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Exploring the Stereoselectivity in the Peterson Reaction of Several 2-Substituted 1-Azabicyclo[2.2.2]octan-3-ones

Janne E. Tønder,[a] Mikael Begtrup,[b] John Bondo Hansen[a] and Preben H. Olesen[a,*]

[a]*Health Care Discovery, Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark*
[b]*Department of Medicinal Chemistry, The Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark*

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Abstract—The Peterson reaction between a series of 2-substituted 1-azabicyclo[2.2.2]octan-3-ones and 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) was explored. (*Z*)-Stereoselectivity was obtained with all 2-substituents, ranging from 65:35 for benzyl to 95:5 for phenylsulphanyl. Different bases were investigated, revealing that an organolithium base is necessary for the reaction to occur. A transition state is suggested, involving a four-membered ring in which the lithium ion is covalently bound α to the silyl-group and chelated to the carbonyl oxygen.

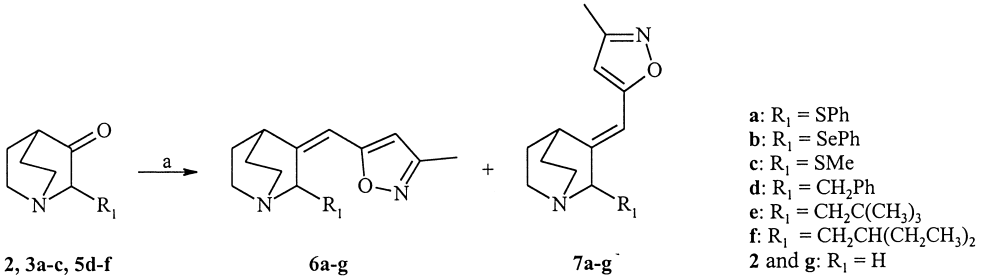
Introduction

In the search for compounds with agonistic effect at the nicotinic acetylcholine receptors, a series of (isoxazole)-methylene-1-azabicyclic compounds were recently prepared.[1] All compounds shared a double bond, connecting an azabicyclic back bone to a substituted isoxazole and for all pairs of (*Z*/*E*)-isomers, the (*Z*)-form possessed the highest affinity; (*Z*)-3-(3-methyl-isoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane (**6g**) being one of the most potent compounds.[1]

In order to develop a (*Z*)-stereoselective synthesis for these compounds the Peterson reaction between the easily available 3-methyl-5-trimethylsilanylmethyl isoxazole[2] (**1**) and derivatives of 1-azabicyclo[2.2.2]octan-3-one (**2**) has now been examined (Scheme 1).

The stereoselectivity of the Peterson reaction may originate in the initial C–C bond forming step to give a β-hydroxysilane or in the subsequent elimination of hexaalkyl disiloxane to give the alkene. When the intermediate β-hydroxysilane can be isolated it has been established that acidic conditions lead to *anti*-elimination, whereas alkaline conditions lead to *syn*-elimination.[3–7]

In the case of stabilised α-silyl carbanions the elimination step is too fast to allow for isolation of the intermediate β-hydroxysilanes. Hence, the stereocontrol must reside in the C–C bond forming step. The factors influencing the stereoselectivity of the C–C bond formation have been examined in a number of studies,[8–11] and it is generally accepted, that (*Z*)-alkenes are favoured. However, even though different transition states have been suggested, no overall mechanistic explanation has been given so far. In



Scheme 1. (a) Organometallic base, 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) in THF, −78°C, N_2; **6a→6g**: $SnBu_3H$, AIBN in methanol, 15 min at 120°C.

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* Corresponding author. Tel.: +45-4443-4886; fax: +45-4443-4547; e-mail: phol@novo.dk

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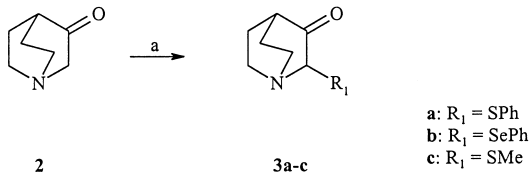


Scheme 2. (a) **a**,**b** (i) LDA in THF, 0°C, N_2, (ii) Electrophile, N_2, **c** (i) LDA in THF, 0°C, N_2, (ii) DMPU, 0°C, N_2, (iii) Electrophile, N_2.

one case[10] a six-membered transition state involving lithium has been suggested. In cases where chelation control is absent an approach-control model was suggested.[11,12] Apparently, the stereoselectivity is highly dependent on the reaction conditions, thereby allowing optimisation of the nature of starting materials and reaction conditions.

In the present work, we report an investigation of some of the factors influencing the (*Z*)-stereoselectivity of the Peterson reaction, by the reaction between α-substituted 1-azabicyclo[2.2.2]octan-3-ones and 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**). We suggest a four-membered transition state, which can explain the observed variations in stereoselectivity. Finally the synthesis of (*Z*)-3-(3-methyl-isoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane (**6g**) via (*RS*)-2-phenylsulphanyl-1-azabicyclo[2.2.2]octan-3-one (**3a**) was attempted.

Results and Discussion

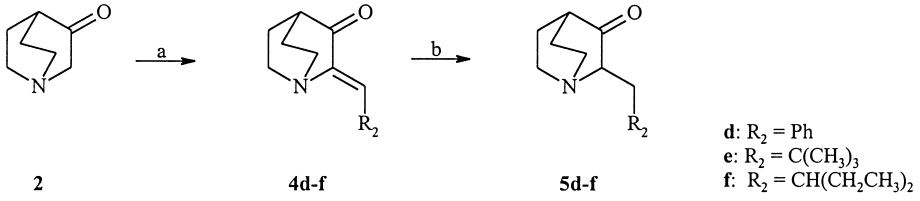
(*Z*)-3-(3-Methyl-isoxazol-5-yl)methylene-1-azabicyclo[2.2.2]-octane (**6g**) was first synthesised directly from 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) and 1-azabicyclo-[2.2.2]octan-3-one (**2**). The result was a mixture of (*Z*)- and (*E*)-isomers in the ratio 60:40. Due to difficulties experienced in the separation of the two isomers, the isolated yield of **6g** was only 28%.[13] In an attempt to increase the (*Z*)-stereoselectivity, a large number of substituents were incorporated in the carbonyl α-position of (**2**). The 2-substituents were selected on basis of steric and electrostatic properties and both π-systems (SPh, SePh, Bn), electronegative atoms (SPh, SePh, SMe) and aliphatic chains ($CH_2C(CH_3)_3$, $CH_2CH(CH_2CH_3)_2$) were introduced. The substituents were introduced by generation of the enolate of 1-azabicyclo[2.2.2]octan-3-one (**2**) by treatment with LDA,[14] followed by addition of electrophile. This gave the 2-substituted 1-azabicyclo[2.2.2]octan-3-ones (**3a**–**c**) in 32–68% isolated yield (Scheme 2). When the electrophile was diphenyl disulphide or dimethyl disulphide, the best yields were obtained using 2.4 equiv. of both LDA and electrophile.[15] Since the stronger S–S bond of dimethyl disulphide is resistant to ketone enolates,[15] DMPU was added to enhance the reactivity.

Three 1-azabicyclo[2.2.2]octan-3-ones with bulky alkyl-substituents in the 2-position were prepared following a modified literature procedure for the synthesis of **5d** (Scheme 3).[16] 1-Azabicyclo[2.2.2]octan-3-one (**2**) was treated with potassium hydroxide in the presence of an aldehyde, giving rise to the expected aldol condensation. Due to their bulkiness, pivalic aldehyde and 2-ethylbutyric aldehyde reacted very slowly to give **4e**,**f** and yields were only 36 and 44%. Nevertheless, the subsequent hydrogenation to give **5e**,**f** was very fast and proceeded in 76 and 96% yield.

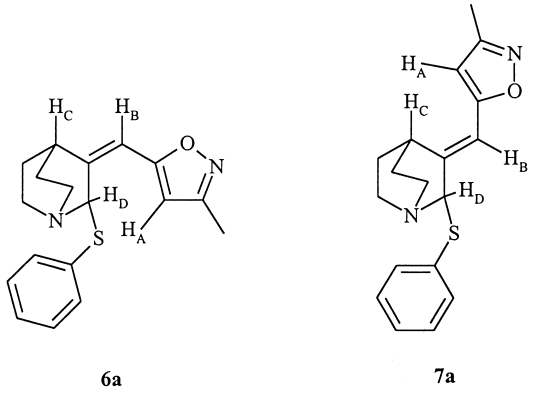
The Peterson reaction of **3a**–**c** and **5d**–**f** with 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) was performed in THF using LDA as the base producing **6a**–**f** and **7a**–**f** in 32–92% yield (Scheme 1). The isomers **6** and **7** were separated by column chromatography and purified by crystallisation of their derived oxalates.

The relative configuration of the (*Z*)- and (*E*)-compounds was determined on the basis of ^{1}H NMR data. After assigning the individual protons from COSY experiments, NOE-effects were used for determination of the spatial arrangement around the double bond. The protons marked H_A–H_D (Scheme 4) were employed in this determination.

In a (*Z*)-compound (i.e. **6a**) NOE-effects were observed between H_A and H_D and between H_B and H_C. Accordingly, in an (*E*)-compound (i.e. **7a**) NOE-effects were observed between H_A and H_C and between H_B and H_D. In the one-dimensional ^{1}H NMR spectrum it proved possible to distinguish between (*Z*)- and (*E*)-compounds by means of the chemical shifts of H_A, H_C and H_D. The largest difference in chemical shifts between (*E*)- and (*Z*)-forms was seen for



Scheme 3. (a) R_2CHO, KOH in methanol. (b) H_2, 10% Pd/C in methanol.



Scheme 4. Protons employed in the structure determination.

Table 1. Variation of base and 2-substituent

Ketone	R_1	Base	Yield (%) (Z+E)	(Z:E) (%)
2[13]	H	LDA	83	60:40
3a	SPh	LDA	72	95:5
3a	SPh	*n*-BuLi	73	80:20
3a	SPh	$KN(SiMe_3)_2$	0	–
3a	SPh	KH	0	–
3b	SePh	LDA	85	75:25
3c	SMe	LDA	32	88:12
5d	CH_2Ph	LDA	79	65:35
5e	$CH_2C(CH_3)_3$	LDA	92	80:20
5f	$CH_2CH(CH_2CH_3)_2$	LDA	81	75:25

δH_C. The signal was shifted almost 1 ppm downfield in the (*E*)-form where the isoxazole is situated closely to H_C.

GC-analysis of the crude product mixture showed that in all cases the (*Z*)-product was the predominant isomer (Table 1). Changing from LDA to *n*-BuLi lowered the stereoselectivity, but still the (*Z*)-isomer was the major product. In contrast to LDA ($pK_A = 36$)[17] and *n*-BuLi ($pK_A = 50$),[17] neither potassium bis(trimethylsilyl)amide ($pK_A = 26$)[17] nor potassium hydride ($pK_A = 35$)[17] lead to alkene formation.

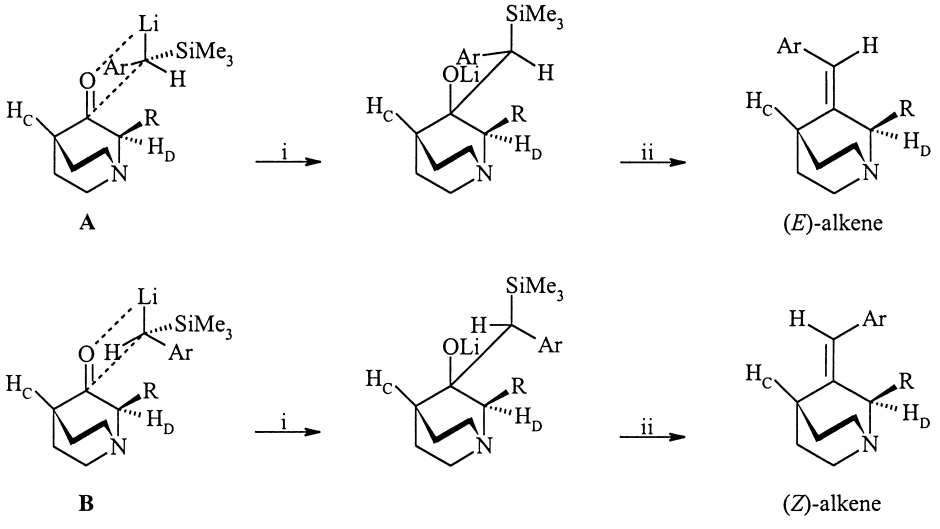
This indicates that the lithium ion is involved in the C–C bond formation step of the Peterson reaction studied. The apparent chelation control exerted by the lithium ion makes it impossible to use the approach-control model, as it was derived for cases in which chelation control is absent.[11,12] In the model proposed by Bell and coworkers[10] the stabiliser of the α-silyl-anion is a nitrogen atom in the 2-oxazolyl group, which enables delocalisation of the negative charge into the oxazole ring. The resulting resonance structure is suggested to be a part of a six-membered transition state, which then determines the stereochemical outcome of the reaction. Such an electron delocalisation is also possible when the stabilising group is 5-isoxazolyl, but the resulting resonance structure is unable to be part of a six-membered ring.

Presumably the lithium ion is involved in a four-membered cyclic transition state with lithium covalently bound to the silyl substituted carbon atom and simultaneously coordinated to the carbonyl oxygen atom (Scheme 5). When racemic ketone was used as the starting material, two enantiomeric transition states are possible. However, as they both lead to the same alkene, only one enantiomer is considered in the following. It is assumed that the Li^+–H^+ interchange in the α-silyllithium species is fast, enabling fast equilibration to the low energy enantiomer.

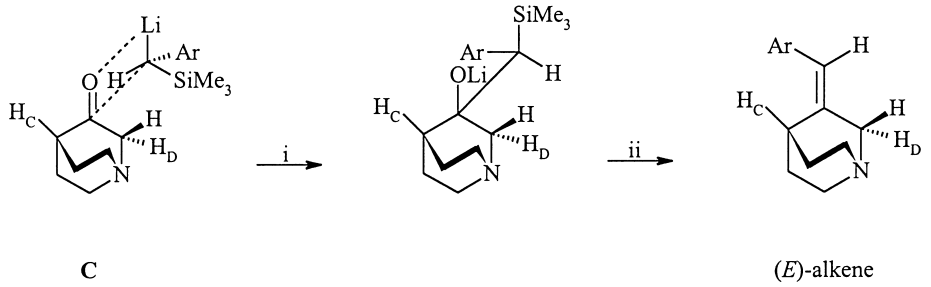
The R-substituent of the ketone probably impedes attack by the α-silyllithium species from the face where it is situated. According to CPK models the trimethylsilyl ($SiMe_3$) group is considerably larger than the isoxazole. Therefore, the $SiMe_3$ group will be oriented opposite to the carbonyl compound as in transition state **A** and **B** (Scheme 5). CPK models also reveal that in the silyllithoxy intermediate, the face with the bridgehead proton (H_C) takes up more space than H_D and R. Thus, transition state **B** leading to the (*Z*)-alkene is more favoured than transition state **A**.

According to this model, the relative amount of (*Z*)-alkene is expected to drop when the size of R is increased. In fact, this trend was observed when the size of R was increased from a sulphur substituent to more bulky selenium or CH_2 substituents. According to MMFF calculations, the volume of the CH_2 group is larger than that of the sulphur atom in the direction of the hydrogen atoms and it will therefore have a larger steric effect on the approaching α-silyllithium species than the sulphur atom.

In the case of R=H, one would expect the reaction to be highly (*Z*)-stereoselective. However, it is possible, that the trimethylsilyl-group can interchange with the isoxazole-group creating another transition state (**C**), now that the



Scheme 5. (i) C–C bond formation; (ii) *syn*-elimination.



C (*E*)-alkene

Scheme 6.

total steric effect of H_D and R is much less around the 2-position in the ketone. As illustrated in Scheme 6 transition state **C** leads to formation of the (*E*)-alkene.

Based on this reasoning, a strategy for the (*Z*)-stereoselective synthesis of **6g** was designed using the phenylsulphanyl group to improve stereocontrol (Scheme 1). The synthesis of **6a** in gram scale via **3a** proceeded in 24% overall yield using recrystallisation for purification in both steps. The final removal of the assisting phenylsulphanyl group by reduction with tributyltin hydride turned out to be difficult, as the yield of **6g** from **6a** was only 12%.

Conclusion

It has proved possible to achieve (*Z*)-stereoselectivity by insertion of a bulky substituent α to the carbonyl group. The observed variations in stereoselectivity could be explained by steric interactions in a transition state in which a lithium ion is taking part.

The (*Z*)-stereoselectivity of the Peterson reaction between 2-substituted 1-azabicyclo[2.2.2]octan-3-ones and 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) decreases with the size of the substituent α to the carbonyl group. This can be rationalised if the C–C bond formation is the rate limiting step passing a four-membered cyclic transition state with lithium covalently bound to the silyl substituted carbon atom and simultaneously coordinated to the carbonyl oxygen atom.

Experimental

General methods and materials

^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC-300 MHz FT-NMR instrument, and COESY, NOESY and ROESY spectra were recorded at 400 MHz on a Bruker AC-400 MHz FT-NMR instrument. Mass spectra were recorded on a Finnigan 5100 mass spectrometer, and melting points (uncorrected) were determined on a Buchi capillary melting point apparatus. IR were recorded with a Perkin–Elmer 1600 spectrometer. Column chromatography was performed on silica gel 60 (70–230 mesh, ASTM, Merck). Elemental analyses were performed by Novo Nordisk Microanalytical Laboratory, Denmark, and were within ±0.4% of the calculated values. TLC was monitored via UV or potassium permanganate spray. All reactions involving moisture-sensitive reagents were performed under N_2 using standard septum techniques. The (*Z*/*E*)-ratios of the crude products were measured by gas chromatography (Chrompack CP9001).

3-Methyl-5-trimethylsilanylmethyl isoxazole (**1**)[2], (*RS*)-2-benzylidene-1-azabicyclo[2.2.2]octan-3-one (**4d**),[16] and (*RS*)-2-benzyl-1-azabicyclo[2.2.2]octan-3-one (**5d**)[16] were synthesised following literature procedures.

Method A

(*RS*)-2-Phenylsulphanyl-1-azabicyclo[2.2.2]octan-3-one (3a). To a solution of diisopropylamine (6.30 mL, 0.048 mol) in THF (150 mL) at 0°C *n*-butyllithium (2.50 M in hexanes, 19.2 mL, 0.048 mol) was added dropwise over a period of 5 min. The resulting yellow solution was stirred at 0°C for 30 min, whereupon 1-azabicyclo[2.2.2]octan-3-one (**2**) (2.50 g, 0.020 mol) dissolved in THF (10 mL) was added. After 30 min at 0°C, diphenyl disulphide (10.5 g, 0.048 mol) was added as a solution in THF (25 mL). Stirring the reaction mixture at 20°C for 2 h was followed by quenching with water (200 mL). The alkaline water phase (pH=11) was extracted with dichloromethane (4×150 mL), and the combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo to give 11.4 g of a yellow oil. Column chromatography (eluent: ethyl acetate/dichloromethane 1:10) gave 2.34 g (50%) of the title product as yellowish crystals.

Mp 116–118°C. MS *m*/*z* (%): 234 (M^++1, 3), 205 (100), 172 (27), 128 (33), 110 (42), 96 (19). IR (KBr, cm^{-1}): 3422, 2944, 2856, 1728, 1472, 1072, 739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 2H, *J*=7 Hz, H_{meta}); 7.32–7.29 (m, 3H, H_{ortho}+H_{para}); 4.76 (s, 1H, NCHSC=); 3.72–3.60 (m, 1H, NCH_2); 3.32–3.18 (m, 1H, NCH_2); 3.10–2.95 (m, 1H, NCH_2); 2.94–2.80 (m, 1H, NCH_2); 2.57 (m, 1H, CH); 2.03 (t, 4H, *J*=7 Hz, CH_2). Anal. ($C_{13}H_{15}NOS$): Calcd C, 66.92; H, 6.48; N, 6.00. Found C, 67.04; H, 6.68; N, 5.98.

The following compounds were prepared according to Method A with the variations stated below.

(*RS*)-2-Phenylselanyl-1-azabicyclo[2.2.2]octan-3-one (3b). In 68% yield starting from LDA (1.2 equiv.), 1-azabicyclo[2.2.2]octan-3-one (**2**) (1.0 equiv.), and phenylselenenyl chloride (1.05 equiv.). Phenylselenenyl chloride was added at −78°C, and the reaction mixture stirred at −78°C for 30 min, before it was allowed to warm up to 20°C.

Mp 90–92°C. MS *m/z* (%): 280 (M^+, 1), 253 (100), 176 (49), 172 (74), 145 (86) 96 (47). IR (KBr, cm^{-1}): 3424, 2948, 2870, 1722, 1477, 1070, 736. ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 2H, H_{meta}); 7.26 (m, 3H, $H_{ortho}+H_{para}$); 5.02 (s, 1H, NCHSeC=); 3.68–3.49 (m, 1H, NCH_2); 3.35–3.16 (m, 1H, NCH_2); 3.09–2.78 (m, 2H, NCH_2); 2.50 (quintet, 1H, *J*=3 Hz, CH); 2.07–1.87 (m, 4H, CH_2). Anal. ($C_{13}H_{15}NOSe$): Calcd C, 55.72; H, 5.40; N, 5.00. Found C, 55.69; H, 5.43; N, 4.95.

(*RS*)-2-Methylsulphanyl-1-azabicyclo[2.2.2]octan-3-one (3c). In 32% yield starting from LDA (2.4 equiv.), 1-azabicyclo[2.2.2]octan-3-one (**2**) (1.0 equiv.), and dimethyl disulphide (2.4 equiv. DMPU (5.0 equiv.) was added and the reaction mixture stirred for 10 min before the addition of dimethyl disulphide. The title compound decomposed when subjected to column chromatography. Thus, the crude product was partly purified by crystallisation with oxalic acid from acetone, followed by a recrystallisation from acetone. The product (white crystals) was used without further purification.

MS *m/z* (%): 171 (M^+, 1), 143 (87), 128 (100), 110 (12), 96 (15). ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (s, 1H, NCHSC=); 3.58–3.45 (m, 1H, NCH_2); 3.31–3.19 (m, 1H, NCH_2); 3.03–2.92 (m, 1H, NCH_2); 2.85–2.72 (m, 1H, NCH_2); 2.48 (quintet, 1H, *J*=3 Hz, CH); 2.19 (s, 3H, CH_3); 2.05–1.90 (m, 4H, CH_2).

Method B (Aldol condensation followed by hydrogenation)

2-(2,2-Dimethyl-propylidene)-1-azabicyclo[2.2.2]octan-3-one (4e). KOH (1.46 g, 0.026 mol) was added to a solution of 1-azabicyclo[2.2.2]octan-3-one (**2**) (11.0 g, 0.087 mol) in methanol (75 mL). When all KOH had dissolved, pivalic aldehyde (9.90 mL, 0.091 mol) was added and the reaction mixture was stirred at 60°C for 12 days. Evaporation followed by filtration through silica gel using ethyl acetate as eluent gave 6.09 g (36%) of **4e** as yellow crystals.

Mp 67–69°C. MS *m/z* (%): 193 (M^+, 63), 178 (6), 165 (100), 150 (66), 137 (30), 122 (100). IR (KBr, cm^{-1}): 3398, 2961, 2868, 1706, 1637, 1252. ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1H, CH=); 3.11–3.00 (m, 2H, NCH_2); 2.92–2.80 (m, 2H, NCH_2); 2.51 (quintet, 1H, *J*=3 Hz, CH); 1.94 (dt, 4H, *J*=7 Hz, 3 Hz, CH_2); 1.20 (s, 9H, CH_3). Anal. ($C_{12}H_{19}NO$) Calcd C, 74.57; H, 9.91; N, 7.25. Found C, 74.62; H, 10.18; N, 7.27.

(*RS*)-2-(2,2-Dimethyl-propyl)-1-azabicyclo[2.2.2]octan-3-one (5e). A suspension of 2-(2,2-dimethyl-propylidene)-1-azabicyclo[2.2.2]octan-3-one (**4e**) (3.00 g, 0.0155 mol) in methanol (250 mL) was hydrogenated in a Parr shaker at 35 psi over 10% Pd/C. After the hydrogen consumption was complete (2 h), the mixture was filtered through Celite and concentrated in vacuo to give 2.92 g (96%) of **5e** as colourless crystals.

Mp 62–64°C. MS *m/z* (%): 195 (M^+, 8), 193 (58), 165 (88), 150 (63), 137 (33), 122 (100). IR (KBr, cm^{-1}): 3413, 2956, 2870, 1718. ^1H NMR (300 MHz, $CDCl_3$) δ 3.16–2.90 (m, 4H, NCH_2); 2.85–2.72 (m, 1H, NCHC=); 2.39 (quintet, 1H, *J*=3 Hz, CH); 2.02–1.83 (m, 4H, CH_2); 1.68 (dd, 1H, *J*=14 Hz, 4 Hz, R–CH_2); 1.47 (dd, 1H, *J*=14 Hz, 8 Hz, R–CH_2); 0.98 (s, 9H, CH_3). Anal. ($C_{12}H_{21}NO$): Calcd C, 73.80; H, 10.84; N, 7.17. Found C, 73.77; H, 11.13; N, 7.19.

The following compounds were prepared according to Method B with the variations stated below.

2-(2-Ethyl-butylidene)-1-azabicyclo[2.2.2]octan-3-one (4f). In 44% yield starting from 1-azabicyclo[2.2.2]octan-3-one (**2**) and 2-ethylbutyric aldehyde, the reaction mixture was stirred at 60°C for 7 days. The resulting colourless oil was crystallised as the oxalate salt.

Mp 96–97°C. MS *m/z* (%): 207 (M^+, 44), 179 (17), 164 (37), 150 (100), 136 (40), 122 (76). IR (KBr, cm^{-1}): 3453, 2964, 2862, 1732, 1661. ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 1H, CH= (*Z*)); 6.11 (s, 1H, CH= (*E*)); 3.19–3.05 (m, 2H, NCH_2); 2.94–2.81 (m, 2H, NCH_2); 2.72–2.58 (m, 1H, CHC=); 2.58 (quintet, 1H, *J*=3 Hz, CH); 1.96 (dt, 4H, *J*=8 Hz, 3 Hz, q-CH_2); 1.60–1.44 (m, 2H, R–CH_2); 1.37–1.22 (m, 2H, CH_2); 0.85 (t, 6H, *J*=7 Hz, CH_3). Anal. ($C_{13}H_{21}NO$, $C_2H_2O_4$): Calcd C, 60.59; H, 7.80; N, 4.71. Found C, 60.66; H, 7.81; N, 4.70.

(*RS*)-2-(2-Ethyl-butyl)-1-azabicyclo[2.2.2]octan-3-one 5f. In 76% yield starting from 2-(2,2-dimethyl-propylidene)-1-azabicyclo[2.2.2]octan-3-one (**4f**), the colourless oil was crystallised as the oxalate salt.

Mp 151–153°C. MS *m/z* (%): 209 (M^+, 1), 181 (42), 152 (100), 124 (11), 111 (56), 110 (42), 96 (28). IR (KBr, cm^{-1}): 3436, 2964, 2877, 1734, 1636. ^1H NMR (300 MHz, $CDCl_3$) δ 3.21–2.98 (m, 3H, NCH_2+NCHC=); 2.98–2.75 (m, 2H, NCH_2); 2.40 (quintet, 1H, *J*=3 Hz, CH); 2.03–1.84 (m, 4H, q-CH_2); 1.72–1.59 (m, 1H, R–CH); 1.57–1.18 (m, 6H, R–CH_2); 0.88 (t, 3H, *J*=7 Hz, CH_3); 0.85 (t, 6H, *J*=7 Hz, CH_3). Anal. ($C_{13}H_{23}NO$, $C_2H_2O_4$): Calcd C, 60.18; H, 8.42; N, 4.68. Found C, 60.21; H, 8.63; N, 4.70.

Method C (Peterson reaction)

(*Z*)-(*RS*)-3-(3-Methyl-isoxazol-5-ylmethylene)-2-phenylsulphanyl-1-azabicyclo[2.2.2]octane (6a) and (*E*)-(*RS*)-3-(3-methyl-isoxazol-5-ylmethylene)-2-phenylsulphanyl-1-azabicyclo[2.2.2]octane (7a). To a solution of diisopropylamine (0.56 mL, 0.0043 mol) in THF (15 mL) at 0°C, *n*-butyllithium (2.50 M in hexanes, 1.80 mL, 0.0043 mol) was added dropwise over a period of 5 min. The resulting yellow solution was stirred at 0°C for 30 min, after which 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) (0.609 g, 0.0036 mol) was slowly added. After 15 min at 0°C the temperature was lowered to −78°C and stirring was continued for another 15 min. Over a period of 10 min (*RS*)-2-phenylsulphanyl-1-azabicyclo[2.2.2]octan-3-one (**3a**) (0.699 g, 0.0030 mol) was added as a solution in THF (35 mL). This was followed by stirring at −78°C for 5 h, after which the reaction was quenched with 1 N HCl (10 mL) and left stirring at 20°C overnight. Ethyl acetate (20 mL) was added to the yellow solution, the layers were separated, and the organic phase extracted with 2×25 mL 1N HCl. The combined aqueous extracts were made alkaline (K_2CO_3) and extracted with dichloromethane (4×25 mL). Drying

($MgSO_4$) and concentration in vacuo gave 0.960 g of a brown oil. Gas chromatography of the crude product showed, that the (*Z*/*E*) ratio was 95:5%. Column chromatography (eluent: methanol/dichloromethane 1:15) gave 0.57 g (61%) (*Z*)-(*RS*)-3-(3-methyl-isoxazol-5-ylmethylene)-2-phenylsulphanyl-1-azabicyclo[2.2.2]octan-3-one (**6a**) as a colourless oil and 0.10 g (11%) as a mixture of **6a** and **7a**. **6a** was crystallised as the oxalate salt.

6a. Mp 167–168°C. MS *m*/*z* (%): 312 (M^+, 35), 279 (9), 203 (100), 162 (70), 148 (12), 134 (32). IR (KBr, cm^{-1}): 3433, 2953, 2813, 1735, 1699, 1569, 1207, 1001, 698. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H, J=7 Hz, H_{meta}); 7.38–7.20 (m, 3H, $H_{ortho}+H_{para}$); 6.31 (d, 1H, J=1 Hz, CH=); 6.13 (s, 1H, isox-H); 5.37 (s, 1H, NCHSC=); 3.92–3.79 (m, 1H, NCH_2); 3.28–3.13 (m, 1H, NCH_2); 2.84–2.69 (m, 2H, NCH_2); 2.57 (m, 1H, CH); 2.28 (s, 3H, CH_3); 1.92–1.63 (m, 4H, CH_2). Anal. ($C_{18}H_{20}N_2OS$, 1.5 $C_2H_2O_4$): Calcd C, 56.37; H, 5.18; N, 6.26. Found C, 56.52; H, 5.31; N, 6.26.

7a. ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 2H, H_{meta}); 7.35–7.18 (m, 3H, $H_{ortho}+H_{para}$); 6.61 (d, 1H, J=3 Hz, CH=); 5.97 (s, 1H, isox-H); 5.18 (s, 1H, NCHSC=); 3.75–3.54 (m, 1H, NCH_2); 3.54 (quintet, 1H, J=3 Hz, CH); 3.28–3.10 (m, 1H, NCH_2); 3.05–2.71 (m, 2H, NCH_2); 2.29 (s, 3H, CH_3); 1.86–1.58 (m, 4H, CH_2).

The following compounds were prepared according to Method C with the variations stated below.

6a and 7a using *n*-butyllithium. *n*-Butyllithium (2.50 M in hexanes, 1.3 molar equivalents) was added at −78°C to a solution of 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) in THF. The reaction mixture was stirred for 30 min at −78°C, before addition of (*RS*)-2-phenylsulphanyl-1-azabicyclo[2.2.2]octan-3-one (**3a**). Gas chromatography of the crude product showed, that the (*Z*/*E*) ratio was 80:20%.

(*Z*)-(*RS*)-3-(3-Methyl-isoxazol-5-ylmethylene)-2-phenylselanyl-1-azabicyclo[2.2.2]octane (6b) and (*E*)-(*RS*)-3-(3-methyl-isoxazol-5-ylmethylene)-2-phenylselanyl-1-azabicyclo[2.2.2]octane (7b). In 85% total yield starting from 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) and (*RS*)-2-phenylselanyl-1-azabicyclo[2.2.2]octan-3-one (**3b**). ^1H NMR of the crude product showed, that the (*Z*/*E*) ratio was 84:16%. Gas chromatography was not possible, as the products decomposed in the oven. Column chromatography (eluent: ethyl acetate) gave 46 mg **7b** as a colourless oil, 141 mg **6b** as a colourless oil, and 607 mg of a **6b**/**7b** mixture. **6b** was crystallised as the hydrochloride salt, and **7b** was crystallised as the oxalate salt.

6b. Mp 206–208°C. MS *m*/*z* (%): 360 (M^++1, 12), 279 (5), 203 (100), 162 (81), 148 (15), 134 (41). IR (KBr, cm^{-1}): 3432, 2956, 2877, 2473, 1748, 1636, 1568, 1419, 1396, 999, 692. ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.64 (m, 2H, H_{meta}); 7.32–7.20 (m, 3H, $H_{ortho}+H_{para}$); 6.21 (d, 1H, J=3 Hz, CH=); 6.10 (s, 1H, isox-H); 5.62 (s, 1H, NCHSC=); 3.98–3.80 (m, 1H, NCH_2); 3.32–3.13 (m, 1H, NCH_2); 2.94–2.68 (m, 2H, NCH_2); 2.52 (m, 1H, CH); 2.28 (s, 3H, CH_3); 1.90–1.61 (m, 4H, CH_2). Anal. ($C_{18}H_{20}N_2OSe$, HCl, 0.25 H_2O): Calcd C, 54.01; H, 5.41; N, 7.00. Found C, 54.13; H, 5.41; N, 6.97.

7b. Mp 134–136°C. MS *m*/*z* (%): 360 (M^++1, 12), 279 (5), 203 (100), 162 (81), 148 (15), 134 (41). IR (KBr, cm^{-1}): 3435, 2959, 2544, 1719, 1635, 1566, 1201, 999, 690. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.59 (m, 2H, H_{meta}); 7.35–7.23 (m, 3H, $H_{ortho}+H_{para}$); 6.56 (d, 1H, J=3 Hz, CH=); 5.93 (s, 1H, isox-H); 5.48 (s, 1H, NCHSeC=); 3.75–3.58 (m, 1H, NCH_2); 3.50 (quintet, 1H, J=4 Hz, CH); 3.32–3.12 (m, 1H, NCH_2); 3.01–2.72 (m, 2H, NCH_2); 2.28 (s, 3H, CH_3); 1.89–1.62 (m, 4H, CH_2). Anal. ($C_{18}H_{20}N_2OSe$, $C_2H_2O_4$): Calcd C, 53.46; H, 4.93; N, 6.23. Found C, 53.16; H, 5.02; N, 5.98.

(*Z*)-(*RS*)-3-(3-Methyl-isoxazol-5-ylmethylene)-2-methylsulphanyl-1-azabicyclo[2.2.2]octane (6c) and (*E*)-(*RS*)-3-(3-methyl-isoxazol-5-ylmethylene)-2-methylsulphanyl-1-azabicyclo[2.2.2]octane (7c). In 75% total yield starting from 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) and (*RS*)-2-methylsulphanyl-1-azabicyclo[2.2.2]octan-3-one (**3c**). Gas chromatography of the crude product showed that the (*Z*/*E*) ratio was 88:12%. **7c** could not be isolated as a pure isomer, and in the ^1H NMR spectrum of the product mixture the overlap of the aliphatic peaks was too pronounced to enable a proper assignment. **6c** (colourless oil) was crystallised as the oxalate salt.

6c. Mp 158–159°C. MS *m*/*z* (%): 250 (M^+, 5), 204 (100), 203 (46), 162 (17), 134 (18). IR (KBr, cm^{-1}): 3433, 3145, 2935, 2559, 1628, 1566, 1409, 1197, 1177, 720. ^1H NMR (400 MHz, MeOD) δ 6.59 (d, 1H, J=3 Hz, CH=); 6.38 (s, 1H, isox-H); 5.98 (s, 1H, NCHSC=); 4.21–4.12 (m, 1H, NCH_2); 3.75–3.66 (m, 1H, NCH_2); 3.45–3.33 (m, 2H, NCH_2); 2.90 (m, 1H, CH); 2.50 (s, 3H, SCH_3); 2.32 (s, 3H, CH_3); 2.25–2.11 (m, 2H, CH_2); 2.07–1.92 (m, 2H, CH_2). Anal. ($C_{13}H_{18}N_2OS$, $C_2H_2O_4$): Calcd C, 52.93; H, 5.92; N, 8.23. Found C, 52.99; H, 5.95; N, 8.16.

(*Z*)-(*RS*)-3-(3-Methyl-isoxazol-5-ylmethylene)-2-benzyl-1-azabicyclo[2.2.2]octane (6d) and (*E*)-(*RS*)-3-(3-methyl-isoxazol-5-ylmethylene)-2-benzyl-1-azabicyclo[2.2.2]octane (7d). In 79% total yield starting from 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) and (*RS*)-2-benzyl-1-azabicyclo[2.2.2]octan-3-one (**5d**). Upon addition of ketone, the reaction mixture was stirred at −78°C for 90 min, followed by 90 min at 20°C. Gas chromatography of the crude product showed that the (*Z*/*E*) ratio was 65:35%. Column chromatography (eluent: ethyl acetate/methanol/ammonium hydroxide 25% in water 94:6:0.5) gave 850 mg **6d** and 440 mg **7d** as colourless oils, which were crystallised with oxalic acid from acetone.

6d. Mp 139–140°C. MS *m*/*z* (%): 294 (M^+, 39), 203 (100), 172 (25), 162 (14), 134 (12). IR (KBr, cm^{-1}): 3438, 2961, 2579, 1743, 1651, 1570, 1194, 996, 701. ^1H NMR (400 MHz, MeOD) δ 7.57 (d, 2H, J=7 Hz, H_{ortho}); 7.40 (t, 2H, J=7 Hz, H_{meta}) 7.32 (quartet, 1H, J=7 Hz, H_{para}); 6.59 (s, 1H, CH=); 6.34 (s, 1H, isox-H); 5.22 (m, 1H, NCHC=); 3.89–3.80 (m, 1H, NCH_2); 3.49–3.21 (m, 5H, NCH_2+CH_2Ph); 3.09 (dd, 1H, J_{gem}=18 Hz, J_{vic}=14 Hz, CH_2Ph); 2.95 (m, 1H, CH); 2.31 (s, 3H, CH_3); 2.25–2.15 (m, 3H, CH_2); 2.08–1.92 (m, 1H, CH_2). Anal. ($C_{19}H_{22}N_2O$, 1.25 $C_2H_2O_4$): Calcd C, 63.46; H, 6.07; N, 6.88. Found C, 63.45; H, 6.39; N, 6.86.

7d. Mp 136–137°C. MS *m*/*z* (%): 294 (M^+, 39), 203 (100), 172 (25), 162 (14), 134 (12). IR (KBr, cm^{-1}): 3433, 2959, 2569, 1720, 1638, 1572, 1417, 1311, 1207, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H, Ph); 5.86 (s, 1H, CH=); 5.82 (s, 1H, isox-H); 3.72 (t, 1H, *J*=9 Hz, NCHC=); 3.45 (m, 1H, CH); 3.28–3.15 (m, 1H, NCH_2); 3.12–2.90 (m, 3H, NCH_2+CH_2Ph); 2.86–2.72 (m, 2H, NCH_2); 2.28 (s, 3H, CH_3); 1.86–1.62 (m, 4H, CH_2). Anal. ($C_{19}H_{22}N_2O$, $C_2H_2O_4$, 0.5 C_3H_6O): Calcd C, 65.36; H, 6.58; N, 6.78. Found C, 65.49; H, 6.43; N, 6.43.

(*Z*)-(*RS*)-3-(3-Methyl-isoxazol-5-ylmethylene)-2-(2,2-dimethyl-propyl)-1-azabicyclo[2.2.2]octane (6e) and (*E*)-(*RS*)-3-(3-Methyl-isoxazol-5-ylmethylene)-2-(2,2-dimethyl-propyl)-1-azabicyclo[2.2.2]octane (7e). In 92% total yield starting from 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) and (*RS*)-2-(2,2-dimethylpropyl)-1-azabicyclo[2.2.2]-octan-3-one (**5e**). Upon addition of ketone, the reaction mixture was stirred at −78°C for 90 min, followed by 90 min at 20°C. Gas chromatography of the crude product showed that the (*Z*/*E*) ratio was 80:20%. Flash chromatography (eluent: ethyl acetate) gave 690 mg **6e**, 58 mg **7e** and 513 mg of a **6e**/**7e** mixture. **6e** and **7e** were crystallised with oxalic acid from acetone to give white powders.

6e. Mp 192–193°C. MS *m*/*z* (%): 274 (M^+, 66), 259 (39), 217 (85), 203 (24), 189 (48). IR (KBr, cm^{-1}): 3431, 3047, 2954, 1713, 1695, 1649, 1570, 1415, 1190, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 1H, CH=); 5.88 (s, 1H, isox-H); 4.14 (m, 1H, NCHC=); 3.26–3.18 (m, 1H, NCH_2); 3.18–2.99 (m, 1H, NCH_2); 2.76–2.60 (m, 2H, NCH_2); 2.42 (m, 1H, CH); 2.28 (s, 3H, CH_3); 1.84–1.54 (m, 5H, CH_2+R–CH_2); 1.46 (dd, 1H, *J*=15 Hz, 2 Hz, R–CH_2); 1.06 (s, 9H, R–CH_3). Anal. ($C_{17}H_{26}N_2O$, $C_2H_2O_4$): Calcd C, 62.62; H, 7.74; N, 7.69. Found C, 62.75; H, 7.89; N, 7.65.

7e. Mp 164–165°C. MS *m*/*z* (%): 274 (M^+, 66), 259 (39), 217 (85), 203 (24), 189 (48). IR (KBr, cm^{-1}): 3429, 3023, 2949, 2878, 1745, 1662, 1588, 1413, 1376, 1199, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (s, 1H, CH=); 5.88 (s, 1H, isox-H); 3.91 (m, 1H, NCHC=); 3.37 (quintet, 1H, *J*=7 Hz, CH); 3.10–2.98 (m, 2H, NCH_2); 2.92–2.82 (m, 1H, NCH_2); 2.77–2.67 (m, 1H, NCH_2); 2.28 (s, 3H, CH_3); 1.79–1.57 (m, 5H, CH_2+R–CH_2); 1.46–1.39 (m, 1H, R–CH_2); 1.00 (s, 9H, R–CH_3). Anal. ($C_{17}H_{26}N_2O$, $C_2H_2O_4$, 0.5 C_3H_6O, 0.5 H_2O): Calcd C, 61.87; H, 7.98; N, 7.04. Found C, 61.94; H, 8.15; N, 6.70.

(*Z*)-(*RS*)-3-(3-Methyl-isoxazol-5-ylmethylene)-2-(2-ethyl-butyl)-1-azabicyclo[2.2.2]octane (6f) and (*E*)-(*RS*)-3-(3-methyl-isoxazol-5-ylmethylene)-2-(2-ethyl-butyl)-1-azabicyclo[2.2.2]octane (7f). In 83% total yield starting from 3-methyl-5-trimethylsilanylmethyl isoxazole (**1**) and (*RS*)-2-(2-ethyl-butyl)-1-azabicyclo[2.2.2]octan-3-one (**5f**). Upon addition of ketone, the reaction mixture was stirred at −78°C for 90 min, followed by 90 min at 20°C. Gas chromatography of the crude product showed that the (*Z*/*E*) ratio was 75:25%. The oily crude product was crystallised with oxalic acid from acetone, and recrystallised in boiling acetone to give 439 mg of **6f** as white crystals. The remaining mixture of **6f** and **7f** was purified by column chromatography (eluent: methanol/dichloromethane 1:10) to give 82 mg pure **7f** as a colourless oil, which was then crystallised with oxalic acid from acetone.

6f. Mp 169–171°C. MS *m*/*z* (%): 288 (M^+, 44), 259 (27), 217 (10), 204 (66), 176 (28). IR (KBr, cm^{-1}): 3434, 2959, 2874, 2566, 1729, 1627, 1571, 1449, 1445, 1378, 1201, 996, 715, 701. ^{1}H NMR (300 MHz, DMSO) δ 6.42 (s, 1H, CH=); 6.33 (s, 1H, isox-H); 4.73 (m, 1H, NCHC=); 3.44–3.10 (m, 4H, NCH_2); 2.79 (m, 1H, CH); 2.22 (s, 3H, CH_3); 2.08–1.08 (m, 11H, CH_2+R–CH_2+R–CH); 0.85 (t, 3H, *J*=7 Hz, R–CH_2); 0.80 (t, 3H, *J*=7 Hz, R–CH_2). Anal. ($C_{18}H_{28}N_2O$, $C_2H_2O_4$): Calcd C, 63.47; H, 7.99; N, 7.40. Found C, 63.50; H, 8.05; N, 7.36.

7f. Mp 131–133°C. MS *m*/*z* (%): 288 (M^+, 44), 259 (27), 217 (10), 204 (66), 176 (28). IR (KBr, cm^{-1}): 3431, 2957, 2875, 1739, 1663, 1599, 1414, 1370, 1200, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 1H, CH=); 5.89 (s, 1H, isox-H); 3.46 (m, 1H, NCHC=); 3.41 (m, 1H, CH); 3.16–2.94 (m, 2H, NCH_2); 2.89–2.70 (m, 2H, NCH_2); 2.28 (s, 3H, CH_3); 1.81–1.19 (m, 11H, CH_2+R–CH_2+R–CH); 0.93–0.83 (m, 6H, R–CH_2). Anal. ($C_{18}H_{28}N_2O$, $C_2H_2O_4$): Calcd C, 63.47; H, 7.99; N, 7.40. Found C, 63.55; H, 8.04; N, 7.30.

(*Z*)-3-(3-Methyl-isoxazol-5-yl)methylene-1-azabicyclo-[2.2.2]octane (6g). $SnBu_3H$ (1.3 mL, 4.8 mmol) and α,α′-azoisobutyronitrile (AIBN) (0.20 g, 1.2 mmol) was added to a stirred solution of (*Z*)-(*RS*)-3-(3-methyl-isoxazol-5-ylmethylene)-2-phenylsulphanyl-1-azabicyclo[2.2.2]octane (**6a**) (0.76 g, 2.4 mmol) in dry toluene (40 mL) at 120°C. Upon stirring for 15 min at 120°C, TLC (methanol/dichloromethane 1:9) showed that all starting material had reacted. The reaction mixture was poured into 1 N HCl (50 mL), whereupon the layers were separated. Extraction with further 2×50 mL 1 N HCl gave an aqueous phase, which was basified (K_2CO_3, pH≈11) and extracted with 4×50 mL dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated. Column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide 25% in water 94:6:0.5) of the crude oil gave 61 mg (12%) of **6g** as a colourless oil. The spectral data of **6g** were identical to those previously published.[1]

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