Diastereo- and Enantioselective Synthesis of Polyfunctional Cyclic Ketones with Neighboring Quaternary and Tertiary Stereogenic Centers via [2,3]-Wittig Rearrangement

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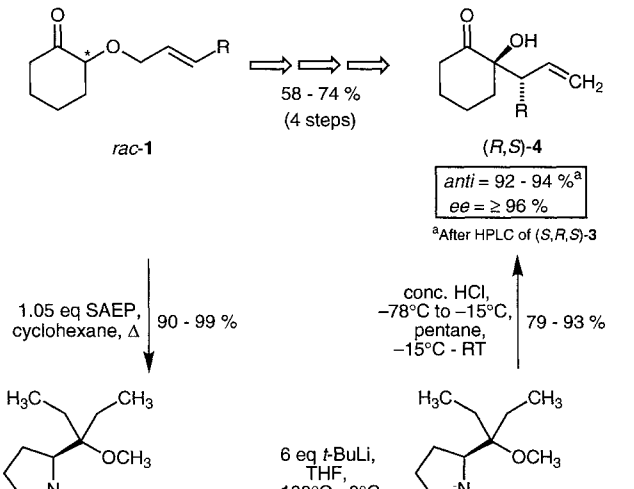
The diastereo- and enantioselective synthesis of β-substituted γ,δ-unsaturated cyclic α-hydroxy ketones **4** with neighboring quaternary and tertiary stereogenic centers via asymmetric [2,3]-Wittig rearrangement of SAEP-hydrazones **2** with good overall yields (58–74%), high *anti*-selectivities (92–94%) and excellent enantiomeric excesses (ee ≥ 96%) is described. The absolute configuration is determined by X-ray structure analysis of the hydrazone **3b** and by ^{1}H NMR NOE measurements.

The diastereo- and enantioselective generation of neighboring quaternary und tertiary stereogenic centers via C–C bond formation is a serious problem in natural product synthesis or drug design.[1] Nowadays methods to produce quaternary stereogenic centers in polyfunctional molecules have been developed,[2–7] but only a few allow the simultaneous generation of an attached tertiary stereogenic center.[8] In particular intramolecular sigmatropic rearrangements, like the asymmetric [3,3]-Carroll rearrangement recently developed in our group,[9] should help to solve this problem.

In the last two decades the [2,3]-Wittig rearrangement has become a powerful tool for stereoselective C–C bond formation.[10, 11] Asymmetric versions of the [2,3]-Wittig rearrangement can be divided by the kind of stereocontrol; the chirality transfer type; the asymmetric induction type; and the chiral base induced type. Only the first two versions have reached a wide synthetic application. The asymmetric [2,3]-Wittig rearrangement has been used to synthesize chiral esters,[12] amides,[13] oxazolines,[14] η^6-arene-Cr(CO)$_3$ complexes,[15] tetrahydropyridines,[16] cyclopentanes,[17] carboxylic acids,[18] and sulfides.[19] Recently, we reported on the asymmetric synthesis of protected β-substituted γ,δ-unsaturated acyclic α-hydroxyaldehydes or cyanohydrins, their application in natural product synthesis[20] and β-substituted γ,δ-unsaturated acyclic α-hydroxy ketones by [2,3]-Wittig rearrangement of α-allyloxyhydrazones.[21]

As an extension of this methodology we now wish to describe a practical diastereo- and enantioselective synthesis of β-substituted γ,δ-unsaturated cyclic α-hydroxy ketones **4** with neighboring quaternary and tertiary stereogenic centers via asymmetric [2,3]-sigmatropic Wittig rearrangement of easily accessible SAEP-hydrazones **2**.



Scheme

Table 1. Enantioselective Synthesis of α-Hydroxy Ketones (*R,S*)-**4** *via* [2,3]-Wittig Rearrangement of SAEP-Hydrazones **2**

3, 4	R	*E*/*Z* 1	Yield (%) 1 → 2	Yield (%) 2 → 3	$[\alpha]_D^{r.t.}$ (*c*, $CHCl_3$) 3	Yield (%) 3 → 4	$[\alpha]_D^{r.t.}$ (*c*, $CHCl_3$) 4	*anti*[a] (%) 3, 4	*ee* (*de*)[b] (%) 3, 4	Config
a	Me	94 : 6	98	81	+ 291.9 (0.93)	80	− 47.2 (1.33)	88 (94)	≥ 96	(*R,S*)
b	Et	91 : 9	99	79	+ 209.5 (1.50)	84	− 55.4 (1.44)	89 (92)	≥ 96	(*R,S*)
c	Pr	98 : 2	90	80	+ 257.7 (0.95)	80	− 100.8 (1.83)	91 (93)	≥ 96	(*R,S*)
d	*i*-Pr	95 : 5	99	77	+ 257.6 (0.78)	79	− 67.4 (1.33)	88 (94)	≥ 96	(*R,S*)
e	*i*-Pen	95 : 5	99	80	+ 257.2 (0.58)	93	− 22.9 (0.63)	74 (94)	≥ 96	(*R,S*)

[a] In parantheses: After purification by HPLC of **3** (Merck, preprepared column, silica gel 7 μm, length 250 mm, Et_2O/pentane).
[b] Determined by ^{1}H and ^{13}C NMR spectroscopy.

As outlined in the Scheme, the (*E*)-configurated (C=N) SAEP-hydrazones **2** can be prepared in excellent yields (90–99%) through a simple condensation of the commericially available chiral auxiliary (*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP)[22] and the racemic ketone **1**, which can be generated in a two-step sequence from (*E*)-allylic alcohol and cyclohexene oxide, in boiling cyclohexane. After purification by column chromatography or Kugelrohr distillation (during the distillation the temperature has to be as low as possible to avoid [1,2]-Wittig rearrangement), the liquid slightly yellow or colorless hydrazones **2** were metalated with a large excess (6 equiv) of *t*-BuLi in tetrahydrofuran at −100 °C and stirred for 1 hour at this temperature. The reaction mixture is then warmed up to −78 °C, stirred for an additional 24 hours and then for 5 hours at 0 °C. During this time the rearrangement takes place and can be monitored by thin layer chromatography. The result-

Table 2. Spectroscopic Data for Rearranged SAEP-Hydrazones (*S,R,S*)-**3**[a]

Product	IR (neat) ν (cm^{-1})	^1H NMR (C_6D_6/TMS) δ, J (Hz)	^{13}C NMR (C_6D_6/TMS) δ	MS (70 eV) m/z (%)
3a	3400, 3080, 2960, 2940, 2880, 2820, 1640, 1460, 1390, 1265, 1165, 1125, 1085, 1020, 910, 740	0.88–0.95 (m, 9H, 3 × CH_3), 1.20–2.00 (m, 12H, 6 × CH_2), 1.79 (m, 1H, NCHC*H*H), 1.95 (m, 1H, NCHCH*H*), 2.28 (m, 2H, COHC*H*H, =CHC*H*), 2.47 (m, 1H, CHNC*H*H), 2.86 (m, 1H, COHCH*H*), 2.96 (m, 1H, CHNCH*H*), 3.26 (s, 3H, OCH_3), 3.51 (m, 1H, C*H*N), 4.98 (s, 1H, O*H*), 5.08 (m, 2H, =CH_2), 6.22 (m, 1H, =C*H*)	8.11, 8.73 (2 × CH_2CH_3), 14.98 (CH_3), 21.72, 24.13, 24.28, 25.49, 26.62, 26.96, 27.44 (7 × CH_2), 39.62 ($COHCH_2$), 42.90 (=CHCH), 50.17 (OCH_3), 57.54 (CH_2N), 72.05 (CHN), 74.73 (COH), 79.64 ($COCH_3$). 115.08 (=CH_2), 141.22 (=CH), 167.12 (C=N	336 (0.3, $M^{+\bullet}$), 235 (100, $M^{+\bullet}-H_3COCEt_2$), 110 (69, $C_6H_8NO^+$), 70 (29, $C_4H_8N^+$)
3b[b]	3402, 3070, 2964, 2937, 2874, 2825, 1638, 1460, 1384, 1265, 1165, 1128, 1115, 1086, 1041, 912, 779	0.84–0.98 (m, 9H, 3 × CH_3), 1.20–1.70 (m, 14H, 7 × CH_2), 1.78 (m, 1H, NCHC*H*H), 1.96 (m, 1H, NCHCH*H*), 2.28, 1H, COHC*H*H), 2.50 (m, 2H, CHNCH*H*, =CHC*H*), 2.88 (d/t, J = 11.4/5.7, 1H, COHCH*H*), 3.00 (m, 1H, CHNC*H*H), 3.26 (s, 3H, OCH_3), 3.52 (m, 1H, C*H*N), 5.01–5.23 (m, 3H, O*H*, =CH_2), 6.06 (m, 1H, =C*H*)	8.11, 8.74 (2 × CH_2CH_3), 12.76 (CH_3), 20.75, 21.63, 24.15, 24.27, 25.47, 26.71, 27.03, 27.44 (8 × CH_2), 39.96 ($COHCH_2$), 50.17 (=CHCH), 51.10 (OCH_3), 57.59 (CH_2N), 72.04 (CHN), 75.13 (COH), 79.68 ($COCH_3$). 117.09 (=CH_2), 139.04 (=CH), 167.35 (C=N)	351 (0.3, $M^{+\bullet}+1$), 249 (90, $M^{+\bullet}-H_3COCEt_2$), 170 (20), 110, (100, $C_6H_8NO^+$), 70 (45, $C_4H_8N^+$), 139.04 (=CH), 167.35 (C=N)
3c	3404, 3070, 2936, 2871, 2826, 1638, 1460, 1420, 1380, 1265, 1165, 1117, 1085, 1054, 912, 735	0.86–0.98 (m, 9H, 3 × CH_3), 1.10–1.70 (m, 16H, 8 × CH_2), 1.79 (m, 1H, NCHC*H*H), 1.97 (m, 1H, NCHCH*H*), 2.20–2.40, (m, 2H, COHC*H*H, =CHC*H*), 2.50 (m, 1H, CHNC*H*H), 2.92 (d/t, J = 11.4/6.0, 1H, COHCH*H*), 3.04 (m, 1H, CHNCH*H*), 3.27 (s, 3H, OCH_3), 3.52 (d/d, J = 9.4/7.1, 1H, C*H*N), 5.01–5.08 (m, 2H, O*H*, =C*H*H), 5.18 (d/d, J = 10.1/2.4, 1H, =CH*H*), 6.07 (m, 1H, =C*H*)	8.12, 8.75 (2 × CH_2CH_3), 14.46 (CH_3), 21.01, 21.67, 24.18, 24.28, 25.50, 26.73, 27.11, 27.46, 30.27 (9 × CH_2), 39.85 ($COHCH_2$), 48.74 (=CHCH), 50.18 (OCH_3), 57.59 (CH_2N), 72.06 (CHN), 75.13 (COH), 79.69 ($COCH_3$). 116.68 (=CH_2), 139.45 (=CH), 167.33 (C=N)	263 (92, $M^{+\bullet}-H_3COCEt_2$), 170 (22), 110, (100, $C_6H_8NO^+$), 70 (51, $C_4H_8N^+$)
3d	3400, 3069, 2938, 2870, 2826, 1636, 1461, 1384, 1365, 1267, 1162, 1134, 1118, 1088, 1051, 914, 734	0.88–0.97 (m, 12H, 4 × CH_3), 1.15–1.70 (m, 13H, CHC*H*, 6 × CH_2), 1.78 (m, 1H, NCHC*H*H), 1.98 (m, 1H, NCHCH*H*), 2.26–2.60 (m, 3H, COHC*H*H, CHNC*H*H, =CHC*H*), 2.90 (m, 1H, COHCH*H*), 3.06 (m, 1H, CHNCH*H*), 3.27 (s, 3H, OCH_3), 3.52 (d/d, J = 9.1/7.1, 1H, C*H*N), 5.03 (d/d, J = 17.5/2.0, 1H, =C*H*H), 5.11 (s, 1H, O*H*), 5.26 (d/d, J = 10.1/2.7, 1H, =CH*H*), 6.07 (m, 1H, =C*H*)	8.13, 8.76 (2 × CH_2CH_3), 18.82 (CH_3), 22.03 (CH_2), 24.11 (CH_3), 24.19, 24.29, 25.49, 26.84, 27.26, 27.47 (6 × CH_2), 27.64 (CHCH), 40.77 ($COHCH_2$), 50.19 (OCH_3), 53.61 (=CHCH), 57.65 (CH_2N), 72.09 (CHN), 76.17 (COH), 79.68 ($COCH_3$), 118.18 (=CH_2), 135.86 (=CH), 168.05 (C=N)	364 (0.2, $M^{+\bullet}$), 263 (100, $M^{+\bullet}-H_3COCEt_2$), 170 (29), 110, (98, $C_6H_8NO^+$), 70 (57, $C_4H_8N^+$)
3e	3397, 3069, 2957, 2873, 2826, 1635, 1462, 1421, 1379, 1266, 1252, 1169, 1135, 1087, 1054, 1008, 976, 913, 784	0.88–0.97 (m, 12H, 4 × CH_3), 1.05–1.75 (m, 17H, CHC*H*, 8 × CH_2), 1.80 (m, 1H, NCHC*H*H), 1.96 (m, 1H, NCHCH*H*), 2.30–2.60 (m, 2H, COHC*H*H, =CHC*H*), 2.50 (m, 1H, CHNC*H*H), 2.92 (d/t, J = 11.4/6.0, 1H, COHCH*H*), 3.11 (m, 1H, CHNCH*H*), 3.27 (s, 3H, OCH_3), 3.54 (m, 1H, C*H*N), 5.05 (d/d, J = 17.5/2.7, 1H, =C*H*H), 5.15 (s, 1H, O*H*), 5.23 (d/d, J = 10.1/2.4, 1H, =CH*H*), 6.25 (m, 1H, =C*H*)	8.12, 8.73 (2 × CCH_2CH_3), 12.97 (CH_3), 13.07 (CH_3), 22.18, 23.94, 24.16, 24.45, 25.05, 25.61, 26.84, 27.46, 27.49 (9 × CH_2), 40.93 ($COHCH_2$), 42.51 (CHCH), 49.17 (OCH_3), 50.20 (=CHCH), 58.03 (CH_2N), 72.23 (CHN), 76.49 (COH), 79.68 ($COCH_3$), 117.76 (=CH_2), 136.80 (=CH), 168.05 (C=N)	392 (0.1, $M^{+\bullet}$), 291 (100, $M^{+\bullet}-H_3COCEt_2$), 170 (32), 110, (99, $C_6H_8NO^+$), 70 (52, $C_4H_8N^+$)

[a] Satisfactory microanalyses and/or HRMS obtained for **3a–g**: C, N, H: ± 0.4 and/or ± 0.0005 amu.
[b] IR ($CHCl_3$).

ing (*E*)-configurated (C=N) α-hydroxyhydrazones **3**, which are slightly yellow or colorless liquids **(3a, c–e)** or colorless crystals **(3b)**, can be isolated in good *anti/syn* diastereoselectivity (74–91% *anti*) and with excellent asymmetric induction (*de* ≥ 96%) by column chromatography. The separation of the *syn*-diastereomer is possible through high pressure liquid chromatography (92–94% *anti*). Acidic cleavage of the hydrazones **3** can be achieved by treatment of the pure hydrazones with concentrated hydrochloric acid at −78 °C, warming up to −15 °C, addition of a high excess of pentane (200 mL/mmol) and stirring the resulting two-phase system at 25 °C until no hydrazone is observed by TLC. After purification by column chromatography the α-hydroxy ketones **4** were obtained in good yields (2 steps, 61–74%), good *anti/syn* selectivities (92–94% *anti*) and excellent enantiomeric excesses (ee ≥ 96%), as slightly yellow or colorless liquids **(4a, c–e)** or colorless crystals **(4b)**.

The diastereomeric excesses and the *anti*-selectivities of the hydrazones **3** were measured by ^{1}H and ^{13}C NMR spectroscopy. The enantiomeric excesses of the ketones **4** were determined by ^{1}H NMR spectroscopy using the chiral co-solvent (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol and by comparison with the corresponding racemate.[23]

The absolute configuration of the rearranged hydrazone **3b** was determined by X-ray structure analysis and shown to be (12*R*,13*S*),[24] based on knowledge of the absolute configuration of C3. The absolute configuration of the corresponding hydrazones **3a, c–e** and of the ketones **4** were assigned based on the assumption of a uniform reaction pathway.

^{1}H NMR NOE measurements of hydrazone **3a** led to the same results for the newly generated stereogenic centers of the major diastereomer and showed that the relative configuration of the minor diastereomer is *syn*.

In contrast to the $E_{CC}Z_{CN}$ configuration of the acylic azaenolates,[20] the azaenolates of the cyclic hydrazones

Table 3. Spectroscopic Data for α-Hydroxy Ketones (*R,S*)-**4**[a]

Product	IR (neat) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) *m/z* (%)
4a	3480, 3074, 2941, 2868, 1710, 1675, 1638, 1446, 1421, 1378, 1366, 1249, 1160, 1117, 1070, 1028, 1002, 916	0.83 (d, *J* = 6.7, 3H, CH_3), 1.43 (m, 1H, COHC*H*H), 1.65–1.80 (m, 3H, COHCH*HC*H_2), 2.13 (m, 1H, COC*H*H), 2.36 (m, 1H, COCH*H*), 2.50 (m, 2H, COCH_2CH_2), 2.74 (d/q, *J* = 9.1/7.1, 1H, =CHC*H*), 3.95 (s, 1H, O*H*), 5.15 (m, 2H, CH_2), 5.80 (m, 1H, =C*H*)	14.30 (CH_3), 21.69 (CH_2), 28.11 (CH_2), 38.13 (CH_2), 39.20 (CH_2), 42.23 (=CHCH), 80.40 (COH), 116.56 (=CH_2), 138.59 (=CH), 214.53 (C=O)	168 (3, $M^{+\cdot}$), 167 (6, $M^{+\cdot}-OH$), 150 (10, $M^{+\cdot}-H_2O$), 135 (21, $M^{+\cdot}-H_2O$, Me), 113 (13, $M^{+\cdot}-C_4H_7^+$), 95 (14, $M^{+\cdot}-H_2O$, $C_4H_7^+$), 57 (100), 55 (98, $C_4H_7^+$)
4b[b]	3481, 3073, 2960, 2939, 2872, 1708, 1639, 1453, 1433, 1379, 1249, 1160, 1115, 1069, 1042, 1004, 917	0.83 (t, *J* = 7.4, 3H, CH_3), 0.85–1.00 (m, 2H, CHCH_2), 1.25–1.45 (m, 2H, COHCH_2), 1.64–1.78 (m, 2H, COHCH$_2$CH_2), 2.15 (m, 1H, COC*H*H), 2.32–2.62 (m, 4H, =CHC*H*, COCH*HC*H_2), 3.94 (s, 1H, O*H*), 5.13 (m, 1H, =CH*H*), 5.25 (m, 1H, =C*H*H), 5.64 (m, 1H, =C*H*)	12.23 (CH_3), 20.75 (CH_2CH_3), 21.61 (CH_2), 28.25 (CH_2), 38.23 (CH_2), 39.54 (CH_2), 50.54 (=CHCH), 80.84 (COH), 118.54 (=CH_2), 136.60 (=CH), 214.87 (C=O)	183 (1, $M^{+\cdot}-H$), 165 (6, $M^{+\cdot}-OH$), 164 (3, $M^{+\cdot}-H_2O$), 135 (21, $M^{+\cdot}-H_2O$, Et), 114 (100), 113 (18, $M^{+\cdot}-C_5H_9^+$), 95 (14, $M^{+\cdot}-H_2O$, $C_5H_9^+$), 69 (35, $C_5H_9^+$)
4c	3481, 3073, 3010, 2939, 2869, 1709, 1638, 1452, 1446, 1420, 1378, 1309, 1248, 1158, 1119, 1077, 1064, 1049, 1004, 917	0.84 (t, *J* = 7.4, 3H, CH_3), 1.00–1.80 (m, 8H, $CH_3CH_2CH_2$/COHCH_2CH_2), 2.16 (m, 1H, COC*H*H), 2.35–2.62 (m, 4H, =CHC*H*, COCH*HC*H_2), 3.93 (s, 1H, O*H*), 5.12 (d/d, *J* = 17.1/2.0, 1H, =CH*H*), 5.23 (d/d, *J* = 10.4/2.0, 1H, =C*H*H), 5.65 (m, 1H, =C*H*)	13.90 (CH_3), 20.46 (CH_2CH_2), 21.67 (CH_2), 28.30 (CH_2), 29.94 ($CHCH_2$), 38.29 (CH_2), 39.53 (CH_2). 48.19 (=CHCH), 80.92 (COH), 118.30 (=CH_2), 136.94 (=CH), 214.92 (C=0)	196 (3, $M^{+\cdot}$), 195 (7, $M^{+\cdot}-H$), 179 (11, $M^{+\cdot}-OH$), 178 (3, $M^{+\cdot}-H_2O$), 163 (41), 153 (6, $M^{+\cdot}-Pr$), 135 (12, $M^{+\cdot}-H_2O$, Pr), 113 (13, $M^{+\cdot}-C_6H_{11}^+$), 95 (37, $M^{+\cdot}-H_2O$, $C_6H_{11}^+$), 83 (57, $C_6H_{11}^+$), 55 (100)
4d	379, 3073, 2955, 2870, 1708, 1673, 1637, 1464, 1452, 1445, 1422, 1385, 1369, 1339, 1247, 1158, 1124, 1065, 1044, 1009, 916	0.84 (d, *J* = 7.1, 3H, CH_3), 0.88 (d, *J* = 6.7, 3H, CH_3), 1.30 (m, 1H, C*H*(CH_3)$_2$), 1.48 (m, 1H, COHC*H*H), 1.60–1.70 (m, 3H, COHCH*HC*H_2), 2.15 (m, 1H, COC*H*H), 2.32–2.57 (m, 4H, CHC*H*/COCH*HC*H_2), 3.93 (s, 1H, O*H*), 5.11 (d/d, *J* = 17.2/2.7, 1H, CH*H*), 5.28 (d/d, *J* = 10.4/2.4, 1H, C*H*H), 5.84 (m, 1H, =C*H*)	18.79 ($CHCH_3$), 21.98 (CH_2), 23.47 ($CHCH_3$), 28.24 ($CHCH_3$), 28.66, (CH_2), 38.60 (=CHCH), 40.89 (CH_2), 53.52 (CH_2), 81.84 (COH), 119.34 (=CH), 215.48 (C=O)	196 (2, $M^{+\cdot}$), 195 (5, $M^{+\cdot}-H$), 179 (4, $M^{+\cdot}-OH$), 153 (8, $M^{+\cdot}-i$-Pr), 135 (9, $M^{+\cdot}-H_2O$, $-i$-Pr), 113 (10, $M^{+\cdot}-C_6H_{11}^+$), 95 (25, $M^{+\cdot}-H_2O$, $C_6H_{11}^+$), 83 (73, $C_6H_{11}^+$), 55 (100)
4e	3477, 3072, 2957, 2874, 1710, 1636, 1463, 1422, 1378, 1337, 1309, 1248, 1233, 1155, 1125, 1107, 1078, 1069, 1047, 1008, 917	0.80 (t, *J* = 7.4, 3H, CH_3), 0.87 (t, *J* = 7.4, 3H, CH_3), 0.95–1.80 (m, 8H, CH(CH_2)$_2$/COHCH_2/COHCH_2CH_2), 1.93 (m, 1H, =CHCHC*H*), 2.15 (m, 1H, COC*H*H), 2.36–2.58 (m, 3H, COCH*HC*H_2), 2.71 (m, 1H, =CHC*H*CH), 3.97 (s, 1H, O*H*), 5.11 (d/d, *J* = 17.8/2.4, 1H, CH*H*), 5.26 (d/d, *J* = 10.1/2.0, 1H, C*H*H), 5.85 (m, 1H, =C*H*)	12.37 (CH_3), 12.47 (CH_3), 22.16 ($CHCH_2$), 23.47 ($CHCH_2$), 24.63, (CH_2), 28.56 (CH_2), 38.69 (CH_2), 40.86 (CH_2), 42.86 (=CHCHCH), 48.77 (=CHCH), 82.24 (COH), 119.13 (=CH_2), 134.44 (=CH), 215.31 (C=O)	225 (1, $M^{+\cdot}+H$), 224 (0.3, $M^{+\cdot}$), 207 (1, $M^{+\cdot}-OH$), 153 (1, $M^{+\cdot}-i$-Pen), 135 (12, $M^{+\cdot}-H_2O$, *i*-Pen), 114 (100), 113, (12, $M^{+\cdot}-C_8H_{15}^+$), 95 (10, $M^{+\cdot}-H_2O$, $C_8H_{15}^+$), 111 (22, $C_8H_{15}^+$)

[a] Satisfactory microanalyses and/or HRMS obtained for **4a–g**: C, H: ±0.4 and/or ±0.0005 amu.
[b] IR ($CHCl_3$).

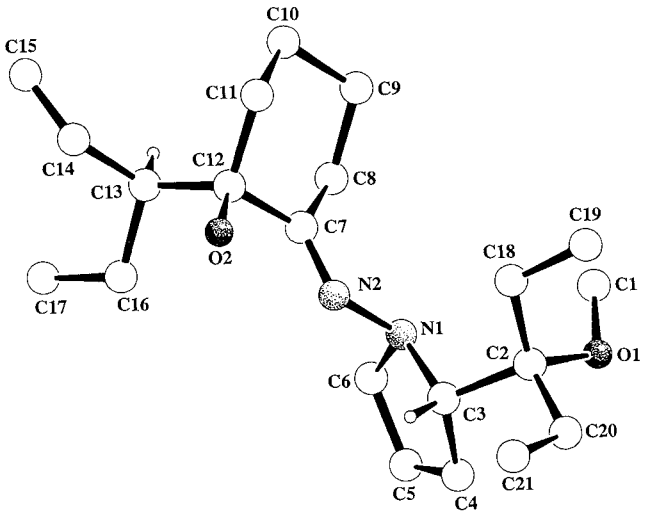
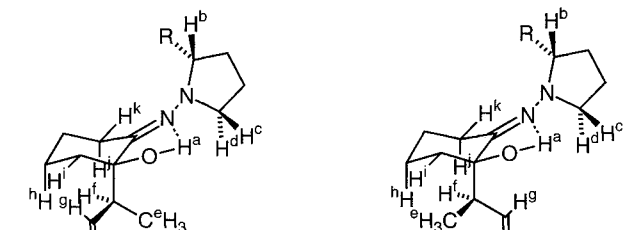


Figure 1. Crystal structure of hydrazone **3b** (SCHAKAL-plot)[29]



$H^a \Leftrightarrow H^b$; $H^c \Leftrightarrow H^e$; $H^d \Leftrightarrow H^k$; $H^f \Leftrightarrow H^h$; $H^f \Leftrightarrow H^j$; $H^g \Leftrightarrow H^i$

(*S,R,S*)-**3a**
major diastereomer

$H^a \Leftrightarrow H^b$; $H^c \Leftrightarrow H^g$; $H^d \Leftrightarrow H^k$; $H^f \Leftrightarrow H^h$; $H^f \Leftrightarrow H^j$; $H^e \Leftrightarrow H^i$

(*S,R,R*)-**3a**
minor diastereomer

Figure 2. NOE effects (hydrazone **3a**)

3 have a $Z_{CC}E_{CN}$ configuration, leading to the observed *anti* diastereoselectivity.

In summary the [2,3]-Wittig rearrangement of cyclic SAEP-hydrazones **2** described here is an efficient route to β-substituted γ,δ-unsturated cyclic α-hydroxy ketones, which should be useful as chiral building blocks in the synthesis of bioactive compounds.

Solvents were dried and purified prior to use. THF was freshly distilled from K under Ar. CH_2Cl_2 was distilled from CaH_2 and stored under Ar. Et_2O and pentane were distilled prior to use. Analytical glass-backed TLC plates (silica gel 60 F_{254}) and silica gel (230–400 mesh) were purchased from Merck, Darmstadt. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Optical rotations were measured using a Perkin–Elmer P241 polarimeter using solvents of Merck Uvasol quality. Microanalyses were obtained with a CHN-O-Rapid elemental analyser. ^1H and ^1C NMR spectra were recorded on a Varian VXR 30, Gemini 300 (300 and 75 MHz) using TMS as internal standard. IR spectra were recorded on a Perkin–Elmer FT/IR 1750 spectrophotometer. MS analyses were obtained on a Varian MAT 212, EI 70 eV. HRMS spectra were recorded on a Finnigan MAT, MAT 95 spectrometer.

The racemic ketones **1** were prepared in a two-step sequence according to the literature procedures:[25] $BF_3 \cdot OEt_2$ catalyzed coupling of cyclohexene oxide (20 mmol) with a large excess of (*E*)-allylic alcohol (100 mmol) in CH_2Cl_2 (100 mL) at 25 °C and then Swern oxidation of the allyloxy alcohol intermediate.

The SAEP-hydrazones **2** were prepared according to the literature procedure[26] from the ketones **1** (10 mmol) and SAEP (11 mmol) in cyclohexane (50 mL) at 80 °C with azeotropic water removal (Dean–Stark trap).

β-Substituted γ,δ-Unsaturated Cyclic α-Hydroxy-SAEP-hydrazones 3; General Procedure:

To a solution of ketone SAEP-hydrazone **2** (2 mmol) in dry THF (25 mL) at −100 °C under an atmosphere of Ar, was added dropwise *t*-BuLi (1.6 M solution in pentane) (12 mmol). This solution was stirred for 30 h under the following conditions: 1 h at −100 °C, 24 h at −78 °C and then 5 h at 0 °C. The reaction mixture was then poured into sat. NH_4Cl (25 mL) and extracted several times with Et_2O. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, pentane/Et_2O, 2:1) afforded the rearranged hydrazones **3** as slightly yellow or colorless liquids **(3a, c–e)** or colorless crystals **(3b)**.

3b ($C_{21}H_{38}N_2O_2$) crystallizes in orthorhombic space group $P2_12_12_1$ (No. 19), $a = 12.517$ (1) Å, $b = 12.7417$ (8) Å, $c = 13.7183$ (6) Å, $V = 2187.96$ Å^3, $Z = 4$, $M_r = 350.55$, $\varrho_{calc} = 1.064$ g cm^{-3}. Enraf–Nonius-CAD4-diffractometer, graphite monochromator, $Cu_{K\alpha}$-radiation ($\lambda = 1.54179$ Å). The structure was solved by direct methods (XTAL3.2).[27] The hydrogen positions were calculated and not refined. 2226 observed reflections ($I > 2\sigma(I)$), employed to refine 227 parameters. $R = 0.079$ ($R_\omega = 0.057$) $\omega = \sigma^{-2}$. Goodness of fit: 2.053. Residual electron density $-0.6/+0.4$ eÅ^{-3}.[28]

β-Substituted γ,δ-Unsaturated α-Hydroxy Ketones 4; General Procedure:

The rearranged hydrazone **3** (1 mmol) was treated with conc HCl (5 mL) at −78 °C and then allowed to warm to −15 °C. Under vigorous stirring pentane (200 mL) was added and the resulting two-phase system was stirred at 25 °C until complete hydrolysis of the starting material was observed (TLC control). The organic phase was separated, washed several times with water, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, pentane/Et_2O, 2:1) afforded the α-hydroxy ketones **4** as slightly yellow or colorless liquids **(4a, c–e)** or colorless crystals **(4b)**.

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