30, 1.38 (2s, 6H, 2CH_3); 2.75 (dd, 1H, *J* = 15, 9, C$\underline{H}$H); 3.23 (dd, 1H, *J* = 15, 3, CH$\underline{H}$); 3.93 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.25 (dd, 1H, *J* = 17, 1.5, COCH$\underline{H}$); 4.43 (m, 1H, COCH)); 7.24 (s, 5H_{arom})	220 (M^+, 5); 92 (59); 91 (57); 72 (100)
(*S*)-**5g**	66 (40)	− 92°	≥95	$C_{14}H_{18}O_4$ (250.3)	1750, 1380, 1230, 1110 (br), 740	1.50 (s, 6H, 2CH_3); 3.72 (dd, 1H, *J* = 11.5, 6, C$\underline{H}$HOBn); 3.90 (dd, 1H, *J* = 11.5, 3, CH$\underline{H}$OBn); 3.95 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.31 (dd, 1H, *J* = 17, 1.5, COCH$\underline{H}$); 4.46 (m, 1H, COCH); 4.60 (s, 2H, OC$\underline{H}_2$Ph); 7.32 (s, 5H_{arom})	250 (M^+, 0.03); 91 (100); 72 (23)
(*S*)-**5h**	68 (53)	−148°	88	$C_{15}H_{20}O_4$ (264.3)	1750, 1380, 1230, 1120	1.43 (s, 6H, 2CH_3); 1.83 (m, 1H, C$\underline{H}$H); 2.22 (m, 1H, CH$\underline{H}$); 3.61 (dd, 2H, *J* = 6.6, 6.0, OCH_2); 3.92 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.25 (dd, 1H, *J* = 17, 1.5, COCH$\underline{H}$); 4.41 (m, 1H, COCH); 5.00 (s, 2H, OC$\underline{H}_2$Ph); 7.33 (s, 5H_{arom})	264 (M^+, 2); 107 (80); 91 (100); 72 (83)
(*S*)-**5i**	73 (41)	−202°	89	$C_9H_{14}O_5$ (202.2)	1750, 1740, 1380, 1220, 1170, 1110	1.46, 1.53 (2s, 6H, 2CH_3); 2.63 (dd, 1H, *J* = 17.4, 8.4, C$\underline{H}$H); 2.95 (dd, 1H, *J* = 17.4, 4.5, CH$\underline{H}$); 3.75 (s, 3H, OCH_3); 4.05 (d, 1H, *J* = 17, COC$\underline{H}$H); 4.40 (dd, 1H, *J* = 17, 1.5, COCH$\underline{H}$); 4.75 (m, 1H, COCH)	202 (M^+, 0.2); 72 (92); 43 (100)

[a] Yield of isolated ketones **5** based on **4**, overall yield of the sequence **1** → **5** in parenthesis.

[b] Determined by ^{1}H-NMR LIS technique and/or based on the de values of the corresponding precursors **4**, see Table 1.

[c] Satisfactory microanalyses obtained: C ± 0.18, H ± 0.25.

[d] RAMP was used as chiral auxiliary.

[e] As by-product, 56% of the corresponding ozonide was isolated.

In conclusion, the lithiated SAMP-/RAMP-hydrazones of 2,2-dimethyl-1,3-dioxan-5-one constitute versatile chiral DHAP-enolate equivalents, which are now being investigated in de *de novo* sugar syntheses using aldol reactions.[25]

The optical rotation values were measured at 23 °C using a Perkin-Elmer P 241 polarimeter. Microanalyses were obtained using a Heraeus CHN-O-Rapid. IR spectra were recorded on a Beckmann Acculab 4 spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian VXR 300 or a Varian EM 390 spectrometer, ^{13}C-NMR using a Varian VXR 300 spectrometer. MS spectra were recorded on a Varian MAT 212 spectrometer. The ozonolyses were carried out with a Fischer-Ozongenerator 502.

(*S*)-(+)-1-(2,2-Dimethyl-1,3-dioxan-5-ylideneamino)-2-methoxymethylpyrrolidine [(*S*)-3]:
In a flask equipped with a Dean–Stark trap (for azeotropic removal of water) and a reflux condenser, 2,2-dimethyl-1,3-dioxan-5-one (**1**; 8.45 g, 65 mmol) and (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) [(*S*)-**2**; 8.46 g, 65 mmol] in benzene (80 mL) are refluxed for 20 h. After cooling, Et_2O (200 mL) is added, and the mixture is washed with water (2 × 10 mL); the organic layer is dried ($MgSO_4$) and evaporated. The crude hydrazone is purified by distillation under reduced pressure to give (*S*)-**3** as a pale yellow oil; yield: 14.2 g (90 %); bp 82–88 °C/0.05 Torr; $[\alpha]_D^{23}$ +230° (neat).

$C_{12}H_{22}N_2O_3$	calc.	C 59.48	H 9.15	N 11.56
(242.3)	found	59.47	9.36	11.34

IR (film): ν = 1460, 1450, 1380, 1370, 1340, 1220, 1155–1040 (br), 835 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.38, 1.42 (2s, 6 H, $2CH_3$); 1.55–2.15 (complex, 4 H, $2\beta NCH_2$); 1.53 (m, 1 H, $NC\underline{H}H$); 3.35 (s, 3 H, OCH_3); 2.90–3.50 (complex, 4 H, $NCH\underline{H}$, NCH, OCH_2); 4.20–4.68 (complex, 4 H, $2CNCH_2$).

MS (70 eV): *m*/*z* (%) = 242 (M^+, 1.5); 139 (43); 98 (60); 70 (100); 43 (30).

The enantiomeric hydrazone (*R*)-**3** is prepared by reaction of **1** (5.2 g, 40 mmol) and RAMP (*R*)-**2** (5.2 g, 40 mmol) in benzene (70 mL) in the same way; yield: 7.9 g (82 %); bp 74–81 °C/0.05 Torr; $[\alpha]_D^{23}$ = −225° (neat).

Metalation and Alkylation; General Procedure:
In a dried, argon-filled round-bottomed flask fitted with a septum cap, a solution of **3** (1 equiv; 5–20 mmol) in anhydrous THF (4 mL/mmol) is cooled to −78 °C. *tert*-Butyllithium (1.1 equiv, 1.7 M solution in *n*-hexane) is added dropwise, and the mixture is stirred for 2 h at −78 °C. The solution of metalated hydrazone is cooled to −100 °C, alkyl halide (1.2 equiv, neat or as a solution in anhydrous THF) is added dropwise, and the mixture is stirred for 1 h at −100 °C and then warmed slowly to room temperature (about 15 h). Finally, Et_2O (30 mL/mmol) is added and the mixture is washed with pH7-buffer (3 mL/mmol) and brine (2 × 3 mL/mmol), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product **4** is heated to 50 °C for a short time if necessary (about 15 min for isomerization from *Z* to *E* isomer; TLC-control) and purified by column chromatography (silica gel, Et_2O/pentane, 1:1–2:5; R_f *E* > R_f *Z*) to give a colorless or pale yellow oil [in the case of (*E,S,S*)-**4d**: colorless solid; mp = 40 °C] (see Tables 1 and 2).

Ozonolysis of Hydrazone 4 to 4-Alkyl-2,2-dimethyl-1,3-dioxan-5-ones 5; General Procedure:
A solution of crude or purified hydrazone **4** (1 equiv; 5–10 mmol) in CH_2Cl_2 (30–50 mL) is cooled to −78 °C under a dry atmosphere (Ar) and ozone (2 equiv, 100 sec/mmol, 55 L/h O_2) is introduced. The mixture is allowed to warm up to room temperature while dry argon is bubbled through; the solvent is evaporated under reduced pressure, and the crude product **5** is purified by column chromatography (silica gel, Et_2O/pentane, 1:2–1:4) to give a colorless liquid (see Table 3).

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1. $(CH_2O)_n$, KOH, EtOAc, 50 °C (73 %)[19] – 2. acetone, $BF_3 \cdot OEt_2$, 15–55 °C (66 %)[20] – 3. Ra–Ni, MeOH, 100 atm H_2, 70 °C (64 %)[21] – 4. $NaIO_4$, H_2O, 20 °C (56 %).[22]
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