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-hydrazone 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 1H NMR NOE measurements.

The diastereo- and enantioselective generation of neighboring quaternary and 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 stereocenter: 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 p6-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-hydroxylaldehydes or cyanohydrins, their application in natural product synthesis20 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-hydrazone 2.

Scheme

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

<table>
<thead>
<tr>
<th>3, 4</th>
<th>R</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
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<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>a</td>
<td>Me</td>
<td>94: 6</td>
<td>98</td>
<td>81</td>
<td>+ 291.9 (0.93)</td>
<td>80</td>
<td>- 47.2 (1.33)</td>
<td>88 (94)</td>
<td>≥ 96</td>
<td>(R,S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Et</td>
<td>91: 9</td>
<td>99</td>
<td>79</td>
<td>+ 209.5 (1.50)</td>
<td>84</td>
<td>- 55.4 (1.44)</td>
<td>89 (92)</td>
<td>≥ 96</td>
<td>(R,S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Pr</td>
<td>98: 2</td>
<td>90</td>
<td>80</td>
<td>+ 257.7 (0.95)</td>
<td>80</td>
<td>- 100.8 (1.73)</td>
<td>91 (93)</td>
<td>≥ 96</td>
<td>(R,S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>i-Pr</td>
<td>95: 5</td>
<td>99</td>
<td>77</td>
<td>+ 257.6 (0.78)</td>
<td>79</td>
<td>- 67.4 (1.33)</td>
<td>88 (94)</td>
<td>≥ 96</td>
<td>(R,S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>i-Pen</td>
<td>95: 5</td>
<td>99</td>
<td>80</td>
<td>+ 257.2 (0.58)</td>
<td>93</td>
<td>- 22.9 (0.63)</td>
<td>74 (94)</td>
<td>≥ 96</td>
<td>(R,S)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In parentheses: After purification by HPLC of 3 (Merck, prepurified column, silica gel 7 μm, length 250 mm, Et2O/pentane).

b Determined by 1H and 13C NMR spectroscopy.
As outlined in the Scheme, the (E)-configured (C=N) SAEP-hydrazones 2 can be prepared in excellent yields (90–99 %) through a simple condensation of the commercially available chiral auxiliary (S)-1-amino-2-[(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP)] 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 metatated with a large excess (6 equiv) of 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-Hydrazone (S,R,S)-3

<table>
<thead>
<tr>
<th>Product</th>
<th>IR (neat) ν (cm⁻¹)</th>
<th>δ, J (Hz)</th>
<th>δ, J (Hz)</th>
<th>MS (70 eV) m/z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>3400, 3090, 2960, 2940, 2880, 2820, 1640, 1460, 1390, 1265, 1165, 1125, 1085, 1020, 910, 740</td>
<td>8.11, 8.73 (2 × CH₂CH₂), 14.98 (CH₃), 21.72, 24.13, 24.28, 25.49, 26.62, 26.96, 27.44 (7 × CH₃), 39.62 (COCH₂), 42.90 (COCH₂), 50.17 (OCH₃), 57.54 (CH₃N), 72.05 (CHN), 74.73 (COH), 79.64 (COCH₂), 115.08 (COCH₂), 141.22 (COCH₂), 167.12 (C=N)</td>
<td>336 (0.3, M⁺⁺⁺), 235 (100, M⁺⁺⁺-H₂COCH₂), 110 (69, C₅H₅N⁻)</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>3402, 3070, 2964, 2937, 2874, 2825, 1638, 1460, 1384, 1265, 1165, 1128, 1115, 1086, 1041, 912, 779</td>
<td>8.11, 8.74 (2 × CH₂CH₂), 12.76 (CH₃), 20.75, 21.63, 24.15, 24.27, 25.47, 26.71, 27.03, 27.44 (8 × CH₃), 39.96 (COCH₂), 50.17 (COCH₂), 51.10 (OCH₃), 57.59 (CH₃N), 72.04 (CHN), 75.13 (COH), 79.68 (COCH₂), 117.09 (COCH₂), 139.04 (COCH₂), 167.35 (C=N)</td>
<td>351 (0.3, M⁺⁺⁺), 249 (90, M⁺⁺⁺-H₂COCH₂), 170 (20), 110, (100, C₅H₅N⁻)</td>
<td></td>
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<tr>
<td>3c</td>
<td>3404, 3070, 2936, 2871, 2826, 1638, 1460, 1480, 1380, 1265, 1165, 1117, 1085, 1054, 912, 735</td>
<td>8.12, 8.75 (2 × CH₂CH₂), 14.46 (CH₃), 21.01, 21.67, 24.18, 24.28, 25.50, 26.73, 27.11, 27.46, 30.27 (9 × CH₃), 39.85 (COCH₂), 48.74 (COCH₂), 50.18 (OCH₃), 57.59 (CH₃N), 72.06 (CHN), 75.13 (COH), 79.69 (COCH₂), 116.68 (COCH₂), 139.45 (COCH₂), 167.33 (C=N)</td>
<td>263 (0.2, M⁺⁺⁺), 263 (100, M⁺⁺⁺-H₂COCH₂), 170 (22), 110, (100, C₅H₅N⁻)</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>3400, 3069, 2938, 2870, 2826, 1636, 1461, 1384, 1365, 1267, 1162, 1134, 1118, 1088, 1051, 914, 734</td>
<td>8.13, 8.76 (2 × CH₂CH₂), 18.82 (CH₃), 22.03 (CH₃), 24.11 (CH₃), 24.19, 24.29, 25.49, 25.64, 27.26, 27.47 (6 × CH₃), 27.64 (CH₃), 40.77 (COCH₂), 50.19 (OCH₃), 53.61 (COCH₂), 57.65 (CH₃N), 72.09 (CHN), 76.17 (COH), 79.68 (COCH₂), 118.18 (COCH₂), 135.86 (COH), 168.05 (C=N)</td>
<td>364 (0.2, M⁺⁺⁺), 263 (100, M⁺⁺⁺-H₂COCH₂), 170 (22), 110, (100, C₅H₅N⁻)</td>
<td></td>
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<tr>
<td>3e</td>
<td>3397, 3069, 2957, 2873, 2826, 1635, 1462, 1421, 1379, 1266, 1252, 1169, 1135, 1087, 1054, 1008, 976, 913, 784</td>
<td>8.12, 8.73 (2 × CH₂CH₂), 12.97 (CH₃), 13.07 (CH₃), 22.18, 23.94, 24.16, 24.45, 25.05, 25.61, 26.84, 27.46, 27.49 (C₂H₅), 170 (32), 110, (9 × CH₃), 40.93 (COCH₂), 42.51 (COCH₂), 49.17 (OCH₃), 50.20 (COCH₂), 58.03 (CH₃N), 72.23 (CHN), 76.49 (COH), 79.68 (COCH₂), 117.76 (COH), 136.80 (COH), 168.05 (C=N)</td>
<td>392 (0.1, M⁺⁺⁺), 291 (100, M⁺⁺⁺-H₂COCH₂), 170 (29), 110, (99, C₅H₅N⁻)</td>
<td></td>
</tr>
</tbody>
</table>

a Satisfactory microanalyses and/or HRMS obtained for 3a-g: C, N, H: ± 0.4 and/or ± 0.0005 amu.

b IR (CHCl₃).

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ing (E)-configured (C=N) α-hydroxyhydrazone 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-hydrazone ketones 4 were obtained in good yield (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 1H and 13C NMR spectroscopy. The enantiomeric excesses of the ketones 4 were determined by 1H NMR spectroscopy using the chiral co-solvent (−)-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 (12R,13S),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.

1H 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 dia stereomer is syn.

In contrast to the E_gZ configuration of the acyclic azaenolates,20 the azaenolates of the cyclic hydrazones

| Table 3. Spectroscopic Data for α-Hydrazone Ketones (R,S)-4 |
|---------------------------------------------|------------------|-----------------|-----------------|
| Product | IR (neat) v (cm⁻¹) | 1H NMR (CDCl₃/TMS) δ, J (Hz) | 13C NMR (CDCl₃/TMS) δ | MS (70 eV) mol% |
| 4a | 3480, 3074, 2941 | 0.83 (d, J = 6.7, 3H, CH₂) | 1.43 (m, 1H, COCHCH₃) | 1.65–1.80 (m, 3H, COHCH₂CH) | 2.13 (m, 1H, COCH₂) | 2.50 (m, 2H, COCH₂CH₃) | 2.74 (d, δ = J = 9.1/1.7, 1H, CH₂) | 5.15 (m, 2H, CH₂) | 8.15 (d, 1H, =CH) |
| 4b | 3481, 3073, 2960 | 0.83 (t, J = 7.4, 3H, CH₃) | 0.85–1.00 (m, 2H, CH₂) | 1.25–1.45 (m, 2H, CH₂) | 1.64–1.78 (m, 2H, COCH₂CH₃) | 1.75 (m, 1H, COCH₂CH₃) | 2.32–2.62 (m, 4H, =CHCH₂CH₂CH₃) | 3.94 (s, 1H, OH) | 5.13 (m, 1H, =CHH) |
| 4c | 3481, 3073, 3010 | 0.84 (t, J = 7.4, 3H, CH₃) | 1.00–1.60 (m, 2H, CH₂) | 1.25–1.45 (m, 2H, CH₂) | 1.64–1.78 (m, 2H, COCH₂CH₃) | 1.75 (m, 1H, COCH₂CH₃) | 2.32–2.62 (m, 4H, =CHCH₂CH₂CH₃) | 3.94 (s, 1H, OH) | 5.13 (m, 1H, =CHH) |
| 4d | 379, 3073, 2955 | 0.84 (d, J = 7.1, 3H, CH₃) | 0.88 (d, J = 6.7, 3H, CH₃) | 1.30 (m, 1H, COCH₂CH₃) | 1.48 (m, 1H, COCH₂CH₃) | 1.60–1.70 (m, 3H, CH₃) | 1.95–2.15 (m, 1H, COCH₂CH₃) | 2.15 (m, 1H, COCH₂CH₃) | 2.50 (m, 2H, COCH₂CH₃) |
| 4e | 3477, 3072, 2957 | 0.80 (t, J = 7.4, 3H, CH₃) | 0.87 (t, J = 7.4, 3H, CH₃) | 0.95–1.80 (m, 8H, CH₂) | 1.89–2.50 (m, 1H, COCH₂CH₃) | 2.15 (m, 1H, COCH₂CH₃) | 2.32–2.57 (m, 4H, CH₂COCH₂CH₃) | 3.94 (s, 1H, OH) | 5.11 (d, δ = J = 17.2/2.7, 1H, CH₂) |

**a** Satisfactory microanalyses and/or HRMS obtained for 4a–g: C, H: ± 0.4 and/or ± 0.0005 amu.

**b** IR (CHCl₃).
The racemic ketones 1 were prepared in a two-step sequence according to the literature procedure.25 BF₃·OEt₂ catalyzed coupling of cyclohexene oxide (20 mmol) with a large excess of (E)-allylic alcohol (100 mmol) in CH₂Cl₂ (100 mL) at 25°C and then Swern oxidation of the allyloxy alcohol intermediate.

The SAEP-hydrazone 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 azotropic water removal (Dean–Stark trap).

**β-Substituted γ,δ-Unsaturated Cyclic α-Hydroxy-SAEP-hydrazone 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. NH₄Cl (25 mL) and extracted several times with Et₂O. The combined organic phase was dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography (silica gel, pentane/Et₂O 2:1) afforded the rearranged hydrazones 3 as slightly yellow or colorless liquids (3a, e–e) or colorless crystals (3b).

3b (C₁₂H₁₆N₂O₃) crystallizes in orthorhombic space group P₂₁2₁2₁ (No. 19), a = 12.517 (1) Å, b = 12.7417 (8) Å, c = 13.7183 (6) Å, V = 2187.96 Å³, Z = 4, Mᵣ = 350.55, μₑμ = 1.064 cm⁻³. Enraf–Nonius-CAD4 diffractometer, graphite monochromator, CuKα radiation (λ = 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 > 2σ(I)), employed to refine 227 parameters. R = 0.079 (Rₑ = 0.057) α = σ⁻². Goodness of fit: 2.053. Residual electron density −0.60 to +0.43 eÅ⁻³.

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

The rearranged hydrazones 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 (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography (silica gel, pentane/Et₂O 2:1) afforded the α-hydroxy ketones 4 as slightly yellow or colorless liquids (4a, e–e) or colorless crystals (4b).

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3 have a ZₓEᵧCN 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.
Hiroi, K.; Abe, J. Heterocycles 1990, 283.