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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of γ-cyano silyl enol ethers

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Abstract

The selective oxidative cleavage of the SAMP-hydrazone moiety of 4-silyloxy-3-enal hydrazones **6**, leading to the corresponding 4-silyloxy-3-alkenenitriles **7**, is reported. A clean, good yielding transformation was observed when *m*-CPBA in CH_2Cl_2 was used as the oxidant, the presence of suspended solid $NaHCO_3$ being essential in preventing hydrolysis of the silyl enol ether moiety. Use of magnesium monoperoxyphthalate (MMPP) led to over-oxidated products, while hydrogen peroxide, in the presence of catalytic methyltrioxorhenium (MTO), was ineffective. Independent measurements of the enantiomeric excesses for compounds **7** demonstrated the absence of racemization during the process.

1. Introduction

Easily available functionalized building blocks, having a single stereogenic center, are highly demanded substrates often required for the synthesis of complex organic frameworks. In previous papers[1,2] we have reported on the synthesis of enantiomerically enriched 1,4-dicarbonyl compounds of this type by the Michael addition of formaldehyde SAMP-hydrazone **1** [SAMP=(*S*)-1-amino-2-(methoxymethyl)pyrrolidine], acting as a chiral d^1-synthon (umpolung)[3,4] to conjugated enones **2**. Deprotection of the hydrazone moiety of 1,4-adducts **3** led to a series of 4-oxoaldehydes **4** and 4-oxonitriles **5** (Scheme 1). Optimal results for this reaction required the presence of a slight excess of dimethylthexylsilyl (TDS) triflate as promoter. Therefore, the 1,4-addition of formaldehyde SAMP-hydrazone **1** led to dimethylthexylsilyl enol ethers **6** as primary adducts, which could also be isolated in good yields and with excellent diastereomeric excesses.

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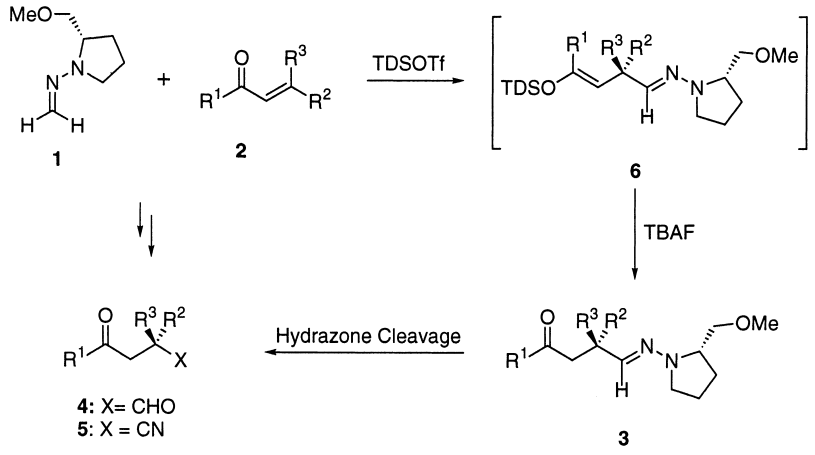
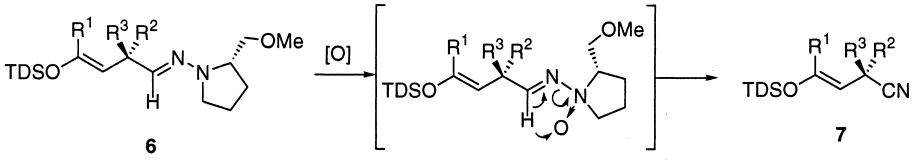


Scheme 1.

2. Results and discussion

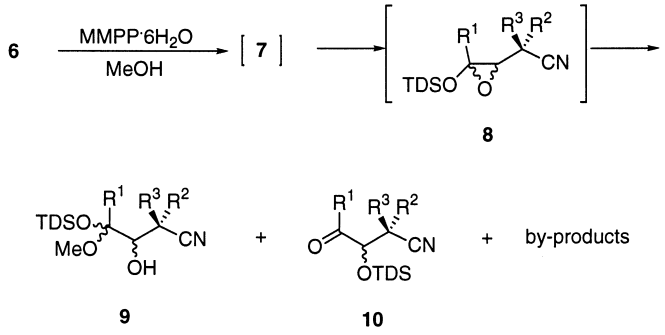
Considering the rich chemistry of silyl enol ethers, it is obvious that the survival of this moiety, after deprotection of the chiral auxiliary, offers interesting additional possibilities for this method. In this paper we wish to report on the selective oxidative cleavage of the hydrazone moiety in adducts **6** to afford interesting γ-cyano silyl enol ethers **7** in good yields and in enantiomerically enriched form (Scheme 2).



Scheme 2.

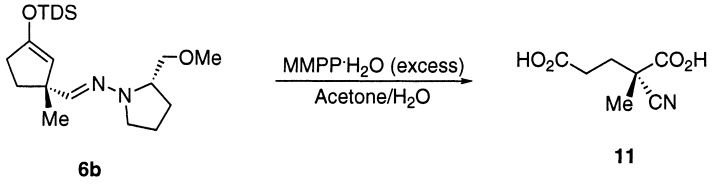
A survey of the literature reveals the existence of a number of methods for the transformation of *N*,*N*-dimethylhydrazones into nitriles, including methylation followed by elimination of the resulting *N*,*N*,*N*-trimethylhydrazonium salts,[5] direct elimination in hyperbasic media,[6] oxidative cleavage by dimethyldioxirane,[7] by hydrogen peroxide in the presence of catalytic 2-nitrobenzeneseleninic acid or other selenium compounds,[8,9] by *m*-CBPA,[10] and by magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$),[11] among others. In spite of this wide range of possibilities, almost no reports have appeared on the extension of these methods to the cleavage of more complicated systems, and in particular to the widely used SAMP derivatives. This is presumably due, in part, to the restrictions imposed to keep sensitive stereogenic centers untouched. Considering the successful use of MMPP·$6H_2O$[11] in this context, according to a number of reports,[1,2,12–21] first experiments for the desired **6** → **7** transformation were carried out using this reagent. Under these conditions, TLC monitoring indicated an initial transformation of the starting hydrazone **6** into products which were later identified as the corresponding nitriles **7**. These compounds, however, did not survive the reaction conditions and were further transformed into complex mixtures of products, in which the presence of compounds **9** and **10** could be detected (Scheme 3).

The formation of compounds **9** and **10** can be explained assuming an initial epoxidation of the enolic double bond of **7** to give an unstable silyloxy oxirane **8** which further suffered ring opening by methanol (→ **9**) or the Rubottom rearrangement[22] (→ **10**), respectively. Attempts to afford a clean 'one-pot'



Scheme 3.

synthesis of α-silyloxy-ɣ-cyanoketones **10** or the corresponding desilylated products were unsuccessful, as forcing conditions led to over-oxidated products. For instance, from the reaction of **6a** with excess MMPP in wet acetone as the solvent, the corresponding dicarboxylic acid **11** was isolated in low yield (Scheme 4).



Scheme 4.

Hydrogen peroxide in the presence of methyltrioxorhenium (MTO) was also investigated as a reagent, as this system has very recently been reported to accomplish both the oxidative cleavage of *N*,*N*-dimethylhydrazones to nitriles[23,24] and the oxidation of trimethylsilyl enol ethers to α-hydroxyketones.[25] Following the prodecure described, however, the unreacted starting material **6** was recovered unaltered after several hours. The lack of reactivity observed for SAMP-hydrazones with respect to the *N*,*N*-dimethyl analogs can be rationalized considering the higher steric hindrance around the nitrogen atom, on one hand, and the stronger aza-enamine character of the pyrrolidine-containing hydrazone system, which makes the amino nitrogen a poorer nucleophile, on the other. Additionally, it can also be concluded that the hindered TDSO-substituted carbon–carbon double bond is much more resistant to this reagent than the TMSO-analogs and also remains untouched under these conditions.

Finally, the desired selective cleavage of the hydrazone moiety of **6** was accomplished by means of *m*-CPBA in the presence of a small amount of suspended solid $NaHCO_3$, which was necessary in order to prevent partial cleavage of the silyl enol ether by the acid.[‡] The results for the synthesis of compounds **7a**–**e** under these conditions are collected in Table 1. A complete, clean transformation was observed in all cases. The somewhat lower isolated yields observed for **7a** and **7c** can be explained by assuming a partial co-evaporation of the product after chromatographic purification. In order to support this hypothesis, transformations **6a** → **7a** and **6c** → **7c** were carried out using $CDCl_3$ as the solvent. After TLC indicated consumption of the starting material, the ^{1}H NMR spectrum of the mixture was recorded, indicating a practically quantitative conversion into the products.

The absence of racemization during the synthesis of compounds **7** was confirmed through the transformation of the tertiary derivatives **7a**,**c**,**e** into their corresponding deprotected 4-oxonitriles **5a**,**c**,**e** by tetrabutylammonium fluoride in the presence of AcOH. The enantiomeric excesses of the latter were

‡ Compounds **3** were chromatographically detected at early stages of the reaction in the absence of $NaHCO_3$.

Table 1
Synthesis of 4-silyloxy-3-alkenenitriles **7a–e**

starting hydrazone	R^1	R^2	R^3	product **7**	time (h)	yield (%)	ee (%)	$[\alpha]^{RT}_D$ (c 1, $CHCl_3$)
(*R*)-**6a**	-$(CH_2)_2$-		H	(*R*)-**7a**	5.5	63	93[a]	+32.2
(*R*)-**6b**	-$(CH_2)_2$-		Me	(*R*)-**7b**	2.5	84	≥98[b]	+23.5
(*S*)-**6c**	-$(CH_2)_2CMe_2$-		H	(*S*)-**7c**	0.6	56	94[a]	+47.8
(*R*)-**6d**	-$(CH_2)_3$-		Me	(*R*)-**7d**	3.5	89	85[b]	+57.4
(*R*)-**6e**	Ph	Ph	H	(*R*)-**7e**	4	84	97[a]	-46.5

a) Estimated indirectly after conversion into the corresponding 4-oxonitriles **5** (see text).

b) Given as de of the corresponding parent hydrazones **6**.

determined as diastereomeric excesses of the corresponding (2*R*,3*R*)-2,3-butanediol-derived ketals (for **5a** and **5e**) or by ^{1}H NMR analysis using europium tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorate [Eu(hfc)$_3$] as the chiral lanthanide shift reagent (for **5e**), as described previously.[1,2] For quaternary compounds **7b** and **7d**, racemization is unlikely to occur and, therefore, their enantiomeric excesses are given as diastereomeric excesses of the parent hydrazones **6b** and **6d**.

In summary, interesting bifunctional building blocks, as are the title compounds, can be obtained in high enantiomeric purity through a simple two-step pathway starting from conjugated enones and formaldehyde SAMP-hydrazone. It should be stressed that some of the synthesized compounds possess all-carbon, quaternary stereogenic centers which are often demanded for the synthesis of a variety of natural products.

3. Experimental

3.1. General experimental data

Melting points were determined using a metal block and are uncorrected. Optical rotations were measured at room temperature. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ with either TMS (0.00

ppm ^{1}H, 0.00 ppm ^{13}C) or $CDCl_3$ (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as an internal reference. FT-IR spectra were recorded for KBr pellets or films. EI mass spectra were obtained at 70 eV, using an ionizing current of 100 μA, an accelerating voltage of 4 kV, and a resolution of 1000 or 10 000 (10% valley definition). The light petroleum ether (PE) used had a boiling range of 40–65°C. Elemental analyses were carried out at the Instituto de Investigaciones Químicas (CSIC-USe) (Seville, Spain).

3.2. Synthesis of 4-dimethylthexylsilyloxy-3-alkenenitriles **7a–e**

3.2.1. General procedure

To a solution of 4-silyloxy-3-enal SAMP-hydrazone **6a–e** (1 mmol) in CH_2Cl_2 (16 mL) was added $NaHCO_3$ (s, 0.5 g) and *m*-CPBA (345 mg, 1.1 mmol). The reaction was monitored by TLC until total consumption of the starting material. The excess of *m*-CPBA was destroyed with saturated Na_2SO_3 solution (a few drops) and the reaction mixture was washed with saturated $NaHCO_3$ solution (2×10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated, and the resulting residue was purified by flash chromatography. Starting hydrazone, chromatography eluants, yields, and spectral and analytical data for compounds **7** are as follows.

3.2.2. (R)-3-[(Dimethylthexylsilyl)oxy]-2-cyclopentenecarbonitrile **7a**

From **6a**, flash chromatography (1:30, Et_2O:PE) afforded 158 mg (63%) of **7a** as an oil: $[\alpha]_D^{RT}$ +32.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.21 (s, 3H), 0.87–0.89 (m, 12H), 1.64 (m, 1H, *J*=6.9 Hz), 2.10–2.20 (m, 1H), 2.22–2.35 (m, 2H), 2.38–2.50 (m, 1H), 3.49–3.57 (m, 1H), 4.56 (q, 1H, *J*=1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.9, 18.3, 19.8, 24.8, 26.3, 31.2, 32.4, 33.8, 97.2, 122.4, 159.2; IR (film, cm^{-1}) 2234, 1641; mass spectrum *m/z* (rel. intensity) 251 M^+ (7%), 182 (3), 167 (38), 139 (100), 114 (22), 73 (18); *m/z* calcd for $C_{14}H_{25}NOSi$: 251.1705; found: 251.1693.

3.2.3. (R)-3-[(Dimethylthexylsilyl)oxy]-1-methyl-2-cyclopentenecarbonitrile **7b**

From **6b**, flash chromatography (1:45, Et_2O:PE) afforded 223 mg (84%) of **7b** as an oil: $[\alpha]_D^{RT}$ +23.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 3H), 0.22 (s, 3H), 0.8–0.9 (m, 12H), 1.43 (s, 3H), 1.64 (m, 1H, *J*=6.9 Hz), 1.8–2.5 (m, 4H), 4.59 (q, 1H, *J*=1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.9, 18.3, 19.9, 24.9, 26.9, 32.5, 33.9, 35.3, 39.9, 104.7, 125.0, 158.2; IR (film, cm^{-1}) 2232, 1643; mass spectrum *m/z* (rel. intensity) 265 M^+ (7), 232 (18), 207 (12), 181 (50), 166 (8), 153 (100); *m/z* calcd for $C_{15}H_{27}NOSi$: 265.1862; found: 265.1862.

3.2.4. (S)-6,6-Dimethyl-3-[(dimethylthexylsilyl)oxy]-2-cyclohexenecarbonitrile **7c**

From **6c**, flash chromatography (1:8, Et_2O:PE) afforded 164 mg (56%) of **7c** as an oil: $[\alpha]_D^{RT}$ +47.8 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.87 (s, 6H), 0.89 (d, 6H, *J*=6.9 Hz), 1.40–1.50 (m, 1H), 1.60–1.70 (m, 2H), 1.95–2.15 (m, 2H), 3.04 (dt, 1H, *J*=3.4, 1.9 Hz), 4.71 (dt, 1H, *J*=1.9, 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.5, −2.6, 18.4, 19.9, 24.2, 24.7, 27.0, 27.1, 31.2, 33.9, 33.9, 38.8, 98.0, 120.5, 153.2; IR (film, cm^{-1}) 2234, 1667; mass spectrum *m/z* (rel. intensity) 293 M^+ (4), 267 (1), 209 (96), 208 (80), 194 (22), 181 (100), 153 (33); *m/z* calcd for $C_{17}H_{31}NOSi$: 293.2175; found: 293.2172.

3.2.5. (R)-3-[(Dimethylthexylsilyl)oxy]-1-methyl-2-cyclohexenecarbonitrile **7d**

From **6d**, flash chromatography (1:8, Et_2O:PE) afforded 249 mg (89%) of **7d** as an oil; $[\alpha]_D^{RT}$ +57.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.19 (s, 3H), 0.86 (s, 6H), 0.88 (d, 6H, *J*=6.9 Hz), 1.36–1.43 (m, 1H), 1.39 (s, 3H), 1.64 (m, 1H, *J*=6.9 Hz), 1.79–1.93 (m, 2H), 2.01–2.07 (m, 2H), 4.71 (dd, 1H, *J*=2.4, 1.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.5, −2.6, 18.4, 19.9, 19.9, 24.8, 27.7,

29.2, 33.2, 33.9, 34.7, 105.9, 124.6, 154.2; IR (film, cm^{-1}) 2228, 1660; mass spectrum *m/z* (rel. intensity) 279 M^+ (2), 252 (7), 195 (96), 194 (90), 180 (14), 168 (51), 167 (100). Anal. calcd for $C_{16}H_{29}NOSi$: C, 68.75; H, 10.46; found: C, 68.99; H, 10.82.

*3.2.6. (*R*)-3-[(Dimethylthexylsilyl)oxy]-2,4-diphenyl-3-butenenitrile **7e***

From **6e**, flash chromatography (1:8, Et_2O:PE) afforded 317 mg (84%) of **7e** as an oil; $[\alpha]_D^{RT}$ −46.5 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.0 (s, 3H), 0.25 (s, 3H), 1.06–1.10 (m, 12H), 1.86 (m, 1H, *J*=6.9 Hz), 5.25–5.27 (m, 2H), 7.40–7.57 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.8, −2.2, 20.1, 20.2, 25.2, 33.1, 33.8, 105.8, 119.7, 126.6, 126.9, 127.8, 128.1, 128.8, 128.9, 153.1; IR (film, cm^{-1}) 2239, 1643; mass spectrum *m/z* (rel. intensity) 362 M^+ (7), 292 (100), 265 (22), 232 (5), 191 (20), 117 (5). Anal. calcd for $C_{24}H_{31}NOSi$: C, 76.34; H, 8.27; N, 3.71; found: C, 76.30; H, 8.29; N, 3.68.

*3.3. Synthesis of 4-oxonitriles **5***

3.3.1. General procedure

To a stirred, cooled (0°C) solution of γ-cyano silyl enol ethers **7** (1 mmol) in dry THF (10 mL) was added AcOH (1.1 mmol) and tetrabutylammonium fluoride (1 M in THF, 1.1 mL, 1.1 mmol). The mixture was then diluted with Et_2O (20 mL) and washed with saturated NH_4Cl solution (2×10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the resulting residue was purified by flash chromatography (Et_2O–PE) to afford pure compounds **5**. Spectral and analytical data were in full agreement with those previously reported.[1] Starting compound **7**, chromatography solvents, and yields are as follows.

*3.3.2. (*R*)-3-Oxocyclopentanecarbonitrile **5a***

From **7a**, flash chromatography (1:1, Et_2O:PE) gave 100 mg (92%) of **5a** as an oil: $[\alpha]_D^{RT}$ +37.0 (*c* 1, $CHCl_3$) [lit.[1] $[\alpha]_D^{21}$ +35.3 (*c* 1, $CHCl_3$)].

*3.3.3. (*S*)-2,2-Dimethyl-5-oxocyclohexanecarbonitrile **5c***

From **7c**, flash chromatography (1:6, Et_2O:PE) gave 149 mg (99%) of crystalline **5c**: mp 63–64°C; $[\alpha]_D^{RT}$ −13.0 (*c* 1, $CHCl_3$) [lit.[1] $[\alpha]_D^{21}$ −11.8 (*c* 1, $CHCl_3$)].

*3.3.4. (*R*)-4-Oxo-2,4-diphenylbutanenitrile **5e***

From **7e**, flash chromatography (1:20, Et_2O:PE) gave 214 mg (91%) of crystalline **5e**: mp 64–65°C; $[\alpha]_D^{RT}$ +15.7 (*c* 1, $CHCl_3$) [lit.[1] $[\alpha]_D^{21}$ +16.2 (*c* 1, $CHCl_3$)].

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