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Addition of dienolates to sulfinimines. Stereoselective synthesis of dihydropyridones

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Abstract—The vinylogous Mannich reaction of sulfinimines with dienolates was investigated. Lithium and trimethylsilyl enolates of ethyl 3-ethoxycrotonate reacted with enantiopure 10-isobornylsulfinimines to give derivatives of δ-aminoacids which were cyclised to 6-aryl substituted derivatives of 2(1*H*)-pyridinones. 6-Aryl substituted 2,4-piperidinediones with either (*S*) or (*R*) configuration were analogously obtained using lithium and TMS enolates of 2,2,6-trimethyl-1,3-dioxin-4-one.

1. Introduction

Derivatives of piperidine are widely spread in nature, mainly as alkaloids and insect defence substances.[1] Most of them show pronounced biological activity and are important for the pharmaceutical industry. This is why the stereoselective synthesis of such compounds is of great interest. Dihydropyridones are valuable starting materials for the synthesis of natural piperidine derivatives.[2] One of the ways to obtain 2(1*H*)-pyridinones is the cycloaddition reaction of Brassard's diene to imines. Several chiral auxiliaries have been used to achieve good enantioselectivity of this reaction. Midland and coworkers used derivatives of α-alkoxy imines which were prepared in several steps from natural aminoacids.[3] The ee of the cycloadduct with Brassard's diene strongly depended on the Lewis acid used and varied from 66% to greater than 98%. Waldman et al. applied imines obtained from aldehydes and valine *tert*-butyl esters.[4] Appropriate dihydropyridones were obtained with excellent stereoselectivities. However, the removal of the chiral auxiliary was not straightforward and was achieved in five steps.

Chiral, non racemic sulfinimines have become important starting materials for the synthesis of several derivatives of amines, aminoacids, aminophosphonic acids, and nitrogen heterocycles.[5] Several optically active sulfinyl group have been prepared for this purpose of which the most useful are *p*-toluenesulfinyl[6] and *t*-butanesulfinyl.[7] In this paper we describe the use of optically active sulfinimines in the reaction with silylated dienes as well as with lithium dienolates leading to enantiomerically enriched dihydropyridones and 2,4-piperidinediones. The chiral auxiliary is derived from 10-isobornylsulfinate which may be recycled without loss of optical activity.[8]

2. Results and discussion

All sulfinimines were prepared from appropriate 10-isobornylsulfinamides and aldehydes according to the published procedure.[8]

The reaction of sulfinimines **1a**–**d** with Brassard's diene **2** gave in the presence of Lewis acid dihydropyridones **3a**–**d** (Scheme 1). Several Lewis acids were tested, however, the most efficient was $BF_3{\cdot}Et_2O$. The progress of the reaction was slow and usually 2–3 days were necessary to obtain reasonable yields of the product. The enantioselectivity observed was modest (Table 1). The presence of an acyclic intermediate in the reaction mixture suggests that the mechanism of dihydropyridone formation is stepwise.

The configuration of the products was determined by conversion of the dihydropyridone **3a** into known piperidone **6** (Scheme 2).[9] Thus, **3a** was hydrolysed to piperidinedione **4a** in hydrochloric acid and reacted with ethanedithiol to give thioketal **5**. The reduction with Raney nickel gave piperidinone **6** which had an opposite optical rotation compared to known (*R*)-(+) enantiomer of **6**. We assumed that the (*S*) configuration at C-6 found in **3a** is the same in the other 6-aryl substituted derivatives **3**.

We next turned our attention to the other *O*-silyl dienolate i.e. 2,2-dimethyl-4-methylene-6-trimethylsilyloxy-4*H*-1,3-dioxine **10** which can be easily obtained from ketene acetone adduct **12**.[10] The reaction with sulfinimines was carried out in dichloromethane at −70°C and usually only 3–4 h were necessary to complete the reaction. The addition of dienolate **10** to sulfinimines was preferably promoted by

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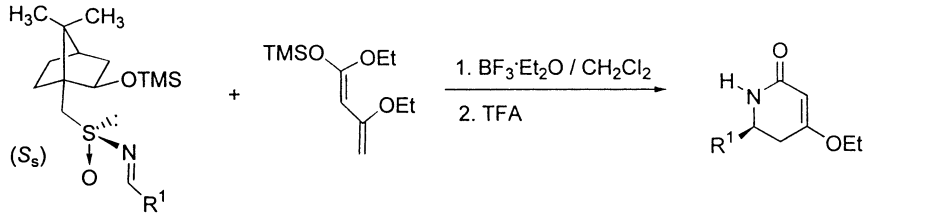

1a R^1 = Ph
1b R^1 = 3'-ClC_6H_4
1c R^1 = 3'-$NO_2C_6H_4$
1d R^1 = 4'-$MeOC_6H_4$

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3a R^1 = Ph
3b R^1 = 3'-ClC_6H_4
3c R^1 = 3'-$NO_2C_6H_4$
3d R^1 = 4'-$MeOC_6H_4$

Scheme 1.

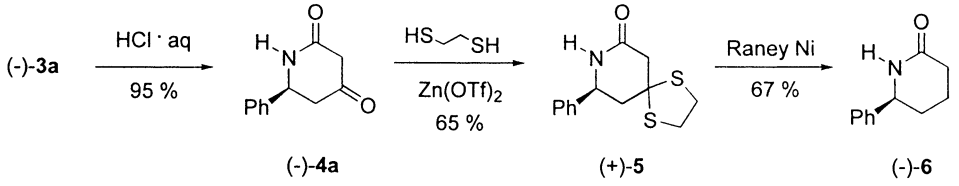
Table 1. Addition of Brassard's diene to sulfinimines **1**

Entry	R^1	Lewis acid	Product	Yield (%)	ee (%)[a]
1	Ph	$EtAlCl_2$	(−)-**3a**[b]	35	58
2	Ph	$BF_3{\cdot}Et_2O$	(−)-**3a**	80	42
3	3′-ClC_6H_4	$BF_3{\cdot}Et_2O$	(−)-**3b**	73	54
4	3′-$NO_2C_6H_4$	$BF_3{\cdot}Et_2O$	(−)-**3c**	61	63
5	4′-$MeOC_6H_4$	$BF_3{\cdot}Et_2O$	(−)-**3d**	27	33

Reaction was carried out in CH_2Cl_2 at rt for 2 days.
[a] The enantiomeric excess of the product was determined by ^1H NMR; see Section 3 for details.
[b] Major enantiomer has (*S*) configuration at C-6 (vide infra).

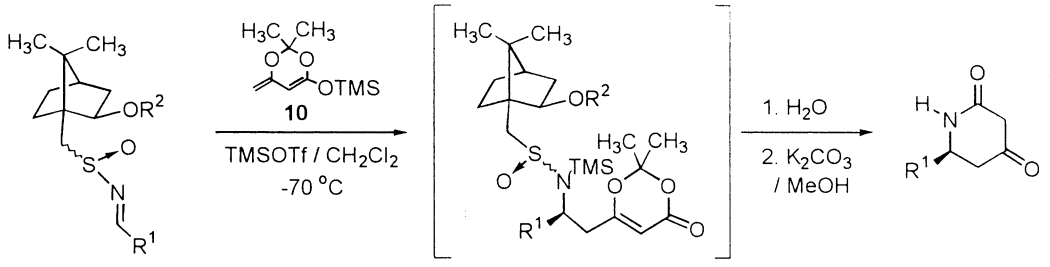
TMSOTf (1.3 equiv.). The reaction mixture contained sulfinamide which was hydrolysed during aqueous workup and subsequently cyclised to 2,4-piperidinedione **4** in MeOH–K_2CO_3 mixture (Scheme 3). 2,4-Piperidinediones can be easily converted to appropriate 4-ethoxy dihydropyridones **3** in anhydrous ethanol solution in the presence of acids. The product possessed the same configuration at the C-6 carbon atom as in the case of the reaction with Brassard's diene. However, the enantiomeric excess for the same substrates **1a**,**b** was much higher (Table 2). The use of the 2-hydroxy substituted derivative of sulfinimine **1b** resulted in a decrease of the ee from 86 to 65% (entry 4) showing that presence of a bulky trimethylsilyl group has an important influence on the stereoselectivity. However, the configuration at the sulfur atom plays a crucial role. The use of (R_S) diastereoisomer of sulfinimine resulted in almost complete lack of enantioselectivity (entry 3 and 5). Zinc triflate did not catalyse the reaction. The use of $Zn(OTf)_2$ followed by addition of TMSOTf gave the product with only 15% ee (entry 6).

It was of great interest to compare the reactivity of trimethylsilyl derivatives with lithium dienolates. The dienolate obtained by deprotonation of ethyl 3-ethoxy crotonate with LDA in THF reacted with sulfinimine at



(-)-**4a** (+)-**5** (-)-**6**

Scheme 2.



(S_S)-**1a** R^1 = Ph, R^2 = TMS
(S_S)-**1b** R^1 = 3'-ClC_6H_4, R^2 = TMS
(S_S)-**1e** R^1 = 2-Furyl, R^2 = TMS
(R_S)-**7** R^1 = 3'-ClC_6H_4, R^2 = TMS
(S_S)-**8** R^1 = 3'-ClC_6H_4, R^2 = H
(R_S)-**9** R^1 = 3'-ClC_6H_4, R^2 = H

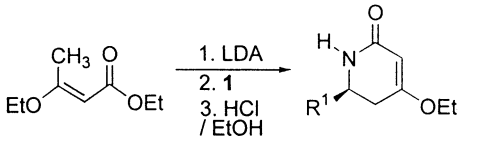
4a R^1 = Ph
4b R^1 = 3'-ClC_6H_4
4e R^1 = 2-Furyl

Scheme 3.

Table 2. Addition of silyl dienolate **10** to sulfinimines promoted by TMSOTf

Entry	R^1	R^2	Sulfinimine	Product	Yield (%)	ee (%)[a]
1	Ph	TMS	(S_S)-**1a**	(−)-**4a**	84	74
2	3′-ClC_6H_4	TMS	(S_S)-**1b**	(−)-**4b**	96	86
3	3′-ClC_6H_4	TMS	(R_S)-**7**	(−)-**4b**	76	3
4	3′-ClC_6H_4	H	(S_S)-**8**	(−)-**4b**	92	65
5	3′-ClC_6H_4	H	(R_S)-**9**	(+)-**4b**	85	13
6[b]	3′-ClC_6H_4	H	(R_S)-**9**	(+)-**4b**	57	15
7	2-Furyl	TMS	(S_S)-**1e**	(+)-**4e**	45	89

Reaction was carried out in CH_2Cl_2 at −70°C for 3 h.
[a] The enantiomeric excess of the product was determined by ^1H NMR; see Section 3 for details.
[b] The additive (1 mol equiv.) of $Zn(OTf)_2$ was used.



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3a R^1= Ph
3b R^1= 3′-ClC_6H_4
3c R^1= 3′-$NO_2C_6H_4$
3e R^1= Furyl

Scheme 4.

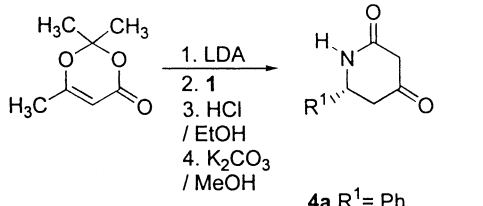
Table 3. Addition of lithium 1,3-diethoxy-1,3-butadienoate to sulfinimines

Entry	Sulfinimine	Product	Yield (%)	ee (%)[a]
1	(S_S)-**1a**	(−)-**3a**	72	85
2	(S_S)-**1b**	(−)-**3b**	60	92
3	(S_S)-**1c**	(−)-**3c**	30	87
4	(S_S)-**1e**	(+)-**3e**	30	88

Reaction was carried out in THF at −30°C.
[a] The enantiomeric excess of the product was determined by ^1H NMR; see Section 3 for details.

−30°C to give sulfinamides which were *N*-deprotected and cyclised to dihydropyridones in ethanolic HCl solution (Scheme 4). The major enantiomer of the product possessed the (*S*) configuration at C-6. The enantiomeric excess was greater than 85% (Table 3). Lowering the temperature below −50°C resulted in formation of the α-coupling product.

Similar results were obtained using the lithium dienolate of dioxinone **12** (Scheme 5). The reaction was carried out at



12

4a R^1= Ph
4b R^1= 3′-ClC_6H_4
4e R^1= Furyl

Scheme 5.

Table 4. Addition of lithium dienolate of **12** to sulfinimines

Entry	Sulfinimine	Product	Yield (%)	ee (%)[a]
1	(S_S)-**1a**	(+)-**4a**	41	87
2	(S_S)-**1b**	(+)-**4b**	23	75
3	(S_S)-**1e**	(−)-**4e**	41	91

Reaction temperature was −30°C except for entry 2 which was −70°C.
[a] The enantiomeric excess of the product was determined by ^1H NMR; see Section 3 for details.

−30°C and only the γ-coupling product was observed in the reaction mixture. It was converted to 2,4-piperidinedione in a standard way. The ee of the product was similar to or higher than that obtained with silyl dienolate **10** (Table 4). However, the product possessed the opposite configuration at C-6.

Simple lithium and silyl enolates having the same geometry give addition products to sulfinimines with opposite stereochemistry.[8] The reactions of dienolates of dioxinone **12** follow this rule. The same configuration of the dihydropyridone in the case of Brassard's diene and lithium 1,3-diethoxy-1,3-butadienoate may result from the different stereochemistry of the enolate.

The results presented here show that the vinylogous Mannich reaction of sulfinimines serves as a useful method for the preparation of 6-substituted enantiomerically enriched dihydropyridones. The best results (up to 92% ee) were obtained using the lithium enolate of 3-ethoxy crotonate. The use of silyloxy or lithium derivatives of ketene acetone adduct resulted in obtaining products with either (*S*) or (*R*) configuration at C-6 and similar ee (up to 91%).

3. Experimental

3.1. General

NMR spectra were recorded at 500 or 200 MHz (^1H). All spectra were referenced to residual solvent peak (chloroform 7.26 and 77.0 ppm for ^1H and ^{13}C, respectively). THF was distilled from sodium in the presence of sodium benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. Brassard's diene[11] and 2,2-dimethyl-4-methylene-6-trimethylsilyloxy-4*H*-1,3-dioxine[10] were prepared according to standard procedure. Sulfinimines **1a**,**d** were synthesised as described.[8] Sulfinimines **1b**,**c**,**e** and **7**–**9** were obtained by condensation of appropriate sulfinamide[8,12] with aldehydes using $Ti(OEt)_4$ at rt.[13] Melting points were not corrected. The enantiomeric excess of the products was determined by integration of the H-6 or the NH resonances in ^1H NMR (500 MHz) spectra using (*S*) or (*R*)-*t*-butylphenylphosphinothioic acid[14] as chiral solvating agent.

3.1.1. (1*S*,2*R*,4*R*,S_S)-7,7-Dimethyl-*N*-(3-chlorophenylmethylene)-2-trimethylsilyloxybicyclo[2.2.1]heptane-1-methanesulfinamide (1b). Yield 88%, colourless crystals, mp 73–77°C. $[\alpha]_D^{20}$=−80.5 (*c*=1.09, $CHCl_3$). IR (KBr) 1601, 1088 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.12 (s, 9H), 0.81 (s, 3H), 1.07 (s, 3H), 1.1–1.25 (m, 1H), 1.35 (m, 1H), 1.65–

1.9 (m, 5H), 2.25 (d, J=12.9 Hz, 1H), 3.61 (d, J=12.9 Hz, 1H), 4.09 (dd, J=4.0, 6.7 Hz, 1H), 7.35–7.50 (m, 2H), 7.69 (dt, J=1.6, 7.1 Hz, 1H), 7.89 (t, J=1.6 Hz, 1H), 8.56 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 0.3, 20.1, 20.5, 27.4, 30.8, 42.1, 44.9, 48.9, 50.3, 57.3, 77.0, 127.8, 128.7, 130.1, 132.1, 135.0, 135.6, 159.7. HR LSIMS calcd for $C_{20}H_{31}{}^{35}ClNO_2SSi$ $(M+H)^+$: 412.1533. Found: 412.1554.

3.1.2. (1*S*,2*R*,4*R*,S_S)-7,7-Dimethyl-*N*-(3-nitrophenylmethylene)-2-trimethylsilyloxybicyclo[2.2.1]heptane-1-methanesulfinamide (1c). Yield 86%, colourless crystals, mp 92–93°C. $[\alpha]_D{}^{25}=-94.6$ (c=0.76, $CHCl_3$). IR (KBr) 1089, 1530, 1348, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 9H), 0.81 (s, 3H), 1.08 (s, 3H), 1.1–1.25 (m, 1H), 1.4–1.6 (m, 1H), 1.65–1.9 (m, 5H), 2.27 (d, J=12.9 Hz, 1H), 3.65 (d, J=12.9 Hz, 1H), 4.09 (dd, J=6.6, 3.8 Hz, 1H), 7.68 (dd, J=7.7, 8.2 Hz, 1H), 8.15 (dt, J=7.7, 1.3 Hz, 1H), 8.35 (ddd, J=8.2, 2.3, 1.1 Hz, 1H), 8.69 (s, 1H), 8.73 (dd, J=2.3, 1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 0.3, 20.1, 20.4, 27.4, 30.8, 42.1, 44.8, 48.9, 50.3, 57.4, 77.0, 123.6, 126.4, 130.0, 134.9, 135.4, 148.6, 158.8. Anal. calcd for $C_{20}H_{30}N_2O_4SSi$: C, 56.84; H, 7.15; N, 6.63. Found: C, 56.87; H, 7.21; N, 6.67.

3.1.3. (1*S*,2*R*,4*R*,S_S)-7,7-Dimethyl-*N*-(2-furylmethylene)-2-trimethylsilyloxybicyclo[2.2.1]heptane-1-methanesulfinamide (1e). Yield 90%, oil, $[\alpha]_D{}^{20}=-82.5$ (c=1.32, $CHCl_3$). IR (neat) 1090, 1614 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 9H), 0.77 (s, 3H), 1.03 (s, 3H), 1.0–1.1 (m, 1H), 1.4–1.8 (m, 6H), 2.22 (d, J=12.8 Hz, 1H), 3.57 (d, J=12.8 Hz, 1H), 4.07 (dd, J=4.0, 6.7 Hz, 1H), 6.53 (dd, J=1.8, 3.5 Hz, 1H), 6.97 (d, J=3.5 Hz, 1H), 7.62 (d, J=1.8 Hz, 1H), 8.40 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 0.2, 20.1, 20.4, 27.4, 30.8, 42.2, 44.7, 48.9, 50.3, 57.3, 76.8, 112.4, 118.7, 146.6, 148.2, 150.5. Anal. calcd for $C_{18}H_{29}NO_3SSi$: C, 58.82; H, 7.95; N, 3.81. Found: C, 58.59; H, 7.91; N, 3.75.

3.2. General procedure for addition of Brassard's diene to sulfinimines

To the solution of sulfinimine **1** (0.53 mmol) in CH_2Cl_2 (4 mL) was added dropwise boron trifluoride etherate (100 mg, 0.71 mmol) at −50°C. The mixture was stirred for 10 min and the solution of Brassard's diene (227 mg, 1.0 mmol) in CH_2Cl_2 (0.7 mL) was added slowly. The mixture was slowly warmed to rt and stirred for two days. Phosphate buffer (pH=7) was added and reaction mixture was extracted three times with CH_2Cl_2. Organic extracts were dried ($MgSO_4$) and evaporated. Resulted oil was dissolved in CH_2Cl_2 (3 mL) and treated with TFA (0.2 mL). After 1 h the solution was neutralised with saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$) and evaporated. The product was purified by chromatography on silica gel (CH_2Cl_2 and EtOH, 45:1, then 30:1).

3.2.1. 5,6-Dihydro-4-ethoxy-6-phenyl-2(1*H*)-pyridinone (3a). Spectral data identical to previously reported.[15]

3.2.2. 6-(3-Chlorophenyl)-5,6-dihydro-4-ethoxy-2(1*H*)-pyridinone (3b). Spectral data identical to previously reported.[15]

3.2.3. 5,6-Dihydro-4-ethoxy-6-(3-nitrophenyl)-2(1*H*)-pyridinone (3c). Colourless crystals, mp 144–148°C. $[\alpha]_D{}^{27}=-84.6$ (c=2.26, $CHCl_3$). IR (KBr) 1669, 1528, 1344 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J=7.0 Hz, 3H), 2.64 and 2.73 (ABMX, J=15.7, 10.0, 6.0, 1.0 Hz, 2H), 3.91 (m, 2H), 4.86 (dd, J=10.0, 6.0 Hz, 1H), 5.14 (s, 1H), 5.81 (br, 1H), 7.58 (t, J=8.0 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 8.20 (ddd, J=8.0, 2.0, 0.9 Hz, 1H), 8.24 (t, J=2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.0, 35.9, 53.3, 64.3, 93.7, 121.3, 122.9, 129.8, 132.3, 143.3, 148.3, 167.2, 169.8. HRMS calcd for $C_{13}H_{14}N_2O_4$: 262.0954. Found: 262.0961.

3.2.4. 5,6-Dihydro-4-ethoxy-6-(4-methoxyphenyl)-2(1*H*)-pyridinone (3d). Colourless crystals, mp 143–147°C. $[\alpha]_D{}^{27}=-35.5$ (c=1.12, $CHCl_3$). IR (KBr) 3181, 1665 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J=7.2 Hz, 3H), 2.4–2.7 (m, 2H), 3.78 (s, 3H), 3.88 (m, 2H), 4.65 (dd, J=10.9, 5.9 Hz, 1H), 5.08 (s, 1H), 5.51 (br, 1H), 6.82–6.93 (1/2 AA′XX′, 2H), 7.21–7.33 (1/2 AA′XX′, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 36.8, 54.1, 55.2, 64.2, 93.5, 114.1, 127.4, 132.7, 159.3, 168.3, 169.6. HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208. Found: 247.1212.

3.2.5. 5,6-Dihydro-4-ethoxy-6-(2-furyl)-2(1*H*)-pyridinone (3e). Brown solid, mp 84–87°C. IR (KBr) 3208, 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J=7.0 Hz, 3H), 2.73 and 2.80 (ABMX, J=16.7, 8.8, 5.8 Hz, 2H), 3.92 (m, 2H), 4.78 (dd, J=8.8, 5.8 Hz, 1H), 5.09 (s, 1H), 5.61 (br, 1H), 6.25 (d, J=3.1 Hz, 1H), 6.34 (dd, J=3.1, 1.8 Hz, 1H), 7.38 (d, J=1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.0, 32.4, 47.8, 64.2, 93.6, 106.2, 110.3, 142.3, 153.1, 167.8, 169.1. HRMS calcd for $C_{11}H_{13}NO_3$: 207.0895. Found: 207.0880.

3.3. Determination of configuration of dihydropyridone 3a

3.3.1. 6-Phenyl-2,4-piperidinedione (4a). To the solution of pyridone **3a** (200 mg, 0.92 mmol) in acetone (4 mL) was added 10% aqueous hydrochloric acid (1 mL) and the mixture was stirred overnight at rt. The excess acetone was evaporated and the residue was extracted with CH_2Cl_2. Organic extracts were dried ($MgSO_4$) and evaporated to give pure **4a** (166 mg, 95%) as colourless solid. Mp 164–168°C. $[\alpha]_D{}^{26}=-48.2$ (c=1.0, $CHCl_3$). ^{1}H NMR data identical to reported.[9] IR (KBr) 3424, 1718, 1672 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 46.7, 47.1, 52.6, 125.9, 128.6, 129.2, 139.2, 169.1, 202.3.

3.3.2. 1-Aza-2-oxo-6-phenyl-1′,3′-dithiaspiro[5,4]decane (5). To the solution of piperidinedione **4a** (166 mg, 0.88 mmol) and ethanedithiol (106 mg, 1.13 mmol) in CH_2Cl_2 (4 mL) was added zinc triflate (383 mg, 1.05 mmol) and the reaction mixture was stirred under reflux for 15 h. The mixture was cooled to rt and water (4 mL) was added. Organic layer was separated and aqueous phase was extracted three times with CH_2Cl_2. Combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (CH_2Cl_2 and EtOH, 15:1) to give colourless solid (150 mg, 65%). $[\alpha]_D{}^{25}=+23.5$ (c=1.04, $CHCl_3$). Spectral data identical to reported.[9]

3.4. 6-Phenyl-2-piperidinone (6)

To the solution of thioketal **5** (140 mg, 0.53 mmol) in ethanol (10 mL) was added freshly prepared Raney nickel (W-2) and the mixture was refluxed for 80 min. The catalyst was removed by decantation and washed several times with EtOH. The combined extracts were filtered trough Celite. Evaporation gave crystals which were purified by chromatography on silica gel (CH_2Cl_2 and MeOH 50:1, then 20:1) to give 62 mg (67%) of colourless crystals. $[\alpha]_D^{22}=-26.7$ (c=1.33, $CHCl_3$). Lit[16] value for (*R*) enantiomer $[\alpha]_D^{20}=+73.6$ (c=1.4, $CHCl_3$). Spectral data identical as reported.[9]

3.4.1. (1*S*,2*R*,4*R*,R_S)-7,7-Dimethyl-*N*-(3-chlorophenylmethylene)-2-trimethylsilyloxybicyclo[2.2.1]heptane-1-methanesulfinamide (7). Yield 92%, oil. $[\alpha]_D^{20}=-122.8$ (c=1.59, $CHCl_3$). IR (film) 1603, 1089 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.12 (s, 9H), 0.83 (s, 3H), 1.07 (s, 3H), 1.06–1.18 (m, 1H), 1.44–1.61 (m, 1H), 1.63–1.91 (m, 5H), 2.71 and 3.19 (AB, J=12.5 Hz, 2H), 3.98 (dd, J=3.8, 7.0 Hz, 1H), 7.34–7.50 (m, 2H), 7.68 (dt, J=1.7, 7.1 Hz, 1H) 7.83 (t, J=1.7 Hz, 1H), 8.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 0.3, 20.1, 20.7, 27.3, 31.4, 42.1, 45.0, 48.8, 50.1, 58.4, 77.1, 127.6, 128.6, 130.1, 132.0, 135.0, 135.7, 159.0. HR LSIMS calcd for $C_{20}H_{31}{}^{35}ClNO_2SSi$ $(M+H)^+$: 412.1533. Found: 412.1546.

3.4.2. (1*S*,2*R*,4*R*,S_S)-7,7-Dimethyl-*N*-(3-chlorophenylmethylene)-2-hydroxybicyclo[2.2.1]heptane-1-methanesulfinamide (8). Yield 77%, colourless crystals, mp 110–115°C. $[\alpha]_D^{20}=+28.4$ (c=1.19, $CHCl_3$). IR (KBr) 3469, 1606, 1085, 1055 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.08 (s, 3H), 1.2–1.45 (m, 1H), 1.6–1.95 (m, 6H), 2.78 and 3.41 (AB, J=13.3 Hz, 2H), 3.51 (br, 1H), 4.03 (dd, J=4.1, 7.2 Hz, 1H), 7.35–7.55 (m, 2H), 7.70 (dt, J=1.6, 7.6 Hz, 1H), 7.81 (t, J=1.6 Hz, 1H), 8.61 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.5, 27.6, 31.4, 39.3, 44.4, 49.1, 51.3, 56.8, 76.3, 127.5, 129.0, 130.4, 132.8, 135.0, 135.3, 161.4. HR LSIMS calcd for $C_{17}H_{22}{}^{35}ClNO_2SNa$ $(M+Na)^+$: 362.0957. Found: 362.0956.

3.4.3. (1*S*,2*R*,4*R*,R_S)-7,7-Dimethyl-*N*-(3-chlorophenylmethylene)-2-hydroxybicyclo[2.2.1]heptane-1-methanesulfinamide (9). Yield 70%, colourless crystals, mp 112–113°C. $[\alpha]_D^{26}=+1.0$ (c=1.06, $CHCl_3$). IR (KBr) 3349, 1604, 1066 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.87 (s, 3H), 1.05 (s, 3H), 1.1–1.3 (m, 1H), 1.5–1.9 (m, 6H), 2.95 and 3.07 (AB, J=13.4 Hz, 2H), 3.54 (br, 1H), 4.15 (dd, J=4.4, 7.6 Hz, 1H), 7.35–7.55 (m, 2H), 7.70 (dt, J=1.6, 7.3 Hz, 1H) 7.90 (t, J=1.6 Hz, 1H), 8.58 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.5, 27.3, 30.8, 38.6, 44.9, 48.5, 50.7, 57.2, 76.8, 128.0, 128.7, 130.2, 132.5, 135.2, 135.2, 160.7. Anal. calcd for $C_{17}H_{22}ClNO_2S$: C, 60.08; H, 6.52; N, 4.12; S, 9.43. Found: C, 59.97; H, 6.68; N, 4.00; S, 9.63.

3.5. Typical procedure for addition of TMS-enol ether to sulfinimines

To the solution of sulfinimine **1a** (165 mg, 0.49 mmol) and TMS-enol ether **10** (178 mg, 0.83 mmol) in CH_2Cl_2 (4 mL) was added TMSOTf (180 mg, 0.81 mmol) at −70°C. The reaction mixture was stirred at −70°C for 3 h followed by addition of water (1.5 mL). The mixture was warmed to rt and basified with saturated solution of $NaHCO_3$. Organic layer was separated and water phase was extracted with CH_2Cl_2. Combined organic extracts were dried ($MgSO_4$) and evaporated. Resulting oil was dissolved in MeOH (4 mL) and solid K_2CO_3 (ca. 200 mg) was added. The suspension was stirred overnight at rt. MeOH was evaporated at rt and the residue was dissolved in water (1.5 mL) followed by acidification with 10% hydrochloric acid. The mixture was extracted three times with CH_2Cl_2. Organic extracts were treated with few drops of etheral solution of HCl and dried overnight over $MgSO_4$. Evaporation of solvents gave oil which was purified by chromatography on silica gel (CH_2Cl_2 and MeOH 45:1, then 30:1). Yield 92 mg (85%).

3.6. General procedure for addition of lithium 1,3-diethoxy-1,3-butadienoate to sulfinimines

To the solution of LDA prepared by addition of *n*-butyllithium (1.6 M in hexane, 0.45 mL, 0.72 mmol) to the solution of diisopropylamine (73 mg, 0.72 mmol) in THF (3 mL) was added dropwise at −70°C solution of ethyl 3-ethoxycrotonate (106 mg, 0.67 mmol) in THF (0.3 mL). The reaction mixture was stirred for 2.5 h at −70°C, and then warmed to −30°C. The solution of sulfinimine **1a** (168 mg, 0.45 mmol) in THF (0.5 mL) was added and the reaction mixture was kept 3.5 h at −30°C. Saturated solution of NH_4Cl was added, and after warming to rt the mixture was extracted with CH_2Cl_2. Combined extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was dissolved in CH_2Cl_2 and ethanolic solution of HCl was added (4.5 mL). The mixture was left at rt for 24 h and evaporated. The residue was dissolved in CH_2Cl_2 (3 mL) and water (2 mL). The mixture was extracted twice with CH_2Cl_2 and combined extracts were dried ($MgSO_4$) and evaporated. The chromatography on silica gel (CH_2Cl_2 and MeOH 45: 1, and then 30: 1) gave 70 mg (72%) of beige crystals.

3.7. General procedure for preparation of 2,4-piperidinediones from diketene–acetone adduct and sulfinimines

To the solution of LDA (1.0 mmol) in THF (3 mL) prepared as above, was added slowly at −70°C solution of dioxinone **12** (1.0 mmol) in THF (0.5 mL). The dienolate was generated for 2 h at −70°C. The reaction mixture was warmed to −40°C and the solution of sulfinimine **1a** (187 mg, 0.5 mmol) was added. The solution was stirred for 3.5 h at −30°C and quenched with sat. solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 and organic extracts were evaporated. The residue was dissolved in ethanolic solution of HCl (4 mL) and left for 1 h. The solution was evaporated, dissolved in MeOH (5 mL) and K_2CO_3 (ca. 200 mg) was added. The suspension was stirred for 24 h, evaporated and dissolved in H_2O. The solution was acidified with 10% aqueous HCl solution and extracted with CH_2Cl_2. Combined extracts were dried ($MgSO_4$) and evaporated. The product was purified by chromatography as described above.

3.7.1. 6-(3-Chlorophenyl)-2,4-piperidinedione (4b). Yellowish solid, mp 102–108°C. IR (KBr) 1671 cm^{-1}. ^1H

NMR ($CDCl_3$) δ 2.75 and 2.91 (ABX, J=4.8, 9.3, 16.0 Hz, 2H), 3.38 (s, 2H), 4.79 (ddd, J=2.0, 4.8, 9.3 Hz, 1H), 6.20 (br, 1H), 7.18–7.23 (m, 1H), 7.31–7.34 (m, 1H), 7.35–7.39 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 46.6, 47.1, 52.2, 124.0, 126.2, 128.8, 130.5, 135.0, 141.3, 169.1, 201.5. HRMS calcd for $C_{11}H_{10}{}^{35}ClNO_2$ 223.0400. Found: 223.0390.

3.7.2. 6-(2-Furyl)-2,4-piperidinedione (4e). Beige crystals, mp 77–82°C. IR (KBr) 3190, 1725, 1671 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.95 and 2.95 (ABX, J=16.6, 5.5 Hz, 2H), 3.34 and 3.39 (AB, J=19.2 Hz, 2H), 4.89 (m, 1H), 6.26 (d, J=3.3, 2.0 Hz, 1H), 6.35 (dd, J=3.3, 2.0, 1H), 6.39 (br, 1H), 7.41 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 42.7, 46.3, 47.1, 107.0, 110.4, 143.0, 151.8, 169.1, 202.0. HRMS calcd for $C_9H_9NO_3$ 179.0582. Found: 179.0577.

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