Asymmetric Synthesis of Pseudo C_2-Symmetric 2-Methyl Substituted 1,3-Diols

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Received 27 September 2001

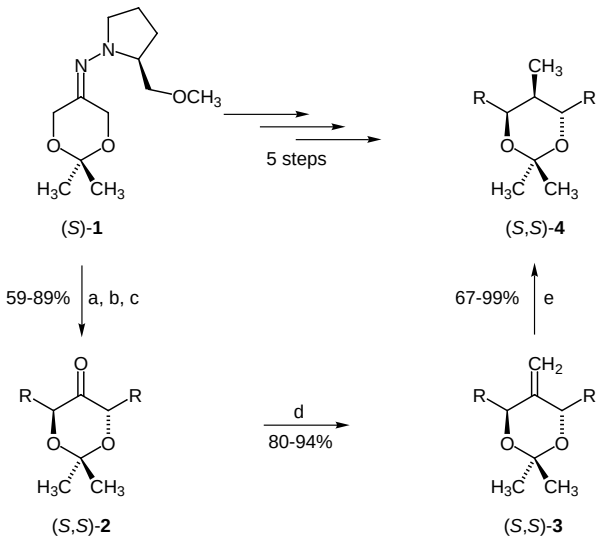
Abstract: The diastereo- and enantioselective synthesis of pseudo C_2-symmetric, 2-methyl substituted, acetonide protected (**4**) and free 1,3-diols **5** employing the SAMP-hydrazone mothodology with virtually complete asymmetric induction (de ≥ 96%, ee ≥ 98–99%) is reported. The efficient protocol involves the asymmetric α,α'-bis-alkylation of hydrazone **1**, the epimerization-free Wittig olefination of the resulting ketones **2** and subsequent hydrogenation of the *exo*-methylene derivatives **3** with $PtO_2 \cdot H_2O$ or Wilkinson's catalyst to afford the acetonide protected title compounds **4** in very good overall yields. Quantitative deprotection with trifluoroacetic acid to the free diols **5** is demonstrated.

Key words: asymmetric synthesis, diols, hydrogenation, Wittig reaction, hydrazones

Due to the large interest in polyene macrolides as challenging targets and pharmacologically interesting compounds, reliable methods for the stereoselective synthesis of C3 fragments consisting of alternating methyl and hydroxy groups are needed.[1] Pseudo C_2-symmetric, 2-methyl substituted 1,3-diols are potent precursors for desymmetrisation reactions and therefore key intermediates for the synthesis of the extended polypropionate units in macrolide antiobiotics.

A variety of different stereoselective approaches to this kind of substrates have been reported. Mostly aldol/reduction pathways[2a–e] are utilized, but there are also other routes as for example the aldol–Tishtchenko reaction,[2f–h] oxymercuration of cyclopropylcarbinols,[2i] photooxygenation of 1-methyl-2,3-diarylcyclopropanes followed by Pd/C-catalyzed hydrogenation[2j] or asymmetric hydrogenation of bisketones.[2k] Most of these methods either need expensive chiral catalysts or do not yield the desired products in high diastereo- and enantiomeric purity.

Herein, we present a general and very efficient route to diastereo- and enantiomerically pure pseudo C_2-symmetric, 2-methyl substituted 1,3-diols. As is depicted in Scheme 1, C_2-symmetric, α,α'-disubstituted ketones (*S*,*S*)-**2** were synthesized employing the SAMP/RAMP-hydrazone method[3] and starting from the SAMP-hydrazone (*S*)-**1** as a synthetic equivalent of dihydroxyacetone phosphate (α,α'-double d^2-synthon).[4] These dioxanones were converted to C_2-symmetric, methylenated, α,α'-disubstituted ketones (*S*,*S*)-**3** by an epimerization-free, high yielding Wittig reaction. Catalytic hydrogenation afforded 4,6-disubstituted 2,2,5-trimethyl-1,3-dioxanes (*S*,*S*)-**4** as the acetonide protected title compounds (Scheme 1).



Scheme 1 *Reagents and conditions*: a) *t*-BuLi, THF, –78 °C, 2 h; RX, –100 °C, 2 h, to r.t. over 15 h. b) *t*-BuLi, THF, –78 °C, 2 h; RX, –100 °C, 2 h, to r.t. over 15 h. c) Ozone, CH_2Cl_2, 15 min. d) $Ph_3P{=}CH_2$, THF, –78 °C to r.t. over 15 h. e) $PtO_2 \cdot H_2O$, H_2 (1 atm), EtOH, r.t., or $(Ph_3P)_3RhCl$, benzene, H_2 (1 atm), r.t.

As shown in Table 1 a variety of C_2-symmetric, α,α'-disubstituted ketones (*S*,*S*)-**2a–e** were synthesized in three steps[3c] starting from SAMP-hydrazone (*S*)-**1** in good overall yields (59–83%) and excellent diastereo- and

Table 1 Asymmetric Synthesis of 4,6-disubtituted 2,2-Dimethyl-1,3-dioxan-5-ones (*S*,*S*)-**2a–e**

2	R	X	Yield[a] (%)	de[b] (%)	ee (%)
(*S*,*S*)-**2a**	*n*-Pr	I	68	≥ 96	> 99[c]
(*S*,*S*)-**2b**	*i*-Pr	I	83	≥ 96	≥ 98[d]
(*S*,*S*)-**2c**	Bn	Br	68	≥ 96	≥ 98[d]
(*S*,*S*)-**2d**	*p*-*t*-BuBn	Br	59	≥ 96	n.d.
(*S*,*S*)-**2e**	$(CH_2)_2Ph$	I	64	≥ 96	> 99[e]

[a] Overall yield starting from (*S*)-**1**.
[b] Determined by ^{13}C NMR spectroscopy.
[c] Determined by gas chromatography on chiral stationary phase (CP chiralsil-dex CB; 0.25 mm × 25 m).
[d] For determination see ref.[3c].
[e] Determined by HPLC on chiral stationary phase (Daicel AD 2; 250 mm × 4.6 mm).

Synlett 2002, No. 1, 28 12 2001. Article Identifier:
1437-2096,E;2002,0,01,0029,0032,ftx,en;G20901ST.pdf.

ISSN 0936-5214

enantiomeric excesses (de ≥ 96%, ee ≥ 98–99%). None of the intermediates had to be purified. The enantiomeric excesses were determined by gas chromatography or HPLC on chiral stationary phases with reference to the corresponding racemic samples.[5]

With diastereo- and enantiomerically pure ketones (*S*,*S*)-**2** in hand, the conversion into methylenated, 4,6-disubstituted 2,2-dimethyl-1,3-dioxan-5-ones (*S*,*S*)-**3a**–**e** was accomplished in good to excellent yields (80–94%) utilizing Wittig olefination conditions.[6] Hence, six equivalents of methyltriphenylphosphonium bromide were converted to the Wittig ylid by deprotonation with *t*-butyllithium in dry THF at –78 °C. Because basic conditions can cause epimerization and racemisation of α-substituted carbonyl compounds, the reaction mixture was allowed to warm to room temperature for 30 minutes in order to decompose any excess of *t*-butyllithium by reaction with THF.[7] After cooling again to –78 °C the ketones (*S*,*S*)-**2** were added to give the desired exocyclic olefins (*S*,*S*)-**3** (Table 2).[8]

Table 2 Synthesis of 5-*exo*-Methylene, 4,6-Disubstituted 2,2-Dimethyl-1,3-dioxan-5-ones (*S*,*S*)-**3a**–**e**

3	R	Yield (%)	de[a] (%)	ee (%)
(*S*,*S*)-**3a**	*n*-Pr	92	≥ 96	> 99
(*S*,*S*)-**3b**	*i*-Pr	80	≥ 96	≥ 98
(*S*,*S*)-**3c**	Bn	90	≥ 96	≥ 98
(*S*,*S*)-**3d**	*p*-*t*-BuBn	92	≥ 96	n.d.
(*S*,*S*)-**3e**	$(CH_2)_2Ph$	94	≥ 96	> 99

[a] Determined by ^{13}C NMR spectroscopy.

Comparing the ^{13}C NMR chemical shifts of the two methyl carbons in the acetonid protection group with those given in literature did not show any evidence for epimerization.[9] However, attempts to carry out the methylenation using the Tebbe[10] or Petasis[11] reagent only proceeded in poor yields or incomplete conversion.

Furthermore, subsequent catalytic hydrogenation of the methylenated, dioxanones (*S*,*S*)-**3** using Wilkinson's[12] catalyst generated a new nonstereogenic and chirotopic carbon atom[13] and gave 4,6-disubstituted 2,2,5-trimethyl-1,3-dioxanes (*S*,*S*)-**4b**–**e** in good to excellent yields (87–99%). The reaction was carried out with 10 mol% of chlorotris(triphenylphosphine)rhodium(I) in dry benzene under hydrogen atmosphere (1 atm) at room temperature and was completed after 4 hours. Only the sterically hindered di-*i*-propyl substituted compound (*S*,*S*)-**3b** needed 30 mol% of catalyst and a longer reaction time of 12 hours for complete conversion. After removal of the solvent non of the products had to be purified. In all cases filtration of the crude reaction mixture through silica gel and florisil® was sufficient to obtain products in purities, which showed suitable spectroscopic data and correct elemental analyses.

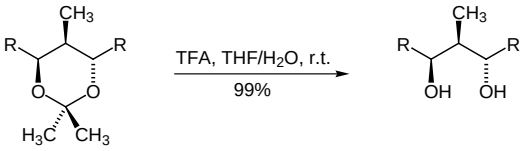
For aliphatic 4,6-disubtituted 5-*exo*-methylene derivatives such as (*S*,*S*)-**3a**, $PtO_2 \cdot H_2O$ catalyzed the hydrogenation under similar conditions[14] in a heterogeneous manner to give (*S*,*S*)-**4a** in 89% yield. However, aromatic substrates, such as (*S*,*S*)-**3e**, showed reduction of the phenyl residue as side reaction, which led to a lower yield (68% compared to 99% using Wilkinson's catalyst) (Table 3).[15]

Table 3 Synthesis of 4,6-Disubstituted 2,2,5-Trimethyl-1,3-dioxanes (*S*,*S*)-**4a**–**e**

4	R	Yield (%)	de[d] (%)	ee (%)
(*S*,*S*)-**4a**	*n*-Pr	89[a]	≥ 96	> 99
(*S*,*S*)-**4b**	*i*-Pr	87[b,c]	≥ 96	≥ 98
(*S*,*S*)-**4c**	Bn	98[b]	≥ 96	≥ 98
(*S*,*S*)-**4d**	*p*-*t*-BuBn	97[b]	≥ 96	n.d.
(*S*,*S*)-**4e**	$(CH_2)_2Ph$	68[a]; 99[b]	≥ 96	> 99

[a] $PtO_2 \cdot H_2O$ as catalyst.
[b] $(Ph_3P)_3RhCl$ as catalyst.
[c] 30 mol% catalyst and 12 h.
[d] Determined by ^{13}C NMR spectroscopy.

Finally, hydrolytic cleavage of the acetonide (*S*,*S*)-**4e** utilizing trifluoroacetic acid (TFA) in THF/water at room temperature afforded the deprotected, pseudo C_2-symmetric diol (*S*,*S*)-**5** in almost quantitative yield (99%) (Scheme 2).[16]



(*S*,*S*)-**4e** (*S*,*S*)-**5**

R = $(CH_2)_2Ph$

Scheme 2

In summary, we have developed a novel and efficient method for the asymmetric synthesis of pseudo C_2-symmetric, 2-methyl substituted 1,3-diols starting from commercially available 2,2-dimethyl-1,3-dioxan-5-one and employing the SAMP/RAMP-hydrazone method with virtually complete asymmetric induction.[17]

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG and the former Hoechst AG for the donation of chemicals.

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(5) Synthesis of 4,6-disubtituted 2,2-Dimethyl-1,3-dioxan-5-ones (*S*,*S*)-**2**: *t*-Butyllithium (11 mmol, 15% in pentane) was added dropwise to a solution of SAMP-hydrazone (*S*)-**1** (10 mmol) in anhyd THF (40 mL) at –78 °C. After stirring for 2 h the mixture was cooled to –100 °C and the electrophile (11 mmol; dissolved in 1 mL anhyd THF), was added slowly. After further stirring for 2 h the reaction mixture was allowed to warm to r.t. over 15 h. The mixture was quenched with pH 7-buffer solution (2 mL) and diluted with Et_2O(80 mL). The organic layer was washed with pH 7-buffer solution (10 mL) and brine (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting monoalkylated SAMP-hydrazone was alkylated again at the α'-position as described above. The obtained 4,6-disubtituted SAMP-hydrazone was dissolved in dichloromethane (50 mL) and flushed with ozone (60 Lh^{-1}) at –78 °C for 15 min. The reaction mixture was allowed to warm to r.t. and flushed with argon. After removal of the solvent under reduced pressure the crude products were purified by flash chromatography (SiO_2; pentane–Et_2O) to afford 4,6-disubtituted 2,2-dimethyl-1,3-dioxan-5-ones (*S*,*S*)-**2**.

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(8) Synthesis of the *exo*-Methylene Derivatives (*S*,*S*)-**3**: *t*-Butyllithium (26.4 mmol, 15% in *n*-pentane) was added dropwise to a suspension of methyltriphenylphosphonium bromide (26.4 mmol) in dry THF (125 mL) at –78 °C and stirring was continued for 15 min. Then the mixture was allowed to warm to r.t. over 30 min and cooled again to –78 °C. Ketone (*S*,*S*)-**3** (4.4 mmol; dissolved in 8 mL dry THF), was added and the reaction mixture was allowed to warm to r.t. over 15 h. The mixture was quenched with water (10 mL) and the aq layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude products were purified by flash chromatography (SiO_2; pentane–Et_2O) to afford the alkenes (*S*,*S*)-**3**.
Analytical data of compound (*S*,*S*)-**3e**: $[\alpha]_D^{24}$ = –94.6 (1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 6 H, C*H*$_3$), 1.83 (m, 2 H, C*H*HCO), 2.04 (m, 2 H, CH*H*CO), 2.65 (ddd, *J* = 13.9, 9.5, 7.1 Hz, 2 H, C*H*HPh), 2.86 (m, 2 H, CH*H*Ph), 4.26 (m, 2 H, C*H*O), 4.78 (t, *J* = 1.8 Hz, 2 H, C*H*$_2$C), 7.14–7.30 (m, 10 H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (*C*H$_3$), 31.4 (*C*H$_2$Ph), 34.3 (*C*H$_2$CO), 69.2 (*C*O), 100.4 (*C*CH$_3$), 103.9 (*C*H$_2$C), 125.8 (*p*CH), 128.3, 128.5 (*C*H, *m*CH), 142.1 (*C*Ph), 152.9 (*C*CH$_2$); MS (CI, methane) *m/z* = 337 [M^++1], 279, 278, 262, 261, 173, 133, 131, 117(100); IR ($CHCl_3$): 3085, 3061, 3026, 2986, 2953, 2933, 2860, 1944, 1870, 1803, 1745, 1652, 1604, 1584, 1544, 1496, 1455, 1432, 1411, 1378, 1323, 1281, 1226, 1183, 1159, 1115, 1087, 1057, 1031, 1000, 970, 957, 896, 865, 819, 802, 750, 700, 652, 622, 582, 518, 486 cm^{-1}; Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 81.97; H, 8.65.

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(15) Synthesis of 4,6-disubstituted 2,2,5-Trimethyl-1,3-dioxanes (*S*,*S*)-**4**: The methylenated 1,3-dioxan-5-ones (*S*,*S*)-**3** (0.5 mmol) and chlorotris(triphenylphosphine)rhodium(I) (10 mol%) were dissolved in anhyd benzene (10 mL) and vigorously stirred at r.t. under hydrogen atmosphere (1 atm) for 4 h. The solvent was removed under reduced pressure and the residue was filtered through silica gel, washed with pentane–Et_2O (10:1), filtered through florisil®, washed with pentane and dried in vacuo to give (*S*,*S*)-**4** as colorless oils.
Analytical data of compound (*S*,*S*)-**4e**: $[\alpha]_D^{24}$ = –2.8 (1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CH), 1.36 (d, *J* = 7.1 Hz, 6 H, C*H*$_3$C), 1.60 (m, 2 H, C*H*HCO), 1.79 (m, 3 H, CH*H*CO, C*H*CH$_3$), 2.56 (m, 2 H, C*H*HPh), 2.81 (m, 2 H, CH*H*Ph), 3.22 (dt, *J* = 8.2, 3.8 Hz, 1 H, C*H*O), 3.85 (m, 1 H, C*H*O), 7.15–7.29 (m, 10 H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7 (*C*H$_3$CH), 24.0 (*C*H$_3$C), 25.1 (*C*H$_3$C), 32.2, 32.3, 32.4, 36.2 (4 C, *C*H$_2$), 40.1 (*C*HCH$_3$), 68.4 (*C*HO), 74.0 (*C*HO), 100.5 (*C*CH$_3$), 125.5, 125.6 (2 C, *p*CH), 128.1, 128.1, 128.2 (4 C, CH, *m*CH), 142.0 (2 C, *C*Ph); MS (EI, 70 eV): *m/z* = 338 [M^+], 323, 146, 134, 131, 117, 104, 92, 91(100); IR ($CHCl_3$): 3513, 3085, 3062, 3026, 2985, 2936, 2875, 2674, 1943, 1870, 1804, 1746, 1713, 1622, 1604, 1585, 1496, 1455, 1432, 1380, 1361, 1279, 1227, 1192, 1161, 1130, 1062, 1038, 997, 961, 941, 910, 871, 800, 749, 700, 618, 573, 514, 480 cm^{-1}; Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.17; H, 9.00.

(16) Synthesis of (3*S*,5*S*)-4-Methyl-1,7-diphenylheptane-3,5-diol (*S*,*S*)-**5**: TFA (0.05 mL) was added to (*S*,*S*)-**4e** (0.3 mmol) in THF (2 mL) and water (1 mL). The mixture was stirred at r.t. until the reaction was completed (TLC control). Concd NH_3 (0.5 mL) and water (1.5 mL) were added and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2; pentane–Et_2O 1:1)

to give (*S*,*S*)-**5** (99%) as colorless solid.
Analytical data of compound (*S*,*S*)-**5**: Mp: 97 °C; $[\alpha]_D^{24}$ = –34.5 (1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.60–1.72 (m, 2 H, C*H*HCO), 1.77–1.90 (m, 3 H, CH*H*CO, C*H*CH_3), 2.63 (m, 2 H, C*H*HPh), 2.78–2.85 (m, 4 H, CH*H*Ph, O*H*), 3.67 (m, 1 H, C*H*OH), 3.98 (m, 1 H, C*H*OH), 7.16–7.30 (m, 10 H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6 (*C*H_3), 32.2, 32.7, 35.7, 37.3 (4 C, *C*H_2), 41.6 (*C*HCH_3), 72.2 (*C*HOH), 75.4 (*C*HOH), 125.7, 125.7 (*pC*H), 128.2, 128.2, 128.3 (4 C, CH, *mC*H), 141.8, 141.8 (*C*Ph); MS (CI, isobutane): *m/z* = 299(100) [M^+ +1], 281, 263; IR ($CHCl_3$): 3855, 3840, 3822, 3808, 3752, 3736, 3712, 3690, 3677, 3650, 3630, 3333, 3084, 3060, 3023, 2940, 2918, 2863, 2371, 2190, 1948, 1870, 1808, 1736, 1719, 1702, 1686, 1655, 1637, 1604, 1543, 1497, 1455, 1440, 1409, 1307, 1232, 1167, 1141, 1121, 1083, 1043, 1004, 949, 930, 907, 886, 810, 770, 731, 480, 466 cm^{-1}; Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.45; H, 9.06.

(17) All new compounds showed suitable spectroscopic data (NMR, MS, IR) and correct elemental analyses.