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Cyclopentannulation of enones with organocuprate reagents containing an acetal or an orthoester function

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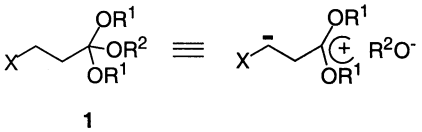
Abstract—1,1-Dimethyl-3-(phenylthio)-propane **4** was deprotonated with *t*-BuLi, then converted to the corresponding organocuprate reagent which, in the presence of HMPA and TMSCl, was added to a variety of enones to give the corresponding silylenol ethers **7**. These were cyclised without purification upon acidic conditions to give the cyclopentannulation products **9**. A similar result was obtained with the corresponding orthoester reagent **6**. This cyclopentannulation sequence is applicable to a wide variety of enones except for those bearing substituents near the reacting centre. © 2002 Published by Elsevier Science Ltd.

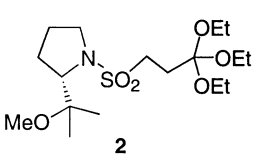
1. Introduction

The power of cycloaddition and cyclocondensation reactions for the construction of a new ring results from their convergent character and often high regio- and stereo-selectivities. Among these, asymmetric addition or condensation reactions of C_3 reagents to olefins have received much attention.[1] Our own group has been involved in the study of the 1,3-dipole equivalents **1** which have been successfully used as annulation reagents of aldehydes, ketones and cyclic enones (Scheme 1).[2] Enantioselective versions of these reactions using the readily available reagents **2** and **3** have recently been reported.[3,4]



1

X = $PhSO_2$, PhSO; R^1, R^2 = Me, Et, CH_2CH_2



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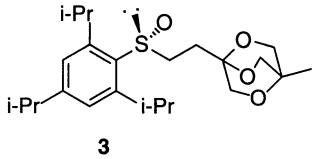


3

Scheme 1.

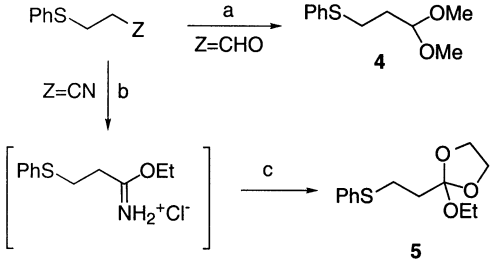
In our continuing search for new cyclopentannulation reagents, we have examined organometallic derivatives of compound **4**. A potential advantage of these complexes over the previously studied reagents **1**–**3** results from the possibility of introducing a chiral ligand on the metal. An elegant example of this type of approach has recently been reported by Feringa's group.[1n,s]

2. Results and discussion

2.1. Synthesis of the C_3 reagents

Both acetal **4** and orthoester **5** were readily prepared by a conventional sequence of reactions (Scheme 2).

The more stable bicyclic orthoester **6** was obtained in excellent yields according to Scheme 3.



Scheme 2. *Reagents and conditions*: (a) $HC(OMe)_3$, montmorillonite k-10, rt, 12 h; (b) HCl_g in CH_2Cl_2, EtOH (1.5 equiv.); (c) $HOCH_2CH_2OH$ (2 equiv.), CH_2Cl_2, 1 day at rt then reflux, 12 h.

Keywords: cyclopentannulation; conjugate addition; Mukaiyama aldol reaction; cuprate reagents; enones; acetal; orthoester.

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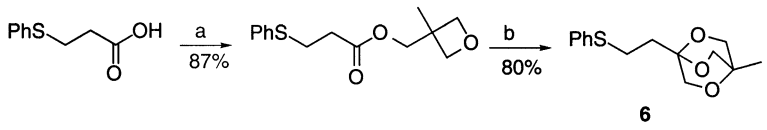
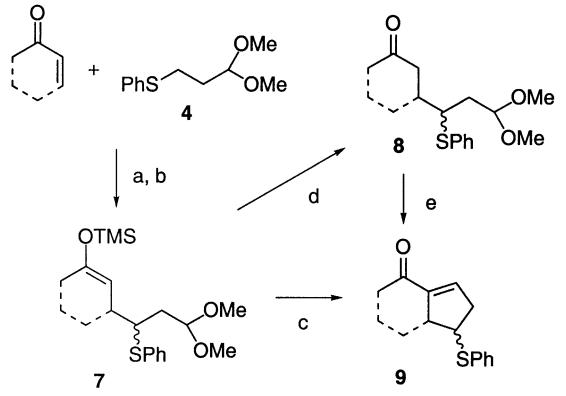


Scheme 3. *Reagents and conditions*: (a) 1,1′-carbonyldiimidazole (1.1 equiv.), 3-methyl-3-oxetanemethanol (1.1 equiv.); (b) $BF_3{\cdot}OEt_2$.



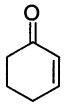
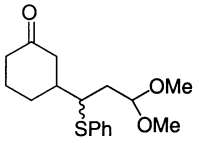
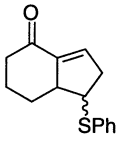
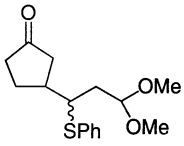
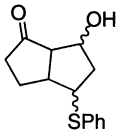
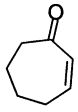
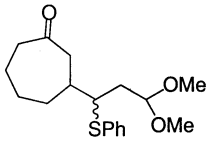
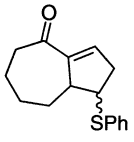
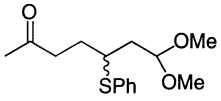
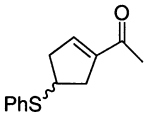
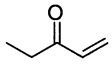
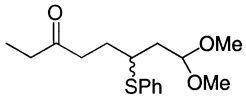
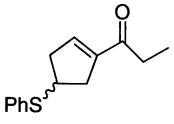
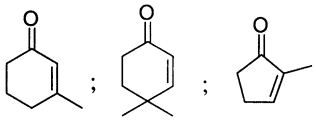
Scheme 4. *Reagents and conditions*: (a) **4**, *t*-BuLi (1.2 equiv.) in THF, HMPA (2.5 equiv.), −78°C, 2 h then $CuBr{\cdot}SMe_2$ (1.2 equiv.), 30 min, −78°C to −40°C; (b) enone (1.1 equiv.), TMSCl (2.5 equiv.), Et_3N (2.5 equiv.), 1 h, −40°C; (c) $TiCl_4$ (1 equiv.), 4 Å MS, CH_2Cl_2, 1 h at −78°C or $SnCl_4$–$ZnCl_2$ (0.1 equiv.), 4 Å MS, CH_2Cl_2, 1 h at −78°C; (d) 1.0 M TBAF (1.2 equiv.) in THF, 0°C, 30 min; (e) 36.5% HCl+THF (25 vol), 3 h, rt.

2.2. Cyclopentannulation reactions

Compound **4** was readily deprotonated at −78°C with *t*-BuLi in THF containing 2.5 equiv. of HMPA (Scheme 4).[5] The resulting organolithium compound was poured into a suspension of $CuBr{\cdot}SMe_2$ in THF. After 30 min at −40°C, a mixture of cyclohexenone, TMSCl and triethylamine was added to the organocuprate reagent and kept for 1 h at −40°C. An aqueous work-up to remove HMPA was found necessary for a successful cyclisation of the intermediately formed silylenol ether **7** which was obtained in nearly pure form after removal of the solvent (Scheme 4; Table 1, Entry a). The cyclisation was successfully performed with $TiCl_4$ or, alternatively, with $SnCl_4$–$ZnCl_2$.[6] Quenching crude **7** with aqueous tetrabutylammonium fluoride yielded ketal **8** which also cyclised upon treatment with HCl. Both cyclisations gave a 3:2 mixture of epimers **9** which were separated by column chromotography.

The same experimental procedure was applied to the

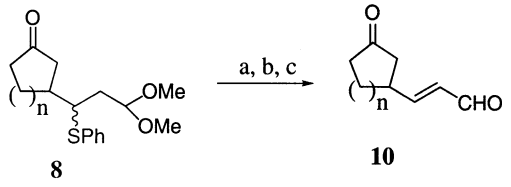
Table 1. Cyclopentannulation of enones

Entry	Enone	Adduct **8**	Yield (%)[a]	Annulation product **9**	Yield (%)[a]
a			87		81
b			85		40
c			82		77
d			88		93
e			75		91
f				Recovery of starting materials or decomposition products	

[a] Pure products.

cyclopentannulation of various enones. The reaction was not sensitive to ring size (Table 1, entries a–c) and could be applied to acyclic enones (entries d, e). However, the sequence was extremely sensitive to substituents at C_3, C_4 and C_5 of cyclohexenone or cyclopentenone (Entry f). For these more crowded systems, enolisation probably competed favorably with 1,4 addition.

The functional density of cyclopentannulation product **9** should make them useful building blocks for synthesis. The lack of stereoselectivity of the 1,4 addition of **4** to the enone is of no importance since the thiophenyl substituent would be eliminated at a later stage. The addition products **8** are also useful synthetic intermediates as shown in Scheme 5.



8 **10**

Scheme 5. *Reagents and conditions*: (a) HOAc–THF–H_2O (3:1:1) 2 h at 60°C; (b) *m*CPBA (1 equiv.), 30 min at 0°C; (c) 1 h in toluene, 70°C.

We also tried to perform the cyclopentannulation of cyclohexenone using the orthoester reagent **5**. This invariably led to decomposition products (Scheme 6). It is conceivable that the sensitive orthoester function of **5** was not compatible with the conditions to generate the organocuprate reagent. This interpretation was supported by the observation that the cyclopentannulation sequence could be successfully performed with the more stable orthoester reagent **6** (Scheme 7). In this case, the cyclisation was effected with the powerful silylating agent $TMSNTf_2$ acting as a Lewis acid catalyst.[7] The resulting cyclopentannulation products are highly functionalised and similar bicyclic compounds have been shown to be easily converted into bicyclic cyclopentenone **12**.

3. Conclusions

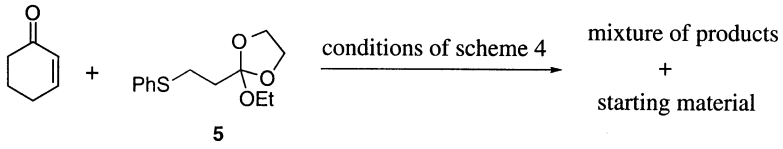
We have described a facile albeit not general method for the cyclopentannulation of enones. The products are densely functionalised. In particular, they contain a phenylthioether function which could be used for the introduction of a double bond by β-elimination via the corresponding sulfoxide or for the formation of an organolithium compound by reductive lithiation. The present work also showed that an organocuprate bearing an α-thioether group could be generated by transmetallation from the corresponding organolithium derivative. Synthetic applications of these cyclopentannulation are being currently explored in our group.

4. Experimental

4.1. General

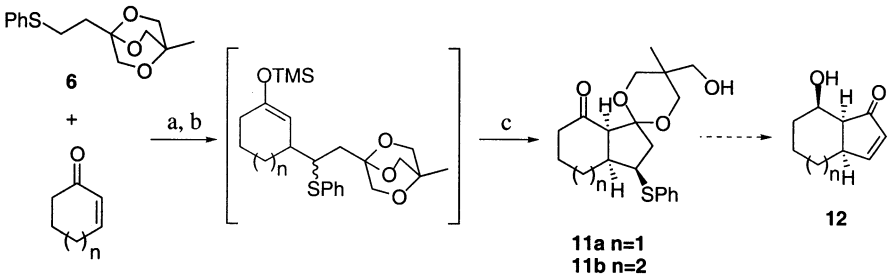
All reaction requiring anhydrous or inert conditions were carried out under an atmosphere of dried argon in flame-dried glassware. All solvents were dried by standard procedures and freshly distilled. Infrared spectra were recorded on a Perkin–Elmer 681 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 or a Varian XL-200 spectrometer. ^{13}C spectra (50 MHz) were recorded on a Varian XL-200 or a VXR-200 spectrometer. Chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Mass spectra were recorded on Varian MAT-44 or Finnigan MAT-TSQ70 spectrometers (electronic impact 70 eV or chemical ionisation with N_2O–CH_4 as ionising gas). Thin-layer chromatography (TLC) was run on precoated silica gel plates (Merck $60F_{254}$). Flash chromatography was carried out using flash silica gel 60 Merck (40–63 μm) as the stationary phase.

4.1.1. [(3,3-Dimethoxypropyl)thio]-benzene (4). This product had been prepared earlier.[8] We found the following procedure more practical:[9] The k-10/trimethyl orthoformate reagent is readily prepared by stirring k-10 montmorillonite



5

Scheme 6.



Scheme 7. *Reagents and conditions*: (a) *t*-BuLi (1.2 equiv.), in THF+HMPA (1.2 equiv.), −78°C to −10°C, 2.5 h, then CuBr·SMe_2 (1.2 equiv.), 20 min at −78°C then 40 min at −40°C; (b) cyclohexenone or cycloheptenone (0.67 equiv.), TMSCl (2.33 equiv.), Et_3N (2.67 equiv.), −78°C to −40°C, 2 h; (c) $TMSNTf_2$ (0.1 equiv.), 1 h at −78°C.

clay (60 g) with trimethyl orthoformate (90 ml), followed by filtration. 2-(Phenylthio)propyl aldehyde (29.5 g, 177.4 mmol) was stirred with the resulting wet cake in 150 ml dry *n*-hexane until TLC showed complete conversion (about 3 h). The product was isolated after filtration, washing the filtrate with sodium bicarbonate solution followed by water, drying and evaporation of the solvent. The product was distilled as a colorless oil at 94–95°C/4.4×10^{-2} mmHg in 95% yield. ^{1}H NMR (200 MHz): 7.39–7.11 (m, 5H), 4.51 (t, J=5.4 Hz, 1H), 3.32 (s, 6H), 2.96 (t, J=7.5 Hz, 2H), 1.94 (dt, J=5.4, 7.5 Hz, 2H); ^{13}C NMR (50 MHz): 136.97, 129.95, 129.68, 126.68, 103.97, 53.88, 33.07, 29.52.

4.1.2. (3-Phenylthio)-dioxolane ethyl orthopropionate (5). Ethanol (6 ml, 103 mmol) was added to a solution of 3-phenylthiopropionitrile (12 g, 73.51 mmol)[10] in 250 ml CH_2Cl_2. The reaction mixture was saturated with HCl gas at −55°C, then kept at −5°C overnight. After warming to room temperature, the solvent was evaporated, and 60 ml CCl_4 were added. This process was repeated three times to remove residual HCl gas. The resulting white solid was dissolved in 100 ml CH_2Cl_2, then ethylene glycol (4.099 ml, 73.51 mmol) was added and the reaction mixture was stirred at room temperature for 24 h, then refluxed overnight. After cooling, the solvent was evaporated. The residue was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 3:1. The column must be washed with 10% Et_3N in cyclohexane/ethyl acetate 3:1 prior to the chromatography. The product **5** (11.22 g, 60%) was obtained as a colorless oil. ^{1}H NMR (300 MHz): 7.35–7.15 (m, 5H), 4.13–3.97 (m, 4H), 3.53 (q, J=7.1 Hz, 2H), 3.05 (t, J=8.4 Hz, 2H), 2.14 (t, J=8.4 Hz, 2H), 1.18 (t, J=7.1 Hz, 3H). HRMS: calculated for $C_{13}H_{18}O_3S$: 254.0976; found: 254.0973.

4.1.3. 3-(Phenylthio)propionate ester of 3-methyl-3-hydroxy-methyloxetane. A solution of 3-(phenylthio)propanoic acid[11] (5 g, 27.43 mmol) in 10 ml CH_2Cl_2 was added to a solution of 1,1′-carbonyldiimidazole (4.893 g, 30.18 mmol) in 20 ml CH_2Cl_2. After stirring the reaction mixture at room temperature for 30 min, 3-methyl-3-oxetanemethanol (3 ml, 30.18 mmol) was added through a syringe. The reaction mixture was stirred for another 34 h until TLC showed the conversion was complete. After removal of the solvent, the residue was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 3:1. The column was washed with 10% Et_3N in cyclohexane/ethyl acetate 3:1 before the chromatography. The product (6.37 g, 87%) was obtained as a colorless oil. ^{1}H NMR (300 MHz): 7.38–7.21 (m, 5H), 4.50 (d, J=6 Hz, 2H), 4.37 (d, J=6 Hz, 2H), 4.18 (s, 2H), 3.18 (t, J=6.9 Hz, 2H), 2.68 (t, J=6.9 Hz, 2H), 1.21 (s, 3H); ^{13}C NMR (50 MHz): 172.47, 135.74, 130.91, 129.74, 127.36, 80.16, 69.57, 39.69, 34.95, 29.78, 21.81; EI-MS: m/z (%)=266($M^{+\cdot}$, 100), 236(11), 182(30), 165(12), 163(8), 137(14), 123(23), 109(24).

4.1.4. 1-(2-Phenylthioethyl)-4-methyl-2,6,7-trioxabicyclo-[2,2,2]-octane (6). Boron trifluoride diethyl etherate (2.598 ml, 20.64 mmol) was added dropwise at 0°C to a solution of 3-phenylthiopropionate ester of 3-methyl-3-hydroxy-methyloxetane (22 g, 82.59 mmol) in 80 ml CH_2Cl_2, then the reaction mixture was stirred for 2.5 h until all the starting material was consumed (TLC analysis). The reaction was then quenched by the addition of triethylamine (22.96 ml, 65.1 mmol), diluted with ether and filtered to remove the amine–BF_3 complex. The filtrate was concentrated and purified by column chromatography on silica gel with cyclohexane/ethyl acetate 4:1. The column was washed with 10% Et_3N in cyclohexane/ethyl acetate 4:1 before the chromatography. The product **6** was obtained as a white solid in 80% yield (17.6 g). FT-IR (cm^{-1}): 2959, 2880, 2360, 1441, 1288, 1046; ^{1}H NMR (300 MHz): 7.33–7.12 (m, 5H), 3.88 (s, 6H), 3.02 (t, J=8.4 Hz, 2H), 2.01 (t, J=8.4 Hz, 2H), 0.79 (s, 3H); ^{13}C NMR (50 MHz): 137.15, 129.59, 129.52, 126.38, 108.97, 73.33, 37.56, 30.98, 27.95, 15.18; EI-MS: m/z (%)=266($M^{+\cdot}$, 100), 236(7), 181(7), 163(13), 144(15), 123(13), 109(16), 55(8); HRMS: calculated for $C_{14}H_{18}O_3S$: 266.0976; found: 266.0975.

4.2. General procedure for the preparation of compound 8

tert-BuLi 1.7 M (3.768 ml, 5.652 mmol) was added to a solution of compound **4** (1 g, 4.71 mmol) and hexamethylphosphoramide (2.048 ml, 11.77 mmol) in THF (8 ml) at −78°C. After stirring at −78°C for 2 h, the reaction mixture was added by the double-ended cannula to another three-necked flask containing a suspension of copper(I) bromide–dimethyl sulfide complex (1.271 g, 6.123 mmol) in 4 ml THF. After 20 min at −78°C and 45 min at −40°C, the solution became orange and clear. Then enone (5.181 mmol), chlorotrimethylsilane (2.092 ml, 16.48 mmol) and triethylamine (2.291 ml, 16.48 mmol) were added at −78°C. After 30 min, the reaction mixture was brought to −40°C (1.5 h), then warmed to room temperature. It was quenched by 1 M solution of tetrabutylammonium fluoride in THF (6.123 ml, 6.123 mmol). After total disappearance of the intermediate silyl enol ether (±15 min), the mixture was diluted with water, filtered through a pad of Celite, extracted with diethyl ether, and washed with cold water four times to remove HMPA completely. Chromatography on silica gel with cyclohexane/ethyl acetate (3:1) gave the product **8**.

4.2.1. 3,3-Dimethoxy-1-(3-oxocyclohexyl)-1-phenylthio-propane (8a): mixture of isomers. Yellow oil, 87% yield. ^{1}H NMR (300 MHz): 7.45–7.18 (m, 5H), 4.68 (dd, J=3.5, 7.6 Hz, 1H), 3.32, 3.31, 3.26, 3.22 (each s, 6H), 3.25–3.15 (m, 1H), 2.55–2.18 (m, 5H), 2.15–1.52 (m, 6H); EI-MS: m/z (%)=308($M^{+\cdot}$, 88), 245(15), 167(50), 135(47), 109(43), 84(99), 75(100), 47(83); HRMS: calculated for $C_{17}H_{24}O_3S$: 308.1446, found: 308.1439.

4.2.2. 3,3-Dimethoxy-1-(3-oxocyclopentyl)-1-phenylthio-propane (8b): mixture of isomers. Yellow oil, 85% yield. ^{1}H NMR (300 MHz): 7.46–7.15 (m, 5H), 4.77 (dd, J=3.6, 7.7 Hz, 1H), 3.35, 3.33, 3.28, 3.26 (each s, 6H), 3.30–3.20 (m, 1H), 2.54–2.04 (m, 5H), 2.04–1.63 (m, 4H); EI-MS: m/z (%)=294($M^{+\cdot}$, 100), 231(16), 153(100), 109(48); HRMS: calculated for $C_{16}H_{22}O_3S$: 294.1289; found: 294.1294.

4.2.3. 3,3-Dimethoxy-1-(3-oxocycloheptyl)-1-phenylthio-propane (8c): mixture of isomers. Yellow oil, 82% yield. ^{1}H NMR (300 MHz): 7.45–7.19 (m, 5H), 4.66 (dd, J=3.3,

8.2 Hz, 1H), 3.314, 3.310, 3.26, 3.25 (each s, 6H), 3.28–3.23 (m, 1H), 2.65–2.62 (m, 1H), 2.52–2.32 (m, 2H), 2.06–1.80 (m, 6H), 1.80–1.22 (m, 4H); EI-MS: *m/z* (%)=322($M^{+\cdot}$, 17), 291(16), 259(15), 181(81), 154(50), 136(43), 84(33), 49(100); HRMS: calculated for $C_{18}H_{26}O_3S$: 322.0816; found: 322.0844.

4.2.4. 7,7-Dimethoxy-5-(phenylthio)heptan-2-one (8d). Yellow oil, 88% yield. FT-IR (cm^{-1}): 2935, 2831, 1716 (C=O), 1125, 1056; ^1H NMR (200 MHz): 7.40–7.15 (m, 5H), 4.67 (t, *J*=5.7 Hz, 1H), 3.29 (s, 3H), 3.27 (s, 3H), 3.26–3.10 (m, 1H), 2.67 (t, *J*=7.3 Hz, 2H), 2.08 (s, 3H), 2.05–1.60 (m, 4H); ^{13}C NMR (50 MHz): 208.28, 135.21, 132.72, 129.47, 127.58, 103.31, 53.98, 53.52, 45.27, 41.07, 38.99, 29.47; EI-MS: *m/z* (%)=282($M^{+\cdot}$, 24), 192(13), 141(100), 115(11), 109(14), 75(27), 43(35); HRMS: calculated for $C_{15}H_{22}O_3S$: 282.1289; found: 282.1284.

4.2.5. 8,8-Dimethoxy-6-(phenylthio)octan-3-one (8e). Yellow oil, 75% yield. FT-IR (cm^{-1}): 2937, 1712 (C=O), 1125, 1056, 747, 693; ^1H NMR (200 MHz): 7.41–7.20 (m, 5H), 4.67 (t, *J*=5.7 Hz, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 3.23–3.14 (m, 1H), 2.65 (t, *J*=7.4 Hz, 2H), 2.46–2.27 (m, 2H), 2.04–1.71 (m, 4H), 1.02 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (50 MHz): 211.50, 135.12, 132.80, 129.57, 127.69, 103.21, 54.05, 53.58, 39.77, 38.94, 36.62, 29.52, 8.45; EI-MS: *m/z* (%)=296($M^{+\cdot}$, 23), 192(17), 155(100), 110(9), 75(24), 57(18); HRMS: calculated for $C_{16}H_{24}O_3S$: 296.1446; found: 296.1447.

4.3. General procedure for the preparation of cyclised compound 9

0.45 ml of 36.5% HCl aq. was added to a solution of compound **8** (2.269 mmol) in 30 ml THF. The reaction mixture was stirred at room temperature for 4 h. The solvent was then removed and the residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ solution and water, dried over $MgSO_4$. Chromatography on silica gel using cyclohexane/ethyl acetate (7:1) as eluent gave the isomer mixture, which could be further separated.

4.3.1. 1-Phenylthio-1,2,5,6,7,7a-hexahydro-4*H*-inden-4-one (9a). 9a 2:3 (*cis*/*trans*) Isomers ratio was measured according to the ^1H NMR of the crude product, The two isomers could be separated by chromatography on silica gel with cyclohexane/ethyl acetate (10:1) as eluent.

cis isomer: FT-IR (cm^{-1}): 3056, 2938, 1683, 1615, 1479, 1232, 1089; ^1H NMR (300 MHz): 7.43–7.25 (m, 5H), 6.57 (dd, *J*=3.3, 5.8 Hz, 1H), 3.55 (dt, *J*=8.3, 9.6 Hz, 1H), 2.93–2.80 (m, 2H), 2.55–2.44 (m, 2H), 2.25–2.11 (m, 2H), 2.05–1.95 (m, 1H), 1.79–1.63 (m, 1H), 1.29 (ddd, *J*=3.3, 12.7, 15.9 Hz, 1H); ^{13}C NMR (50 MHz): 198.88, 144.29, 137.07, 135.75, 132.37, 129.66, 127.71, 54.31, 52.40, 40.83, 40.63, 30.80, 24.04; EI-MS: *m/z* (%)=[$(M+1)^+$, 100], 227(24), 180(14), 135(98), 117(17), 107(12), 92(10), 79(11); HRMS: calculated for $C_{15}H_{16}OS$: 244.0921; found: 244.0926.

trans isomer: ^1H NMR (300 MHz): 7.42–7.26 (m, 5H), 6.66 (dd, *J*=3, 5.6 Hz, 1H), 4.25 (dt, *J*=1.2, 6.9 Hz, 1H), 3.32–3.24 (m, 1H), 2.97–2.86 (m, 1H), 2.62–2.47 (m, 2H), 2.32–2.21 (m, 1H), 2.10–1.91 (m, 2H), 1.83–1.69 (m, 2H); ^{13}C NMR (50 MHz): 199.34, 143.23, 136.78, 132.43, 130.67, 129.59, 126.94, 51.27, 50.00, 40.97, 40.60, 27.18, 24.21.

4.3.2. One isomer of compound 9b. FT-IR (cm^{-1}): 3430 (bs), 2939, 2360, 1741, 1480, 1438; ^1H NMR (300 MHz): 7.44–7.26 (m, 5H), 3.89–3.83 (m, 1H), 3.52–3.42 (m, 1H), 2.59–2.10 (m, 5H), 1.65 (dd, *J*=3.3, 12.5 Hz, 2H), 1.32–1.23 (m, 2H); ^{13}C NMR (50 MHz): 218.97, 134.51, 133.32, 129.79, 128.22, 71.49, 52.98, 48.43, 40.81, 36.87, 36.40, 34.72; EI-MS: *m/z* (%)=248(M^+, 100), 153(9), 149(10), 136(8), 121(11), 110(26), 93(15); HRMS: calculated for $C_{14}H_{16}O_2S$: 248.0871; found: 248.0870.

4.3.3. Compound 9c. 3:5 (*cis*/*trans*) Isomers ratio was measured according to the ^1H NMR of the crude product. The two isomers could be isolated by chromatography on silica gel with cyclohexane/ethyl acetate (7:1) as eluent.

cis isomer: FT-IR (cm^{-1}): 2922, 1679, 1608, 1438, 1320, 1175; ^1H NMR (300 MHz): 7.38–7.24 (m, 5H), 6.69 (dd, *J*=2.7, 4.4 Hz, 1H), 3.45 (dt, *J*=6.2, 8.3 Hz, 1H), 2.97 (ddt, *J*=2.5, 2.7, 8.3 Hz, 1H), 2.87–2.78 (m, 1H), 2.61–2.42 (m, 3H), 2.15–1.93 (m, 3H), 1.58–1.27 (m, 3H); ^{13}C NMR (50 MHz): 200.38, 147.31, 139.91, 136.14, 131.68, 129.63, 127.42, 52.92, 52.76, 45.45, 40.65, 37.02, 31.02, 25.84; EI-MS: *m/z* (%)=259[$(M+1)^+$, 8], 149(100), 131(30), 121(68), 105(38), 93(51), 79(19); HRMS: calculated for $C_{16}H_{18}OS$: 258.1078; found: 258.1077.

trans isomer: ^1H NMR (300 MHz): 7.35–7.26 (m, 5H), 6.74 (dd, *J*=1.0, 3.2 Hz, 1H), 4.04 (dt, *J*=8.0, 9.6 Hz, 1H), 3.08–3.01 (m, 1H), 2.82 (ddd, *J*=3.2, 8.0, 18.5 Hz, 1H), 2.62–2.42 (m, 3H), 2.31–2.25 (m, 1H), 2.12–1.91 (m, 2H), 1.55–1.27 (m, 3H); ^{13}C NMR (50 MHz): 201.05, 149.31, 139.36, 127.01, 129.98, 129.58, 126.74, 50.65, 48.29, 45.10, 38.99, 32.17, 31.07, 25.49.

4.3.4. 1-[3-(Phenylthio)cyclopent-1-enyl]ethan-1-one (9d). Yellow oil, 93% yield from **8d**. FT-IR (cm^{-1}): 3058, 2943, 1667 (C=O), 1374, 740, 691; ^1H NMR (200 MHz): 7.35–7.18 (m, 5H), 6.64 (bs, 1H), 4.03–3.90 (m, 1H), 3.16–2.80 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (50 MHz): 196.41, 144.84, 141.94, 136.27, 131.01, 129.50, 127.10, 43.54, 41.99, 38.99, 27.00; EI-MS: *m/z* (%)=218($M^{+\cdot}$, 100), 175(13), 109(84), 93(7), 65(12), 43(75); HRMS: calculated for $C_{13}H_{14}OS$: 218.0765; found: 218.0766.

4.3.5. 1-[3-(Phenylthio)cyclopent-1-enyl]propan-1-one (9e). Yellow oil, 91% yield from **8e**. FT-IR (cm^{-1}): 2975, 1667 (C=O), 740, 691; ^1H NMR (200 MHz): 7.35–7.14 (m, 5H), 6.63 (bs, 1H), 4.00–3.92 (m, 1H), 3.12–2.98 (m, 2H), 2.71–2.60 (m, 4H), 1.08 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (50 MHz): 199.48, 144.01, 140.65, 136.25, 130.82, 129.50, 127.00, 43.21, 41.90, 39.06, 32.45, 8.82; EI-MS: *m/z* (%)=232($M^{+\cdot}$, 100), 175(9), 109(84), 149(9), 123(30), 110(30), 93(14), 65(15), 57(32); HRMS: calculated for $C_{14}H_{16}OS$: 232.0921; found: 232.0926.

4.4. General procedure for the preparation of α,β-unsaturated ketoaldehydes 10

A solution of compound **8** (1.82 mmol) in 10 ml of acetic

acid–water–tetrahydrofuran (v/v/v=3:1:1) was kept at 65°C for 2.5 h until TLC showed complete hydrolysis. The solvents were evaporated and the residue was dissolved in diethyl ether and washed with sat. Na_2CO_3 solution and water. It was then dried over $MgSO_4$, filtered, and concentrated. The resulting aldehyde was dissolved in 6 ml CH_2Cl_2, and a solution of 3-chloroperoxybenzoic acid (438.4 mg, 1.829 mmol) in 5 ml CH_2Cl_2 was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 1 h, then diluted with 20 ml CH_2Cl_2 and washed with sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, filtration, and concentration, the residue was dissolved in 13 ml toluene and the mixture was refluxed for 4 h. Purification by column chromatography on silica gel using cyclohexane/ethyl acetate (3:2) as eluent gave the product **10**.

4.4.1. *trans*-3-(3-Oxocyclohexyl)-2-propenal (10a). Yellow oil, 72% yield from **8a**. FT-IR (cm^{-1}): 2938, 1709, 1685, 1653; ^1H NMR (200 MHz): 9.54 (d, *J*=7.6 Hz, 1H), 6.80 (dd, *J*=6.2, 15.8 Hz, 1H), 6.11 (ddd, *J*=1.4, 7.6, 15.8 Hz, 1H), 2.94–1.58 (m, 9H); ^{13}C NMR (50 MHz): 209.64, 194.29, 159.48, 132.07, 46.13, 41.70, 41.51, 30.45, 25.99; EI-MS: *m/z* (%)=152($M^{+\cdot}$, 100), 134(77), 123(72), 106(75), 94(96), 91(10); HRMS: calculated for $C_9H_{12}O_2$: 152.0837; found: 152.0842.

4.4.2. *trans*-3-(3-Oxocyclopentyl)-2-propenal (10b). Yellow oil, 77% yield from **8b**. FT-IR (cm^{-1}): 2964, 1734, 1684, 1653; ^1H NMR (200 MHz): 9.56 (d, *J*=7.7 Hz, 1H), 6.90 (dd, *J*=7.0, 15.6 Hz, 1H), 6.14 (ddd, *J*=1.2, 7.7, 15.6 Hz, 1H), 3.20–3.11 (m, 1H), 2.60–1.78 (m, 6H); ^{13}C NMR (50 MHz): 216.62, 193.90, 158.67, 132.71, 44.04, 40.18, 38.37, 29.31; EI-MS: *m/z* (%)=139[$(M+1)^+$, 100], 121(42), 109(28), 92(80), 77(98), 67(50), 65(36), 55(25); HRMS: calculated for $C_8H_{10}O_2$: 138.0680; found: 138.0677.

4.4.3. *trans*-3-(3-Oxocycloheptyl)-2-propenal (10c). Yellow oil, 75% yield from **8c**. FT-IR (cm^{-1}): 2937, 1716, 1684, 1653; ^1H NMR (200 MHz): 9.51 (d, *J*=7.7 Hz, 1H), 6.78 (dd, *J*=6.5, 15.7 Hz, 1H), 6.11 (ddd, *J*=1.1, 7.7, 15.7 Hz, 1H), 2.69–2.52 (m, 5H), 2.50–2.19 (m, 4H), 1.78–1.48 (m, 2H); ^{13}C NMR (50 MHz): 212.41, 194.38, 161.01, 131.69, 48.30, 44.55, 39.54, 36.24, 28.79, 24.44; EI-MS: *m/z* (%)=166(M^+, 67), 152(100), 139(95), 107(44), 93(43), 79(47); HRMS: calculated for $C_{10}H_{14}O_2$: 166.0993; found: 166.0997.

4.4.4. Cyclopentannulation reactions with reagent 6. *tert*-BuLi 1.7 M (3.9 ml, 5.856 mmol) was added by syringe to a solution of 1-(2-thiophenylethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane (1.3 g, 4.88 mmol) and hexamethylphosphoramide (2.264 ml, 13.01 mmol) in 10 ml THF at −78°C. After stirring for 2 h at −78°C, kept at −10°C for 30 min, and then cooled to −78°C again. The resulting reaction mixture was added by the double-ended cannula to a suspension of copper(I) bromide–dimethyl sulfide complex (1.216 g, 5.856 mmol) in 4 ml THF. After stirring for 20 min at −78°C and another 40 min at −40°C, the reaction solution became orange and clear. The mixture was cooled to −78°C again. Enone (3.253 mmol), chlorotrimethylsilane (1.445 ml, 11.38 mmol) and triethylamine (1.809 ml, 13.01 mmol) were added, after stirring for 30 min, the mixture was kept at −40°C for another 1.5 h. The reaction was quenched by water, diluted with diethyl ether, filtered through a pad of Celite. The organic phase was separated, the water phases were extracted with diethyl ether, the combined organic phase was washed with cold water four times to remove the HMPA completely, dried over $MgSO_4$, filtered and concentrated to afford the crude silyl enol ether.

The crude silyl enol ether was dissolved in 18 ml CH_2Cl_2, the mixture was cooled to −78°C, $TMSNTf_2$ (79 μl, 0.325 mmol) was added. After stirring at −78°C for 1 h, the reaction was quenched with water, diluted with 20 ml CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated. Chromatography on silica gel with cyclohexane/ethyl acetate (1:2) afforded the product.

4.4.4.1. Preparation of 11a. White powder solid, 55% yield. FT-IR (cm^{-1}): 3446 (OH), 3034, 2945, 2864, 1705 (C=O), 1152, 1047; ^1H NMR (300 MHz): 7.40–7.21 (5H, m), 3.76–3.57 (m, 3H), 3.43 (d, *J*=11.3 Hz, 2H), 2.76 (d, *J*=7.1 Hz, 1H), 2.67 (dd, *J*=7.6, 12.8 Hz, 2H), 2.54–2.33 (m, 3H), 2.03 (dd, *J*=12.0, 12.4 Hz, 2H), 1.95–1.86 (m, 1H), 1.61–1.42 (m, 2H), 0.70 (s, 3H); ^{13}C NMR (50 MHz): 209.88, 126.18, 131.10, 129.68, 127.28, 109.19, 69.05, 67.99, 65.17, 63.66, 48.69, 44.68, 41.96, 38.50, 35.18, 24.13, 22.65, 17.66; EI-MS: *m/z* (%)=362($M^{+\cdot}$, 5), 266(19), 253(100), 144(11), 109(10), 84(13); HRMS: calculated for $C_{20}H_{26}O_4S$: 362.1551; found: 362.1547.

4.4.4.2. Preparation of 11b. White powder solid, 58% yield. FT-IR (cm^{-1}): 3469 (OH), 3056, 2928, 2857, 1702 (C=O), 1150, 1047; ^1H NMR (300 MHz): 7.38–7.17 (m, 5H), 3.85–3.53 (m, 5H), 3.41 (d, *J*=11.7 Hz, 1H), 3.33 (d, *J*=11.7 Hz, 1H), 3.02 (d, *J*=13.1 Hz, 1H), 2.76–2.41 (m, 4H), 2.18–1.88 (m, 5H), 1.59–1.21 (m, 3H), 0.66 (s, 3H); ^{13}C NMR (50 MHz): 211.35, 126.34, 131.43, 129.42, 127.02, 108.92, 68.91, 67.13, 65.50, 63.91, 50.52, 45.47, 44.45, 39.86, 35.08, 32.01, 30.34, 25.32, 17.62; EI-MS: *m/z* (%)=($M^{+\cdot}$, 5), 268(15), 267(100), 165(5), 137(5), 109(6), 57 (7); HRMS: calculated for $C_{21}H_{28}O_4S$: 376.1708; found: 376.1712.

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References

1. Reviews: (a) Ramaiah, M. *Synthesis* **1984**, 529. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1–20. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. More recent papers: (d) Hua, D. H.; Venkataraman, S.; Coulter, M. J.; Sinal-Zingde, G. *J. Org. Chem.* **1987**, *52*, 719–728. (e) Binger, P.; Schafer, B. *Tetrahedron Lett.* **1988**, *29*, 529–530. (f) Trost, B. M.; Acemoglu, M. *Tetrahedron Lett.* **1989**,

30, 1495–1498. (g). Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569. (h) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907–6910. (i) Datta, A.; Schmidd, R. R. *Tetrahedron Lett.* **1993**, *34*, 4161–4164. (j) Janson, M.; Kvarnstrom, I.; Svenssen, S. C. T.; Classon, B.; Samuelsson, B. *Synthesis* **1993**, 129–133. (k) Brengel, G. P.; Rithner, C.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 5144–5146. (l) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas III, C. F. *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132. (m) Przezdziecka, A.; Stepanenko, W.; Wicha, J. *Tetrahedron: Asymmetry* **1999**, *10*, 1589–1598. (n) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104–1105. (o) Labrosse, J. R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527–529. (p) Bui, T.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951–6954. (q) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861–870. (r) Chiacchio, U.; Rescifina, A.; Bkaithan, M.; Piperno, A.; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425–3433. (s) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2001**, 735–736.

2. (a) Lombaert, S. D.; Nemery, I.; Roekens, B.; Carretero, J. C.; Kimmel, T.; Ghosez, L. *Tetrahedron Lett.* **1986**, *27*, 5099–5102. (b) Carretero, J. C.; Lombaert, S. D.; Ghosez, L. *Tetrahedron Lett.* **1987**, *28*, 2135–2138.
3. Huart, C.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 634–636.
4. Renard, M.; Ghosez, L. *Tetrahedron* **2001**, *57*, 2597–2608.
5. Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, *23*, 1961–1964.
6. (a) Mukaiyama, T.; Izawa, T.; Saigo, K. *Chem. Lett.* **1974**, 15–16. (b) Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 323–326.
7. Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497–5500.
8. Behzadi, A.; Owen, L. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 25–29.
9. Taylor, E. C.; Chiang, C. S. *Synthesis* **1977**, 467.
10. Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235–239.
11. Ahn, Y.; Cohen, T. *J. Org. Chem.* **1994**, *59*, 3142–3150.