Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 995–1002

TETRAHEDRON: *ASYMMETRY*

α-Thiosubstituted chiral imines/secondary enamines: their use in the asymmetric Michael reaction

Mohammed Nour,[a] Kimny Tan,[a] Christian Cavé,[a,*] David Villeneuve,[b] Didier Desmaële,[b] Jean d'Angelo [b] and Claude Riche [c]

[a] *Unité de Molécules d'Intérêt Biologique, UFR Pharmacie, B.P. 87900, 21079 Dijon Cedex, France*
[b] *Unité de Chimie Organique associée au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris-Sud, 5, rue J.-B. Clément, 92296 Châtenay-Malabry, France*
[c] *ICSN, CNRS, Avenue de la Terrasse, 91198 Gif sur Yvette, France*

Received 16 December 1999; accepted 10 January 2000

Abstract

The asymmetric Michael reaction between 2-thiosubstituted chiral imines/secondary enamines derived from (*S*)-1-phenylethylamine and electrophilic alkenes (methyl acrylate, MVK) was investigated. 2-Phenylthio derivatives furnished the expected Michael adducts with excellent ee. By contrast, an in situ elimination of *p*-toluenesulfenic acid took place when using the *p*-toluenesulfinyl analogs.

1. Introduction

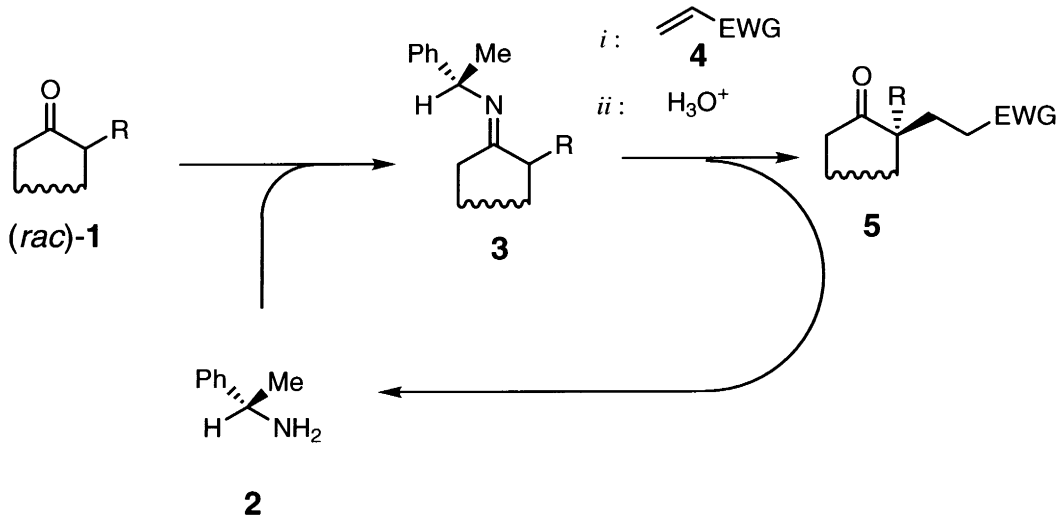
Since our first report in 1985, considerable attention has been given to the use of chiral imines in the asymmetric Michael reaction *under neutral conditions.*[1] This reaction indeed provides one of the most efficient tools for the enantioselective elaboration of quaternary carbon centers, frequently encountered in architecturally complex natural compounds (terpenes, steroids, alkaloids, etc).

Basically, addition of chiral imines **3**, derived from racemic 2-alkylcyclanones **1** and optically active 1-phenylethylamine **2**, to electrophilic alkenes **4** furnished Michael adducts **5** with an excellent yield and a high degree of regio- and stereoselectivity (Scheme 1).

It is worthy of note that the presence of an α-alkoxy substituent in starting cyclanone **1** (R=OMe, OBn) does not significantly alter the two remarkable features of this reaction, namely the high degree of regio- and stereochemical control.[2] The aim of this paper was to extend this Michael reaction to the α-thiosubstituted analogs **1** (R=SPh, S(O)Ph), because the expected Michael adducts **5** would offer

* Corresponding author. E-mail: christian.cave@u-bourgogne.fr

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00021-5

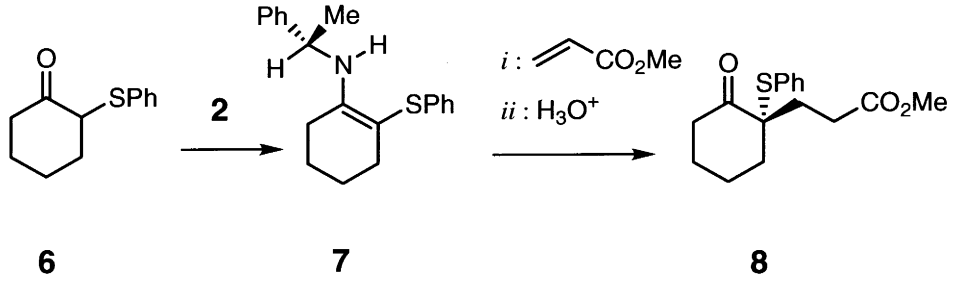


Scheme 1.

attractive opportunities of 'transfer of chirality', e.g. via sigmatropic rearrangements involving the sulfur atom.[3]

2. Results and discussion

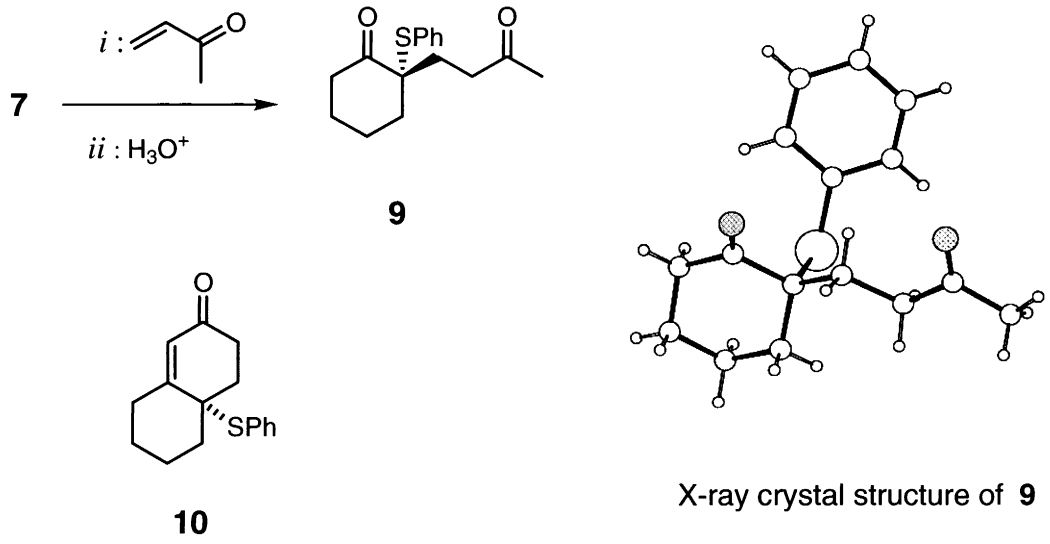
Condensation of 2-phenylthiocyclohexanone **6**[4] with (*S*)-1-phenylethylamine **2** gave compound (*S*)-**7**, as the unique α-sulfenylenamine form.[5] Addition of this crude enamine to methyl acrylate (THF, 24 h at 20°C) furnished, after hydrolytic work-up, Michael adduct (*S*)-**8** with a 68% yield. The ee of **8** (93%) was determined by ^{1}H NMR spectroscopy, after addition of Eu(hfc)$_3$ as chiral shift reagent. The depicted absolute configuration of **8** was deduced from mechanistic considerations (vide infra) (Scheme 2).



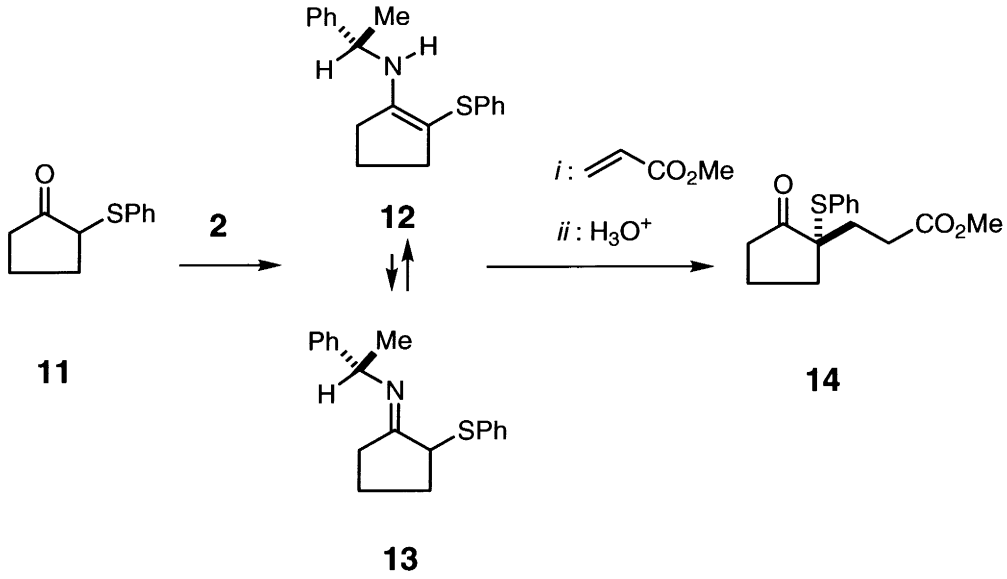
Scheme 2.

Addition of enamine (*S*)-**7** to methyl vinyl ketone (THF, 12 h at 0°C) afforded Michael adduct (*S*)-**9** in 60% yield and a 95% ee, accompanied by ca. 10% of octalone (*S*)-**10**. The structural assignment for compound **9** was verified by X-ray diffraction analysis, including the absolute configuration, based on the anomalous diffusion of the sulfur atom (Bijvoet method) (Scheme 3).

When **2**-phenylthiocyclopentanone **11**[4] was condensed with amine (*S*)-**2**, a mixture of enamine **12** and tautomeric imine **13** was obtained in the respective ratio of 4:1. Addition of this crude mixture to methyl acrylate (THF, 24 h at 20°C) gave the expected Michael adduct (*S*)-**14** (ee=92%), albeit in low yield (25%). Only polymeric material was obtained when methyl acrylate was replaced by methyl vinyl ketone in this reaction (Scheme 4).

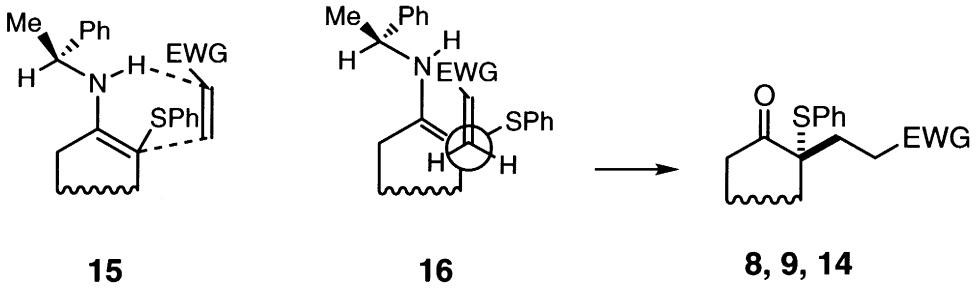


Scheme 3.



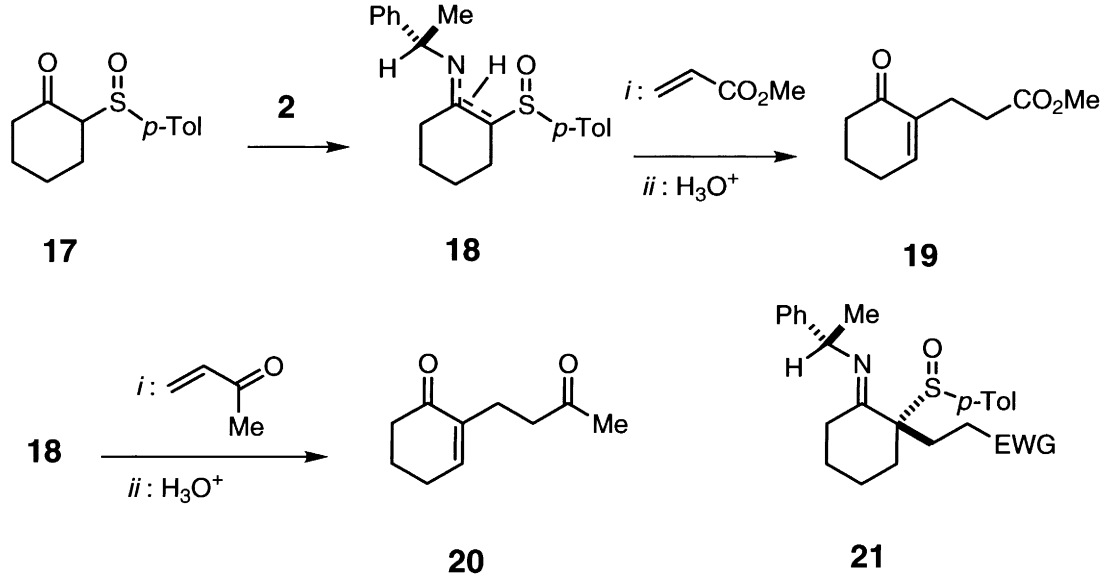
Scheme 4.

It is of particular interest to note that the stereochemical outcome observed in the previous Michael reactions using α-phenylthioenamines **7** and **12** follow the general mechanistic rule we have established in this series.[6] In accordance with this mechanism, the reaction proceeds through the 'aza-ene-synthesis-like' transition state **15**, in which the proton borne by the nitrogen atom of thioenamine is transferred to the α-carbon atom of the electrophilic alkene, concertedly with the creation of the C–C bond. This requires a *synclinal* arrangement of the two reactants, as shown in the corresponding compact approach **16**. According to such a model, the alkylation takes place predominantly *anti* to the bulky phenyl ring of the chiral amine moiety portrayed in its energetically preferred conformation minimizing the $A^{1,3}$-type strain (C–H bond more or less eclipsing the enamine ring). This accounts for the absolute configuration in adducts **8**, **9** and **14** (Scheme 5).



Scheme 5.

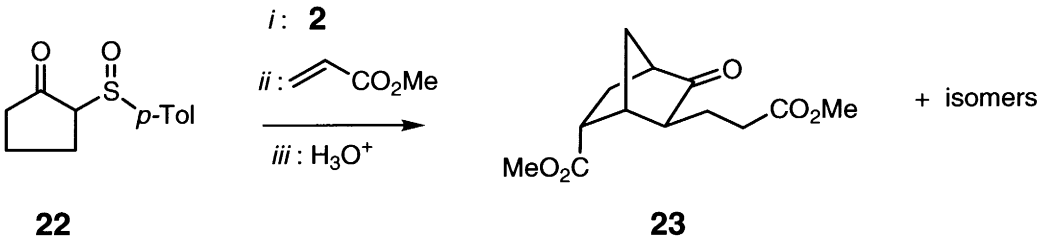
A nearly equimolar mixture of tautomeric sulfinylimine/sulfinylenamine forms **18** was obtained in the condensation between 2-*p*-toluenesulfinylcyclohexanone **17**[7] and amine (*S*)-**2**. Surprisingly, addition of **18** to methyl acrylate (THF, 40 h at 45°C) and to methyl vinyl ketone (THF, 48 h at 20°C) furnished cyclohexenones **19**[8] (83% yield) and **20** (40% yield), respectively. Thus, an in situ, unusually facile elimination of *p*-toluenesulfenic acid took place in these reactions, presumably at the level of the intermediary sulfinylimines **21** (Scheme 6).



Scheme 6.

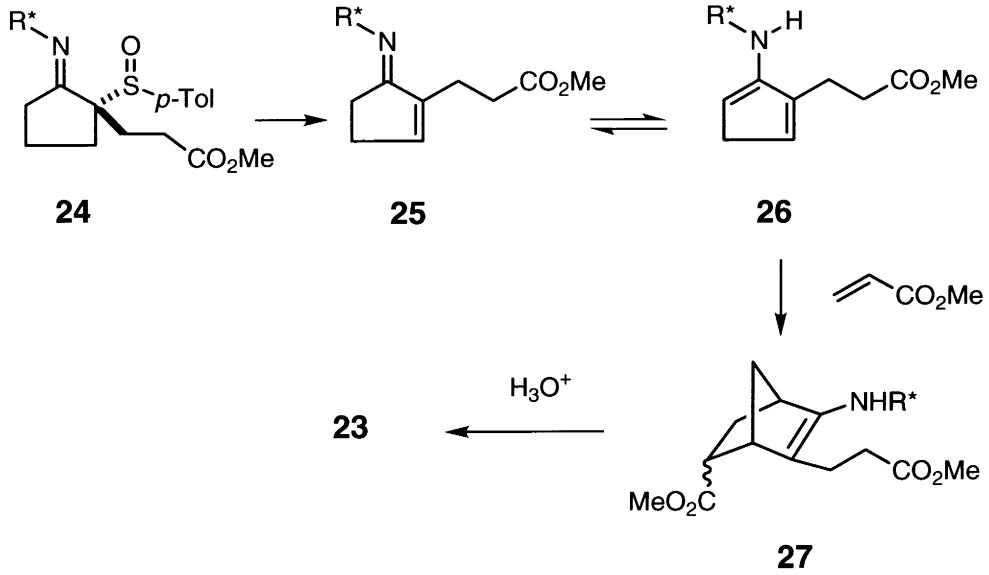
Another unexpected result was obtained when the above sequence of reactions was applied to the five-membered series. Thus, employing 2-*p*-toluenesulfinylcyclopentanone **22**[7] as starting cyclanone and an excess of methyl acrylate as electrophilic alkene, a norbornane derivative was isolated with a 60% yield, as a mixture of three diastereomers in the ratio 3:1:1, established by gas chromatography. Stereochemistry of the major isomer was tentatively assigned as **23**, on the basis of NMR spectroscopy including COSY, HMQC, HMBC and NOESY experiments. However, this compound exhibited a very low ee (ca. 10%) (Scheme 7).

Formation of compound **23** and diastereomeric congeners can be interpreted as follows. Addition of sulfinylimine/sulfinylenamine resulting from the condensation between **22** and **2** to methyl acrylate would give primarily Michael adduct **24**. This probably underwent elimination of *p*-toluenesulfenic acid, furnishing α-ethylenic imine **25**, in tautomeric equilibrium with the very reactive aminocyclopentadiene



Scheme 7.

26. Diels–Alder cycloaddition of **26** with methyl acrylate then afforded norbornene **27**, subsequently hydrolyzed into norbornanone **23** (Scheme 8).



Scheme 8.

3. Experimental

3.1. General

Infrared (IR) spectra were obtained on a Perkin–Elmer 881 spectrometer as neat films between NaCl plates or KBr pellets. Only the most significant absorptions are listed. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 P (200 and 50 MHz, for ^{1}H and ^{13}C, respectively), or a Bruker ARX 400 (400 and 100 MHz, for ^{1}H and ^{13}C, respectively) spectrometer. Recognition of methyl, methylene, methine and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin–echo sequence. Optical rotations were measured at 20°C on a Polax L polarimeter in a 1 dm cell. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). Column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM). Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive pressure of nitrogen. Organic layers were

dried over anhydrous $MgSO_4$. Chemicals obtained from commercial suppliers were used without further purification. All elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin–Elmer 2400 analyzer.

3.2. (S)-(1-Phenylethyl)-(2-phenylsulfenylcyclohex-1-enyl)amine **7**

A solution of 2-phenylthiocyclohexanone **6** (0.93 g, 4.5 mmol), (*S*)-1-phenylethylamine **2** (0.55 g, 4.5 mmol) and *p*-toluenesulfonic acid (10 mg) in anhydrous toluene (80 mL) was refluxed for 12 h with azeotropic removal of water. The solution was cooled to 20°C and the solvent was removed in vacuo to afford the crude enamine **7** as a yellow oil; IR (film, cm^{-1}) 3300, 1618, 1581; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.45–6.85 (m, 10H), 5.5 (d, J=7.0 Hz, 1H), 4.2 (quint., J=7.0 Hz, 1H), 2.35–1.60 (m, 4H), 1.40–1.20 (m, 4H), 1.05 (d, J=7.0 Hz, 3H).

3.3. (S)-3-(2-Oxo-1-phenylsulfenylcyclohexyl)propionic acid methyl ester **8**

To the enamine **7** (0.31 g, 1.0 mmol) were added freshly distilled methyl acrylate (1.0 g, 12 mmol), hydroquinone (5 mg) and THF (20 mL). The stirred mixture was heated at 20°C for 24 h and 5 mL of 20% aqueous acetic acid were added. The mixture was stirred for 3 h. The solvents were removed under reduced pressure and 1N hydrochloric acid (10 mL) was added. The mixture was extracted with ether and the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (1:1 hexane:dichloromethane) gave keto ester **8** (199 mg, 68%) as a colorless oil; $[\alpha]_D^{20}=-195$ (c 1.0, MeOH); IR (film, cm^{-1}) 1735, 1705, 1438; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.30–7.10 (m, 5H), 3.56 (s, 3H), 3.25 (ddd, J=14.5, 13.2, 6.2 Hz, 1H), 2.55–2.15 (m, 3H), 2.05–1.50 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 206.9 (C), 173.8 (C), 136.2 (2 CH), 129.8 (C), 129.5 (CH), 129.0 (2 CH), 60.9 (C), 51.6 (CH_3), 37.8 (CH_2), 36.4 (CH_2), 29.8 (CH_2), 28.8 (CH_2), 26.9 (CH_2), 21.2 (CH_2); anal. calcd: C, 65.72: H, 6.89; found: C, 64.98: H, 6.75.

3.4. (S)-2-(3-Oxobutyl)-2-phenylsulfenylcyclohexanone **9**

To the enamine **7** (0.155 g, 0.5 mmol) were added at 0°C freshly distilled methyl vinyl ketone (1.0 g, 15 mmol), hydroquinone (3 mg) and THF (10 mL). The stirred mixture was kept at 0°C for 12 h and 5 mL of 10% aqueous acetic acid were added. The mixture was stirred for 1 h. The solvents were removed under reduced pressure and 1N hydrochloric acid (10 mL) was added. The mixture was extracted with dichloromethane and the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (1:1 hexane:dichloromethane) gave adduct **9** (83 mg, 60%) as colorless crystals; mp 62–63°C (hexane); $[\alpha]_D^{20}=-187$ (c 2.0, MeOH); IR (film, cm^{-1}) 1717, 1700, 1438; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.30–7.10 (m, 5H), 3.35 (ddd, J=14.0, 13.3, 6.1 Hz, 1H), 2.60–2.30 (m, 3H), 2.05 (s, 3H), 2.00–1.50 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 207.8 (C), 207.0 (C), 136.0 (2 CH), 129.8 (C), 129.3 (CH), 128.8 (2 CH), 61.0 (C), 38.1 (CH_2), 37.8 (CH_2), 36.6 (CH_2), 29.8 (CH_2), 28.4 (CH_2), 26.7 (CH_2), 21.1 (CH_3); anal. calcd: C, 69.53; H, 7.29; found: C, 69.48; H, 7.42. Crystal data: $C_{16}H_{20}O_2S$, Mw=276.38, crystal of 0.40×0.10×0.02 mm, orthorhombic, space group P 21 21 21, Z=8, a=6.927(3), b=12.778(6), c=35.064(8) Å, V=3103.6(21) $Å^3$, d_{calc}=1.183 g cm^{-3}, F(000)=1184, λ=1.54180 Å (Cu$K\alpha$), μ=1.812 mm^{-1}, Nonius CAD4 diffractometer, theta range: 2.52–67.87°, 3484 collected reflections, 3051 unique (R_{int}=0.0446), 1328 observed ($I>2\sigma(I)$), full-matrix least-squares (SHELXL93), R=0.0529 for 1328 observed reflections, wR_2=0.1304 for 3051 unique reflections, goodness of fit=0.944, residual electron density between −0.233 and 0.207 eA^{-3},

absolute configuration was established by comparison of selected Bijvoet pairs of reflections; for the 28 largest calculated differences ($F_{calc}(+++)$–$F_{calc}(---)$) only one observed difference was wrong, the two molecules of the asymmetric unit adopt a similar conformation.

3.5. (S)-3-(2-Oxo-1-phenylsulfenylcyclopentyl)propionic acid methyl ester **14**

A solution of 2-phenylthiocyclopentanone **11** (0.29 g, 1.5 mmol), (*S*)-1-phenylethylamine **2** (0.18 g, 1.5 mmol) and *p*-toluenesulfonic acid (10 mg) in anhydrous toluene (20 mL) was refluxed for 12 h with azeotropic removal of water. The solution was cooled to 20°C and the solvent was removed in vacuo to afford a crude mixture of enamine **12** and imine **13** as a brown oil. To this crude was added freshly distilled methyl acrylate (2.0 g, 23 mmol), hydroquinone (5 mg) and THF (20 mL). The stirred mixture was heated at 20°C for 24 h and 5 mL of 20% aqueous acetic acid were added. The mixture was stirred for 3 h. The solvents were removed under reduced pressure and 1N hydrochloric acid (10 mL) was added. The mixture was extracted with ether and the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (1:1 hexane:dichloromethane) gave keto ester **14** (104 mg, 25%) as a colorless oil; $[\alpha]_D^{20}=-79.4$ (*c* 0.38, MeOH); IR (film, cm^{-1}) 1735, 1700, 1438; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.40–7.10 (m, 5H), 3.56 (s, 3H), 2.70–2.50 (m, 2H), 2.40–1.80 (m, 6H), 1.70–1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 201.7 (C), 173.3 (C), 136.9 (2 CH), 129.5 (CH), 129.4 (C), 128.7 (2 CH), 60.1 (C), 51.5 (CH_3), 35.4 (CH_2), 34.2 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 17.8 (CH_2); anal. calcd: C, 64.72; H, 6.52; found: C, 64.52; H, 6.70.

3.6. 3-(6-Oxo-cyclohex-1-enyl)propionic acid methyl ester **19**

A mixture of 4.40 g of 5 Å molecular sieves, 0.40 g of silica and 0.80 g of basic alumina was activated by heating for a few minutes at 0.05 torr with a free flame. After cooling, a solution of 1-phenylethylamine **2** (0.57 g, 4.7 mmol) in 5 mL of THF was added, followed by ceto-sulfoxide **17** (1.30 g, 4.0 mmol) in 3 mL of THF. The suspension was vigorously stirred at 20°C for 18 h. The reaction mixture was then filtered and the solid residue was repeatedly washed with anhydrous THF. The organic filtrate was concentrated under reduced pressure (0.05 torr, 40°C) to leave a yellow oil (1.28 g) which was used directly in the next step. To the crude imine **18** (0.50 g, 1.47 mmol) were added freshly distilled methyl acrylate (2.60 g, 30 mmol) and hydroquinone (5 mg). The stirred mixture was heated at 45°C for 40 h. After cooling to 20°C, 20% aqueous acetic acid (5 mL) and THF (20 mL) were added, and the mixture was stirred for 3 h. The solvents were removed under reduced pressure and 1N hydrochloric acid (10 mL) was added. The mixture was extracted with ether and the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (20:10 hexane:ethyl acetate) gave enone ester **19** (220 mg, 83%) as a colorless oil. IR (film, cm^{-1}) 1739, 1674, 1436; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.72 (t, *J*=1.4 Hz, 1H), 3.58 (s, 3H), 2.50–2.25 (m, 8H), 2.05–1.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 199.1 (C), 173.0 (C), 146.3 (CH), 138.0 (C), 51.5 (CH_3), 38.4 (CH_2), 33.1 (CH_2), 26.1 (CH_2), 25.5 (CH_2), 23.0 (CH_2).

3.7. 2-(3-Oxobutyl)cyclohexen-2-one **20**

To the crude imine **18** (0.38 g, 1.12 mmol) obtained as described above were added freshly distilled methyl vinyl ketone (1.0 g, 14.3 mol) and hydroquinone (5 mg), and the reaction mixture was stirred at 20°C for 48 h. Aqueous acetic acid (5 mL, 20%) and THF (20 mL) were then added, and the mixture was stirred for 3 h. The solvents were removed under reduced pressure and 1N hydrochloric acid (10 mL)

was added. The mixture was extracted with ether and the combined organic phases were washed with brine, dried and concentrated. Chromatographic purification over silica gel (20:10 hexane:ethyl acetate) gave enone **20** (75 mg, 40%) as a colorless oil. IR (film, cm^{-1}) 1715, 1669; ^1H NMR ($CDCl_3$, 200 MHz) δ: 6.79 (t, J=1.5 Hz, 1H), 2.50–2.20 (m, 8H), 2.12 (s, 3H), 2.00–1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 208.4 (C), 199.5 (C), 146.7 (CH), 138.3 (C), 42.5 (CH_2), 38.5 (CH_2), 29.9 (CH_3), 26.0 (CH_2), 24.5 (CH_2), 23.0 (CH_2).

*3.8. 6-(2-Methoxycarbonylethyl)-5-oxo-bicyclo[2.2.1]heptane-2-carboxylic acid methyl ester **23***

A solution of 1-phenylethylamine **2** (0.72 g, 5.9 mmol) in 2 mL of THF and ceto-sulfoxide **22** (1.1 g, 5.0 mmol) in 2 mL of THF were added to 2 g of catalyst prepared as above. The suspension was vigorously stirred at 20°C for 18 h. The reaction mixture was then filtered and the solid residue was repeatedly washed with anhydrous THF. The organic filtrate was concentrated under reduced pressure (0.05 torr, 40°C) to leave a colorless oil (1.28 g) which crystallized on standing. To this crude were added freshly distilled methyl acrylate (5 mL) and hydroquinone (5 mg). The stirred mixture was heated at 45°C for 40 h. After cooling to 20°C, 20% aqueous acetic acid (5 mL) and THF (20 mL) were added, and the mixture was stirred for 3 h. The solvents were removed under reduced pressure and 1N hydrochloric acid (10 mL) was added. The mixture was extracted with ether and the collected organic phases were concentrated. Chromatographic purification over silica gel (20:10 hexane:ethyl acetate) gave a colorless oil (0.77 g, 60%). GC analysis revealed the presence of three isomers in a 3:1:1 ratio. Careful chromatography provided an analytical sample of major isomer **23** as a colorless oil: IR (film, cm^{-1}) 1743, 1738; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.68 (s, 3H), 3.65 (s, 3H), 3.04 (ddd, J=11.4, 5.7, 1.2 Hz, 1H), 2.69 (m, 1H), 2.59 (dd, J=4.9, 1.1 Hz, 1H) 2.43 (m, 2H), 2.05 (ddd, J=13.8, 11.4, 4.9 Hz, 1H), 1.98–1.80 (m, 4H), 1.68–1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 216.2 (C), 173.2 (C), 172.8 (C), 51.5 (CH_3), 51.1 (CH_3), 49.6 (CH), 47.3 (CH), 44.1 (CH), 42.7 (CH), 35.5 (CH_2), 31.8 (CH_2), 26.6 (CH_2), 23.8 (CH_2).

References

1. For a recent report in this field, see: Thominiaux, C.; Roussé, S.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2015–2021, and references cited therein.
2. Desmaële, D.; d'Angelo, J. *Tetrahedron Lett.* **1989**, *30*, 345–348. See also: Desmaële, D.; d'Angelo, J.; Bois, C. *Tetrahedron: Asymmetry* **1990**, *1*, 759–762; Desmaële, D.; Pain, G.; d'Angelo, J. *Ibid*. **1990**, *3*, 863–866.
3. For an example, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, pp. 503–572.
4. Seebach, D.; Tescher, M. *Tetrahedron Lett.* **1973**, *51*, 5113–5116.
5. In sharp contrast, a unique α-sulfenylimine form was reported for a closely related compound (**3d** in this reference): Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159–161.
6. Tran Huu Dau, M. E.; Riche, C.; Dumas, F.; d'Angelo, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1059–1064.
7. Coates, R. M.; Pigott, H. D. *Synthesis* **1975**, 319–320.
8. Barillier, D.; Benhida, R.; Vazeux, M. *Phosphorus, Sulfur, and Silicon* **1993**, *78*, 83–95.