A simple preparation of *syn*-NH-amide aldols and amide-Baylis–Hillman adducts *via* a Michael–aldol tandem process

Akio Kamimura,*[a] Yoji Omata,[a] Hiromasa Mitsudera[a] and Akikazu Kakehi[b]

[a] *Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Ube 755-8611, Japan*
[b] *Department of Material Engineering, Faculty of Engineering, Shinshu University, Nagano 380-8553, Japan*

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The thiolate- or selenolate-induced Michael–aldol tandem process using secondary α,β-unsaturated amides gave α-phenylthio- or α-phenylseleno-methyl-β-hydroxy amides *syn*-selectively, which were readily converted into NH-amide aldols or Baylis–Hillman adducts.

Introduction

NH-amide aldol units often form part of the structure of natural products and are also regarded as a useful precursor to access β-lactam rings which are prepared through the intramolecular S_N2 displacement of their hydroxy group or equivalent with the amide nitrogen.[1] Despite their synthetic potential, the preparation of the NH-amide aldols has been rather complicated[2] due to the existence of the acidic amide-proton;[3] selective deprotonation of the α-position is usually difficult on treatment of the NH-amide with strong bases. To overcome the problem, one of the known solutions is use of two equivalents of strong base which generate α,*N*-dianions of the amides or thioamides.[4] The aldol reaction of this α,*N*-dianion, however does not always provide a sufficient yield of aldol adduct or give sufficient stereoselectivity.[5] Consequently, an alternative non-basic approach to the aldol reaction of the NH-amide enolate has been of interest. Recently, we have found a new Michael–aldol tandem procedure that gives α-phenylthio- or α-phenylseleno-alkyl-β-hydroxy esters stereoselectively.[6] Here, we report the application of the tandem process to acrylamide which gives secondary or tertiary α-phenylthio- or α-phenylseleno-alkyl-β-hydroxy amides in a stereoselective manner. Subsequent reductive or oxidative treatment of the tandem adducts provides a useful preparation of NH-amide aldols or amide–Baylis–Hillman adducts which are not obtained in appreciable yield under the normal Baylis–Hillman reaction conditions.[7]

Results and discussion

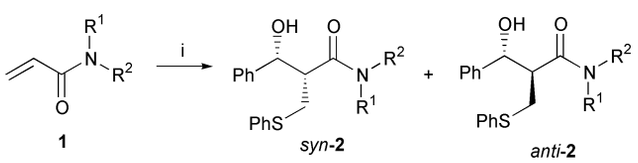
To a mixture of one equivalent of lithium thiophenolate in CH_2Cl_2, the *N*-substituted acrylamide was added; the precipitate of lithium thiophenolate partially dissolved. Benzaldehyde was then added and the mixture became a pale yellow homogeneous solution, which was allowed to stir at −30 °C for 15 h. After the usual work-up, the desired tandem adduct **2** was isolated in good yield (Scheme 1). The results are summarised in Table 1.

The reaction of *N*-benzylacrylamide gave the desired NH-amide aldol **2a** in 64% yield (entry 1). To our surprise, only a very small amount of the simple Michael adduct of the thiol or unreacted acrylamide were observed in the crude reaction mixture. Thus, the acidic NH proton did not quench the enolate intermediate before the desired aldol reaction occurred. The stereoselectivity was, however, rather poor and the adduct consisted of two of the possible diastereomers in a ratio of about 6:4. To improve the stereoselectivity, the reaction conditions and the R^1 amide residues were varied. For secondary amides, *N*-*tert*-butylacrylamide underwent the tandem reaction to give **2b** in satisfactory yields with good stereoselectivity (entry 2). As we expected, when the reaction was performed at a lower temperature the formation of **2b** occurred with better selectivity but in poor to moderate yields (entries 3 and 4). The reaction with tertiary acrylamides proceeded smoothly and resulted in the formation of tandem adducts. For example, *N*,*N*-dibenzylacrylamides afforded tandem adduct **2c** in good yield with good *syn*-selectivity (entry 5), which is in contrast to mono-*N*-benzylamide which afforded a mixture of the two diastereomers (entry 1). *syn*-Selectivity was observed in the reaction of the *N*,*N*-diisopropyl derivative, but the yield of **2d** was poor (entry 6). Curiously, the stereoselectivity disappeared in the reaction with a cyclic acrylamide which gave a mixture of two diastereomers in about 2:1 ratio (entry 7). Use of magnesium as the counter cation of the thiolate was also effective in the preparation of tandem adduct **2b** in 75% yield, but the *syn*:*anti* ratio was 70:30.

Table 1 The tandem amide–Michael–aldol reaction to benzaldehyde

Entry	R^1	R^2	*T*/°C	**2**	Yield (%)[a]	*syn*:*anti*[b]
1	Bn	H	−30 to rt	**2a**	64	59:41
2	Bu-*t*	H	−30 to rt	**2b**	72	95:5
3	Bu-*t*	H	−50	**2b**	11	96:4
4	Bu-*t*	H	−30	**2b**	58	98:2
5	Bn	Bn	−30 to rt	**2c**	75	86:14
6	Pr-*i*	Pr-*i*	−30 to rt	**2d**	28	90:10
7	-$(CH_2)_5$-		−30 to rt	**2e**	75	64:36

[a] Isolated yield. [b] Determined by ^{1}H-NMR or HPLC analyses.



Scheme 1 *Reagents*: i, PhSLi, CH_2Cl_2, PhCHO.

We next applied these reaction conditions to other aldehydes (Scheme 2). The results are summarised in Table 2. Aromatic aldehydes gave the NH-amide aldols **2** in good yields with high

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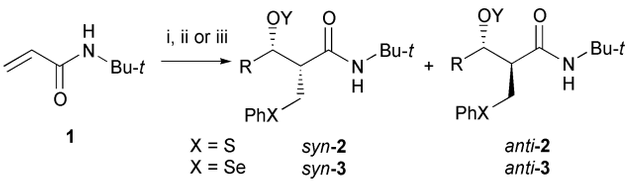
Table 2 The Michael–aldol reaction with various aldehydes

Entry	R	X	Y	Method	Product	Yield (%)[a]	*syn*:*anti*[b]
1	*p*-Cl-C_6H_4-	S	H	A	**2f**	83	93:7
2	*p*-MeO-C_6H_4-	S	H	A	**2g**	62	93:7
3	2-furyl	S	H	A	**2h**	64	93:7
4	$C_{10}H_7$-	S	H	A	**2i**	48	86:14
5	C_5H_{11}-	S	H	A	**2j**	14	*n/d*
6	Ph	Se	H	A	**3a**	82	87:13
7	*p*-Cl-C_6H_4-	Se	TBS	B	**3b**	67	89:11
8	*p*-MeO-C_6H_4-	Se	H	A	**3c**	80	87:13
9	2-furyl-	Se	TBS	B	**3d**	52	89:11
10	C_5H_{11}-	Se	H	A	**3e**	0	—

[a] Isolated yield. [b] Determined by ^{1}H-NMR or HPLC analyses.

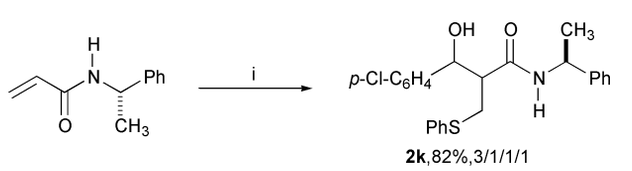


Scheme 2 *Reagents*: i, PhSLi, CH_2Cl_2, RCHO, −30 °C to rt, 15 h; ii, PhSeLi, ether, RCHO, −10 °C to rt, 15 h; iii, PhSeLi, ether, RCHO, −10 °C to rt, 15 h then TBSCl, ImH, DMF.

syn-selectivity (entries 1–4), while the reaction with an aliphatic aldehyde only gave the aldol product in a poor yield (entry 5). Selenolate anions, generated from the *in situ* treatment of PhSeSePh with MeLi, also promoted the reaction efficiently and the seleno-analogue **3** was isolated in good yield (entry 6). The diastereoselectivity of the reaction was of a level similar to the reaction with thiolate. The yields of **3** were improved when the aldehyde was added before the acrylamide. The present procedure was applied to other aromatic aldehydes and the desired tandem adducts **3** were obtained in good yields (entries 7–9). Due to difficulties in removing trace amounts of the side product, simple conjugate adducts of selenolate to acrylamide, in some cases the tandem adducts were isolated as their *O*-protected form (entries 7 and 9). The aliphatic aldehyde tested did not give the tandem adduct (entry 10).

The stereochemistry of adducts **2** were determined by X-ray crystallographic analyses and NMR spectral comparison. For example, the major isomer of compound **2b** was obtained as a single crystal, whose X-ray crystallographic analysis indicated the configuration between C2 and C3 to be *syn*. In *syn*-**2b**, the H3 signal appeared at 5.03 ppm, while the H3 signal in the minor *anti*-**2b** was observed at 4.93 ppm. The NMR spectra for all the compounds **2** reported in Table 2 showed the same pattern; the major isomer's proton appeared downfield. Consequently, we concluded that the major configuration of all compounds **2** was *syn*, which was the same stereochemical preference as for the analogous tandem reaction with *tert*-butyl acrylates. For tertiary amides, a single crystal of the major isomer of **2d** was also isolated and the X-ray crystallographic analysis for the compounds revealed the configuration to be *syn*.

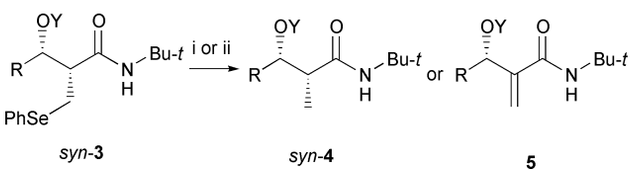
To investigate the possibility of extending the reaction for asymmetric synthesis, an optically active acrylamide was used for the reaction (Scheme 3). Although the adduct **2h** was



Scheme 3 *Reagents*: i, PhSLi, CH_2Cl_2, *p*-Cl-C_6H_4CHO, −30 °C to rt, 15 h.

isolated in good yield, it contained all of the four possible diastereomers, one of which was formed as the major product.

The transformation of the phenylseleno group in compound **3** under reductive or oxidative conditions was examined (Scheme 4). The results are summarised in Table 3.



Scheme 4 *Reagents*: i, Bu_3SnH, AIBN, toluene, reflux; ii, H_2O_2, THF, 0 °C.

Reduction of the phenylseleno group to a hydrogen was readily achieved on treatment with Bu_3SnH; *syn*-NH-amide aldols **4** were obtained in good yields. No epimerisation during the radical process was observed, and the initial diastereomeric ratio in **3** was maintained in the diastereomeric ratio in product **4**. It should be noted that this two-step preparation of NH-amide aldol **4** contains neither an *N*-deprotection nor a hydrolysis–amidation step which are often carried out in the multi-step preparations of the NH-amide aldols. Consequently, the present method provides a useful preparation of *syn*-aldols of free NH-amides.

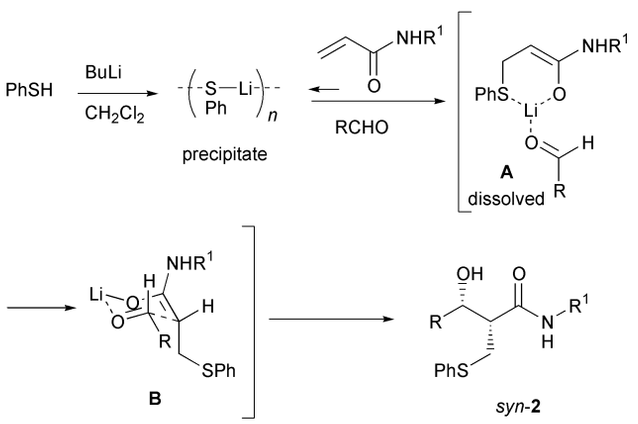
Although the α-methylene aldol adducts, we call the amide–Baylis–Hillman adducts, are regarded as useful synthetic building blocks, the direct Baylis–Hillman reaction with acrylamide resulted in the formation of the adducts in poor yields.[7] For example, a mixture of **1a**, benzaldehyde and catalytic amounts of DABCO, which is a typical Baylis–Hillman procedure, did not afford the desired adduct **5a** after 7 days of reaction time; all the starting materials were recovered unchanged. Although some modification of the reaction conditions such as use of high pressure conditions, irradiation by microwaves or use of aqueous media, enhanced the reaction rate, the yield of amide–Baylis–Hillman adducts remained at an unsatisfactory level.[8] On the other hand, treatment of **3** with hydrogen peroxide proceeded smoothly with elimination of selenoxide, giving the desired amide–Baylis–Hillman adduct **5** in high yields. Thus, this two step sequence provides an alternative and practical route to obtain the amide–Baylis–Hillman adducts from acrylamide quickly.

Although the reaction mechanism is not clear at present, we assume that the reaction proceeds through the following steps outlined in Scheme 5; firstly the three components, thiolate, acrylamide and aldehyde, coordinate to a lithium cation to form an NH-amide enolate complex **A** which is soluble in CH_2Cl_2. In this complex, geometry of the enolate must be *Z* because the lithium cation and the thiolate anion are likely to approach the acrylamide from the same side when forming complex **A**. Additionally, amide enolates usually prefer the *Z*-configuration when generated under basic conditions.[9] No

Table 3 Conversion of **3** into NH-amide aldols **4** or amide–Baylis–Hillman adducts **5**

Entry	3	R	Y	4	Yield (%)[a]	*syn*:*anti*[b]	5	Yield (%)[a]
1	**3a**	Ph	H	**4a**	81	87:13	**5a**	94
2	**3b**	*p*-Cl-C_6H_4-	TBS	**4b**	92	88:12	**5b**	93
3	**3c**	*p*-MeO-C_6H_4-	H	**4c**	82	83:17	**5c**	77
4	**3d**	2-Furyl-	TBS	**4d**	95	88:12	**5d**	85

[a] Isolated yield. [b] Determined by ^{1}H-NMR or HPLC analyses.



Scheme 5

NH-deprotonation occurs due to the weak basicity of thiolate. The intermediate then undergoes a six-membered ring transition state **B**, which affords aldol **2** with *syn*-configuration favourably.

The present methodology will provide a short and useful approach to the NH-amide aldols and amide–Baylis–Hillman adducts from secondary acrylamides. Further investigation on this chemistry is underway in our laboratory.

Experimental

All ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on a JEOL EX-270 (270 MHz for ^{1}H and 67.5 MHz for ^{13}C) or a Bruker Advance 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer. *J* Values are given in Hz. All the reactions in this paper were performed under a nitrogen atmosphere. Solvents used in the reactions described here were dried over the appropriate drying agents (K for THF, Na for ether and toluene, and CaH_2 for all other solvents) and distilled under nitrogen before use. Aldehydes were purified by distillation. Acrylamides were prepared from the appropriate amine and acryloyl chloride. Bu_3SnH, thiophenol and diphenyl diselenide were from Aldrich and were used without further purification.

General procedure for the Michael–aldol tandem reaction with thiolate anions. *N*-*tert*-Butyl-3-hydroxy-3-phenyl-2-(phenylthiomethyl)propionamide *syn*-2b

To a solution of thiophenol (0.128 g, 1.16 mmol) in CH_2Cl_2 (2 cm^3) was added butyllithium in hexanes (1.6 M, 0.7 cm^3, 1.12 mmol) at −78 °C and lithium thiophenolate precipitated as a white solid. To the heterogeneous mixture, *N*-*tert*-butylacrylamide (0.129 g, 1.02 mmol) and benzaldehyde (0.109 g, 1.03 mmol) were added at −30 °C; the reaction mixture turned to a pale yellow solution, which was allowed to warm to room temperature for 15 h. Aqueous HCl (1 M, 5 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 30 cm^3). The organic phase was washed with brine (10 cm^3) and dried over Na_2SO_4. After filtration and removal of the solvent *in vacuo*, flash chromatography (silica gel, hexane–ethyl acetate 5:1 v/v) of the crude residue gave **2b** (0.248 g, 71%) as a white solid; mp 114 °C (Found: C, 69.74; H, 7.37; N, 4.06. $C_{20}H_{25}NO_2S$ requires C, 69.94; H, 7.34; N, 4.08%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–3300, 3000 and 1640; δ_H(270 MHz, $CDCl_3$) 1.29 (s, 9 H), 2.36 (dt, *J* 3.6, 7.1, 1 H), 3.16 (d, *J* 6.9, 2 H), 4.31 (br, 1 H), 5.10 (d, *J* 3.3, 1 H), 5.44 (br, 1 H), 6.95 (dd, *J* 1.3, 7.2, 2 H) and 7.13–7.36 (m, 8 H); δ_C(67.5 MHz, $CDCl_3$) 28.6, 29.4, 51.7, 52.7, 73.6, 126.0, 127.5, 128.2, 128.3, 129.0, 129.5, 135.3, 140.9 and 173.0.

***N*-Benzyl-3-hydroxy-3-phenyl-2-(phenylthiomethyl)propionamide 2a.** The title compound **2a** was prepared from *N*-benzylacrylamide (0.162 g, 1.00 mmol) as a white solid (0.240 g, 64%); mp 136 °C (Found: C, 73.11; H, 6.18; N, 3.78. $C_{23}H_{23}NO_2S$ requires C, 73.18; H, 6.14; N, 3.71%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–3250, 3000 and 1620; δ_H(270 MHz, $CDCl_3$) 2.54 (dt, *J* 4.3, 7.3, 1 H), 3.23 (d, *J* 7.3, 2 H), 4.04 (d, *J* 1.7, 1 H), 4.37 (d, *J* 5.6, 2 H), 5.13 (d, *J* 4.0, 1 H), 5.95 (br, 1 H), 6.93 (dd, *J* 1.7, 7.9, 2 H), 7.07–7.18 (m, 4 H) and 7.24–7.35 (m, 9 H); δ_C(67.5 MHz, $CDCl_3$) 29.5, 43.7, 52.8, 73.7, 125.9, 126.0, 127.6, 127.8, 128.2, 128.4, 128.7, 129.0, 135.0, 137.4, 140.7 and 173.5.

***N*,*N*-Dibenzyl-3-hydroxy-3-phenyl-2-(phenylthiomethyl)-propionamide *syn*-2c.** The title compound **2c** was prepared from *N*,*N*-dibenzylacrylamide (0.250 g, 0.99 mmol). Flash chromatography of the crude product using hexane–ethyl acetate as the eluent gave *syn*-**2c** as a white solid (0.295 g, 64%); mp 106 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–3300, 3000 and 1640; δ_H(270 MHz, $CDCl_3$) 1.96 (d, *J* 11.5, 1 H), 3.12 (dd, *J* 2.5, 14.3, 1 H), 3.33 (dd, *J* 11.6, 14.5, 1 H), 4.14 (d, *J* 15.8, 1 H), 4.22 (s, 1 H), 4.36 (d, *J* 17.5, 1 H), 4.73 (s, 1 H), 4.95 (s, 1 H), 5.54 (d, *J* 15.2, 1 H), 6.62–6.67 (m, 4 H), 6.76 (m, 2 H), 7.03–7.09 (m, 3 H) and 7.20–7.41 (m, 11 H); δ_C(67.5 MHz, $CDCl_3$) 28.2, 46.0, 50.7, 50.8, 73.1, 125.2, 125.5, 125.8, 126.7, 127.1, 127.4, 127.5, 127.8, 127.9, 128.6, 128.8, 129.0, 135.5, 136.3, 137.1, 140.2 and 176.7. Further elution gave *anti*-**2c** as a white solid (0.050 g, 11%); mp 99 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–3300, 3000 and 1600; δ_H(270 MHz, $CDCl_3$) 3.22 (dt, *J* 3.4, 7.0, 1 H), 3.36 (dd, *J* 6.8, 13.7, 1 H), 3.50 (dd, *J* 7.4, 13.7, 1 H), 3.94 (d, *J* 17.2, 1 H), 4.03 (d, *J* 16.8, 1 H), 4.34 (d, *J* 14.8, 1 H), 4.55 (d, *J* 14.9, 1 H), 5.17 (dd, *J* 3.6, 9.1, 1 H), 5.25 (d, *J* 8.9, 1 H), 6.63 (d, *J* 6.6, 2 H), 6.87–6.99 (m, 2 H) and 7.16–7.30 (m, 14 H); δ_C(67.5 MHz, $CDCl_3$) 34.8, 46.7, 47.9, 49.8, 73.7, 125.7, 126.4, 126.5, 127.3, 127.4, 127.5, 128.0, 128.4, 128.5, 128.7, 129.1, 129.6, 135.2, 135.4, 136.1, 142.8 and 174.6.

***N*,*N*-Diisopropyl-3-hydroxy-3-phenyl-2-(phenylthiomethyl)-propionamide *syn*-2d.** The title compound **2d** was prepared from *N*,*N*-diisopropylacrylamide (0.159 g, 1.02 mmol) as a white solid (0.107 g, 28%); mp 130 °C (Found: C, 70.97; H, 8.01; N, 3.80. $C_{22}H_{29}NO_2S$ requires C, 71.12; H, 7.87; N, 3.77%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–3300, 3000 and 1590; δ_H(270 MHz, $CDCl_3$) 0.87 (d, *J* 6.6, 3 H), 1.08 (d, *J* 6.6, 3 H), 1.32 (d, *J* 6.6, 3 H), 1.38 (d, *J* 6.9, 3 H), 3.16 (td, *J* 3.6, 10.6, 1 H), 3.24–3.37 (m, 3 H), 3.81 (m, *J* 6.5, 1 H), 4.41 (s, 1 H), 4.94 (d, *J* 3.6, 1 H) and 6.94–7.37 (m, 10 H); δ_C(67.5 MHz, $CDCl_3$) 20.5, 20.6, 20.7, 29.8, 29.9, 46.4, 48.1, 49.2, 74.7, 125.3, 126.2, 127.2, 127.6, 128.4, 128.6, 136.2, 141.7 and 173.3.

1-Piperidino-3-hydroxy-3-phenyl-2-(phenylthiomethyl)propan-1-one 2e. The title compound **2e** was prepared from *N*,*N*-diisopropylacrylamide (0.146 g, 1.05 mmol) as a white solid

(0.282 g, 75%); mp 110 °C (Found: C, 70.97; H, 8.01; N, 3.80. $C_{22}H_{29}NO_2S$ requires C, 71.12; H, 7.87; N, 3.77%); $\nu_{max}(CHCl_3)$/cm^{-1} 3300, 3000–2800 and 1600; *syn*-**2e**: δ_H(270 MHz, $CDCl_3$) 1.15–1.56 (m, 6 H), 3.15–3.32 (m, 5 H), 3.41–3.50 (m, 1 H), 3.61 (dd, *J* 6.6, 13.2, 1 H), 4.56 (s, 1 H), 4.97 (d, *J* 3.3, 1 H), 6.91 (d, *J* 8.1, 2 H), 7.07–7.16 (m, 3 H) and 7.27–7.41 (m, 5 H); δ_C(67.5 MHz, $CDCl_3$) 24.3, 25.5, 26.4, 29.5, 43.1, 46.3, 47.2, 74.2, 125.5, 126.0, 127.5, 127.6, 128.4, 128.9, 135.8, 141.2 and 172.4.

***N-tert*-Butyl-3-hydroxy-3-(4-chlorophenyl)-2-(phenylthiomethyl)propionamide *syn*-2f.** The title compound **2f** was prepared from *N-tert*-butylacrylamide (0.127 g, 1.00 mmol) and *p*-chlorobenzaldehyde (0.141 g, 1.00 mmol) as a white solid (0.314 g, 83%); mp 129 °C (Found: C, 63.61; H, 6.44; N, 3.71. $C_{20}H_{24}ClNO_2S$ requires C, 63.56; H, 6.40; N, 3.71%); $\nu_{max}(CHCl_3)$/cm^{-1} 3450–3350, 3000 and 1650; δ_H(270 MHz, $CDCl_3$) 1.31 (s, 9 H), 2.30 (dt, *J* 8.9, 4.0, 1 H), 3.04–3.17 (m, 2 H), 4.50 (br, 1 H), 5.07 (d, *J* 3.0, 1 H), 5.50 (br, 1 H), 6.98 (dd, *J* 1.9, 7.6, 2 H), 7.12–7.21 (m, 3 H), 7.25 (d, *J* 8.1, 2 H) and 7.32 (d, *J* 8.4, 2 H); δ_C(67.5 MHz, $CDCl_3$) 28.6, 29.5, 51.9, 52.4, 72.9, 126.1, 127.3, 128.4, 128.5, 129.1, 133.2, 135.0, 139.4 and 173.0.

***N-tert*-Butyl-3-hydroxy-3-(4-methoxyphenyl)-2-(phenylthiomethyl)propionamide *syn*-2g.** The title compound **2g** was prepared from *N-tert*-butylacrylamide (0.128 g, 1.00 mmol) and *p*-anisaldehyde (0.144 g, 1.06 mmol) as a white solid (0.230 g, 62%); mp 108 °C (Found: C, 67.32; H, 7.37; N, 3.73. $C_{21}H_{27}NO_3S$ requires C, 67.53; H, 7.29; N, 3.75%); $\nu_{max}(CHCl_3)$/cm^{-1} 3400–3300, 2950 and 1640; δ_H(270 MHz, $CDCl_3$) 1.28 (s, 9 H), 2.34 (quintet, *J* 4.5, 1 H), 3.10–3.22 (m, 2 H), 3.82 (s, 3 H), 4.23 (br, 1 H), 5.04 (d, *J* 4.0, 1 H), 5.45 (br, 1 H), 6.89 (dd, *J* 2.0, 6.6, 2 H), 7.01 (dd, *J* 1.4, 8.0, 2 H), 7.10–7.22 (m, 3 H) and 7.25 (d, *J* 8.9, 2 H); δ_C(67.5 MHz, $CDCl_3$) 28.4, 29.7, 51.4, 53.3, 55.2, 73.3, 113.5, 125.6, 127.1, 128.1, 128.8, 133.1, 135.5, 158.8 and 172.6.

***N-tert*-Butyl-3-hydroxy-3-(2-furyl)-2-(phenylthiomethyl)-propionamide *syn*-2h.** The title compound **2h** was prepared from *N-tert*-butylacrylamide (0.128 g, 1.00 mmol) and furfural (0.098 g, 1.02 mmol) as a colourless oil (0.218 g, 64%) (Found: C, 64.50; H, 7.10; N, 4.04. $C_{18}H_{23}NO_3S$ requires C, 64.84; H, 6.95; N, 4.20%); $\nu_{max}(CHCl_3)$/cm^{-1} 3400–3300, 3000 and 1640; δ_H(270 MHz, $CDCl_3$) 1.29 (s, 9 H), 2.61 (td, *J* 4.3, 9.8, 1 H), 3.22 (dd, *J* 9.8, 14.2, 1 H), 3.29 (dd, *J* 4.0, 13.9, 1 H), 4.00 (br, 1 H), 5.07 (d, *J* 4.0, 1 H), 5.52 (br, 1 H), 6.33–6.38 (m, 2 H) and 7.14–7.36 (m, 5 H); δ_C(67.5 MHz, $CDCl_3$) 28.5, 30.4, 50.6, 51.6, 68.9, 107.4, 110.4, 126.0, 128.6, 129.0, 135.4, 141.7, 153.4 and 172.2.

***N-tert*-Butyl-3-hydroxy-3-(1-naphthyl)-2-(phenylthiomethyl)-propionamide *syn*-2i.** The title compound **2i** was prepared from *N-tert*-butylacrylamide (0.128 g, 1.00 mmol) and 1-naphthaldehyde (0.160 g, 1.02 mmol) as a white solid (0.188 g, 48%); mp 125 °C (Found: C, 73.35; H, 6.98; N, 3.53. $C_{24}H_{27}NO_2S$ requires C, 73.25; H, 6.91; N, 3.56%); $\nu_{max}(CHCl_3)$/cm^{-1} 3400–3300, 3000 and 1640; δ_H(270 MHz, $CDCl_3$) 1.30 (s, 9 H), 2.61 (td, *J* 3.0, 7.6, 1 H), 3.12–3.18 (m, 2 H), 4.73 (br, 1 H), 5.55 (br, 1 H), 5.90 (d, *J* 2.6, 1 H), 6.60 (dd, *J* 1.3, 8.9, 2 H), 6.81–6.93 (m, 3 H), 7.42–7.56 (m, 2 H) and 7.74–7.93 (m, 4 H); δ_C(67.5 MHz, $CDCl_3$) 28.6, 29.8, 50.3, 51.8, 70.8, 122.3, 124.6, 125.3, 125.4, 125.5, 126.2, 127.6, 128.1, 128.7, 129.1, 129.8, 133.8, 134.8, 135.7 and 173.5.

***N-tert*-Butyl-3-hydroxy-2-(phenylthiomethyl)octanamide 2j.** The title compound **2j** was prepared from *N-tert*-butylacrylamide (0.130 g, 1.02 mmol) and hexanal (0.101 g, 1.00 mmol) as a white solid (0.046 g, 14%); mp 59 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 3400–3300, 3000 and 1650; δ_H(270 MHz, $CDCl_3$) 0.88 (t, *J* 6.6, 3 H), 1.34 (s, 9 H), 1.27–1.51 (m, 8 H), 2.13–2.19 (m, 1 H), 3.20 (dd, *J* 9.6, 13.9, 1 H), 3.27 (dd, *J* 4.6, 13.5, 1 H), 3.66 (d, *J* 2.0, 1 H), 3.87 (d, *J* 5.6, 1 H), 5.46 (br, 1 H) and 7.17–7.37 (m, 5 H); δ_C(67.5 MHz, $CDCl_3$) 14.0, 22.5, 25.6, 28.6, 30.5, 31.7, 33.8, 50.8, 51.6, 71.9, 126.3, 129.1, 129.3, 135.8 and 173.5.

***N*-[(*S*)-1-phenylethyl]-3-hydroxy-3-(4-chlorophenyl)-2-(phenylthiomethyl)propionamide 2k.** The same procedure as described above from *N*-[(*S*)-1-phenylethyl]acrylamide (0.176 g, 1.00 mmol) and *p*-chlorobenzaldehyde (0.141 g, 1.00 mmol) gave an inseparable diastereomeric mixture of **2k** a white solid (0.347 g, 82%); mp 140–142 °C (Found: C, 67.32; H, 5.75; N, 3.28. $C_{24}H_{24}ClNO_2S$ requires C, 67.67; H, 5.68; N, 3.29%); $\nu_{max}(CHCl_3)$/cm^{-1} 3400–3200, 3000 and 1620; δ_H(400 MHz, $CDCl_3$) 1.38 (d, *J* 6.9, 3 H), 2.41–2.45 (m, 1 H), 3.09–3.20 (m, 2 H), 4.24 (s, 1 H), 5.04–5.09 (m, 2 H), 6.88–6.90 (m, 1 H) and 7.06–7.36 (m, 15 H); δ_C(100 MHz, $CDCl_3$) 22.0, 30.1, 49.4, 49.6, 52.6, 53.1, 53.4, 73.4, 73.5, 126.8, 126.5, 126.6, 127.3, 127.7, 127.8, 127.9, 128.8, 128.9, 129.0, 129.1, 129.4, 129.5, 129.6, 133.8, 135.1, 139.8, 142.8 and 173.0.

General procedure for the Michael–aldol tandem reaction with selenolate anions. *N-tert*-Butyl-3-hydroxy-3-phenyl-2-(phenylselenomethyl)propionamide *syn*-3a

Methyllithium in ether (1.5 M, 2.0 cm^3, 3.0 mmol) was added to a solution of diphenyl diselenide (0.937 g, 3.00 mmol) in ether (4 cm^3) at room temperature until the yellow colour of the diselenide disappeared. The colourless solution was maintained at the same temperature for 1 hour and then cooled to −10 °C. Benzaldehyde (0.350 g, 3.30 mmol) was added to the mixture and the resulting mixture was allowed to stir for 15 min. To the mixture, *N-tert*-butylacrylamide (0.256 g, 2.01 mmol) was added and the reaction mixture was allowed to warm to room temperature for 15 h. Aqueous HCl (1 M, 10 cm^3) was added and the resulting mixture was extracted with ethyl acetate (3 × 30 cm^3). The organic phases were combined and dried over Na_2SO_4. After filtration and removal of the solvent *in vacuo*, the crude product was purified by flash chromatography (silica gel, hexane then hexane–ethyl acetate 5:1 v/v) to give desired tandem product **3a** (0.641 g, 82%) as a white solid; mp 113 °C (Found: C, 61.38; H, 6.61; N, 3.52. $C_{20}H_{25}NO_2Se$ requires C, 61.53; H, 6.45; N, 3.59%); $\nu_{max}(CHCl_3)$/cm^{-1} 3400–3300, 2950 and 1640; δ_H(270 MHz, $CDCl_3$) 1.29 (s, 9 H), 2.38 (ddd, *J* 4.0, 5.3, 9.3, 1 H), 3.08 (dd, *J* 5.3, 13.2, 1 H), 3.16 (dd, *J* 9.3, 12.9, 1 H), 4.70 (s, 1 H), 5.07 (d, *J* 3.6, 1 H), 5.41 (br, 1 H) and 7.11–7.37 (m, 10 H); δ_C(67.5 MHz, $CDCl_3$) 23.3, 28.5, 51.6, 54.0, 74.2, 126.0, 126.5, 127.5, 128.2, 129.1, 129.6, 131.2, 141.0 and 173.0.

***N-tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-3-(4-chlorophenyl)-2-(phenylselenomethyl)propionamide *syn*-3b.** Methyllithium in ether (1.5 M, 2.0 cm^3, 3.0 mmol) was added to a solution of diphenyl diselenide (0.936 g, 3.00 mmol) in ether (4 cm^3) at room temperature until the yellow colour of the diselenide disappeared. The colourless solution was maintained at the same temperature for 1 hour and then cooled to −10 °C. 4-Chlorobenzaldehyde (0.423 g, 3.01 mmol) was added to the mixture and the resulting mixture was allowed to stir for 15 min. To the mixture, *N-tert*-butylacrylamide (0.255 g, 2.01 mmol) was added and the reaction mixture was allowed to warm to room temperature for 15 h. Aqueous HCl (1 M, 10 cm^3) was added and the resulting mixture was extracted with ethyl acetate (3 × 30 cm^3). The organic phases were combined and dried over Na_2SO_4. After filtration and removal of the solvent *in vacuo*, the crude product was dissolved in dry DMF (4 cm^3). Imidazole (1.226 g, 18.01 mmol) and *tert*-butyldimethylchlorosilane (1.211 g, 8.04 mmol) were added to the solution and the reaction mixture was allowed to stir at 50 °C for 37 h. DMF was removed *in vacuo* and the residue was subjected to flash column chromatography (hexane then hexane–ethyl acetate 3:1 v/v) to give tandem product **3b** (0.722 g, 67%) as a white solid; mp 111 °C (Found: C, 57.87; H, 7.22; N,

2.66. $C_{26}H_{38}ClNO_2SeSi$ requires C, 57.93; H, 7.10; N, 2.60%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3300, 3000–2900 and 1660; δ_H(270 MHz, $CDCl_3$) −0.20 (s, 3 H), 0.09 (s, 3 H), 0.91 (s, 9 H), 1.10 (s, 9 H), 2.44 (ddd, *J* 4.0, 7.6, 10.6, 1 H), 3.24 (dd, *J* 10.6, 12.2, 1 H), 3.43 (dd, *J* 3.9, 12.2, 1 H), 4.78 (d, *J* 8.3, 1 H), 4.91 (s, 1 H), 7.27 (d, *J* 8.2, 2 H), 7.18–7.32 (m, 5 H) and 7.50 (dd, *J* 1.5, 8.2, 2 H); δ_C(67.5 MHz, $CDCl_3$) −4.7, 17.9, 25.6, 25.9, 28.3, 28.8, 51.0, 58.5, 75.8, 126.3, 128.0, 128.1, 129.0, 131.1, 131.8, 133.2, 141.0 and 169.8.

***N-tert*-Butyl-3-hydroxy-3-(4-methoxyphenyl)-2-(phenylselenomethyl)propionamide *syn*-3c.** The title compound **3c** was prepared from *N-tert*-butylacrylamide (0.254 g, 2.00 mmol) and *p*-anisaldehyde (0.412 g, 3.02 mmol) as a white solid (0.669 g, 80%); mp 106 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3550–3450, 3100 and 1680; δ_H(270 MHz, $CDCl_3$) 1.27 (s, 9 H), 2.37 (dt, *J* 4.0, 7.6, 1 H), 3.07–3.19 (m, 2 H), 3.81 (s, 3 H), 4.07–4.20 (br, 1 H), 4.99 (d, *J* 4.0, 1 H), 5.42 (br, 1 H), 6.85 (d, *J* 8.9, 2 H) and 7.13–7.38 (m, 7 H); δ_C(67.5 MHz, $CDCl_3$) 23.7, 28.4, 51.4, 54.4, 55.1, 73.8, 113.5, 126.4, 127.1, 129.0, 131.2, 132.1, 133.3, 158.8 and 172.6.

***N-tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-3-(2-furyl)-2-(phenylselenomethyl)propionamide *syn*-3d.** The title compound **3d** was prepared from *N-tert*-butylacrylamide (0.128 g, 1.00 mmol) and furfural (0.146 g, 1.52 mmol) as a colourless oil (0.257 g, 52%) (Found: C, 58.69; H, 7.57; N, 2.71. $C_{24}H_{37}NO_3SeSi$ requires C, 58.28; H, 7.54; N, 2.83%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 3350, 3000–2850 and 1660; δ_H(270 MHz, $CDCl_3$) −0.16 (s, 3 H), 0.05 (s, 3 H), 0.86 (s, 9 H), 1.15 (s, 9 H), 2.79 (dt, *J* 5.5, 8.5, 1 H), 3.27 (dd, *J* 5.6, 13.5, 1 H), 3.32 (dd, *J* 8.6, 12.5, 1 H), 4.84 (d, *J* 8.2, 1 H), 5.44 (br, 1 H), 6.19 (d, *J* 3.3, 1 H), 6.29 (dd, *J* 2.0, 3.3, 1 H), 7.18–7.38 (m, 4 H) and 7.49 (dd, *J* 2.0, 7.9, 2 H); δ_C(67.5 MHz, $CDCl_3$) −4.9, 18.3, 25.9, 26.0, 28.8, 29.2, 51.3, 55.3, 70.3, 108.6, 110.5, 126.7, 129.4, 131.7, 142.1, 154.0 and 170.3.

General procedure for the reductive removal of the phenylseleno group from tandem adducts 3. *N-tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-3-(4-chlorophenyl)-2-methylpropionamide *syn*-4b

A solution of **3b** (0.269 g, 0.50 mmol, *syn*:*anti* = 89:11), Bu_3SnH (0.184 g, 0.63 mmol) and AIBN (0.017 g, 0.10 mmol) in toluene (2 cm^3) was heated at 110 °C for 4 h. The resulting mixture was subjected to flash chromatography (silica gel, hexane–ethyl acetate 20:1 then 10:1 v/v) to give **4b** (0.176 g, 92%, *syn*:*anti* = 88:12) as a colourless oil (Found: C, 62.55; H, 8.92; N, 3.69. $C_{20}H_{34}ClNO_2Si$ requires C, 62.55; H, 8.92; N, 3.65%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 3300, 3000–2800 and 1650; δ_H(270 MHz, $CDCl_3$) 0.01 (s, 3 H), 0.05 (s, 3 H), 0.87 (s, 9 H), 1.16 (s, 9 H), 1.18 (d, *J* 6.9, 3 H), 2.27 (quintet, *J* 6.9, 1 H), 4.70 (d, *J* 7.6, 1 H), 5.12 (br, 1 H) and 7.26 (s, 4 H); δ_C(67.5 MHz, $CDCl_3$) −4.7, 14.1, 18.0, 25.7, 28.5, 28.8, 50.7, 51.5, 76.2, 127.9, 128.0, 132.9, 141.8 and 172.4.

***N-tert*-Butyl-3-hydroxy-3-phenyl-2-methylpropionamide *syn*-4a.** The title compound **4a** was prepared from **3a** (0.158 g, 0.41 mmol) as a white solid (0.078 g, 81%); mp 144 °C (Found: C, 71.11; H, 9.04; N, 5.89. $C_{14}H_{21}NO_2$ requires C, 71.46; H, 8.99; N, 5.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–3300, 3000 and 1650; δ_H(270 MHz, $CDCl_3$) 1.07 (d, *J* 7.3, 3 H), 1.31 (s, 9 H), 2.37 (dq, *J* 3.8, 7.6, 1 H), 4.12 (d, *J* 1.9, 1 H), 5.02 (dd, *J* 2.3, 3.4, 1 H), 5.35 (br, 1 H) and 7.33–7.34 (d, 5 H); δ_C(67.5 MHz, $CDCl_3$) 11.4, 28.6, 47.6, 51.3, 74.1, 126.1, 127.3, 128.1, 141.7 and 175.6.

***N-tert*-Butyl-3-hydroxy-3-(4-methoxyphenyl)-2-methylpropionamide *syn*-4c.** The title compound **4c** was prepared from **3c** (0.211 g, 0.50 mmol) as a white solid (0.109 g, 82%); mp 85 °C (Found: C, 67.78; H, 8.78; N, 5.23. $C_{15}H_{23}NO_3$ requires C, 67.90; H, 8.74; N, 5.28%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450–3300, 3000 and 1650; δ_H(270 MHz, $CDCl_3$) 1.07 (d, *J* 7.3, 3 H), 1.31 (s, 9 H), 2.35 (dq, *J* 3.6, 6.9, 1 H), 3.80 (s, 3 H), 4.00 (br, 1 H), 4.96 (d, *J* 3.6, 1 H), 5.36 (br, 1 H), 6.86 (d, *J* 8.9, 2 H) and 7.26 (d, *J* 8.1, 2 H); δ_C(67.5 MHz, $CDCl_3$) 11.5, 28.6, 47.7, 51.2, 55.2, 73.8, 113.5, 127.2, 133.9, 158.8 and 175.6.

***N-tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-3-(2-furyl)-2-methylpropionamide *syn*-4d.** The title compound **4d** was prepared from **3d** (0.161 g, 0.32 mmol) as a white solid (0.105 g, 95%); mp 81 °C (Found: C, 63.37; H, 9.66; N, 4.17. $C_{18}H_{33}NO_3Si$ requires C, 63.67; H, 9.80; N, 4.13%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3300, 3000–2850 and 1660; δ_H(270 MHz, $CDCl_3$) 0.00 (s, 3 H), 0.06 (s, 3 H), 0.86 (s, 9 H), 1.18 (d, *J* 6.6, 3 H), 1.19 (s, 9 H), 2.60 (quintet, *J* 6.9, 1 H), 4.75 (d, *J* 7.3, 1 H), 5.64 (br, 1 H), 6.19 (d, *J* 3.3, 1 H), 6.30 (dd, *J* 2.0, 3.3, 1 H) and 7.34 (t, *J* 1.0, 1 H); δ_C(67.5 MHz, $CDCl_3$) 13.7, 18.0, 25.6, 25.7, 28.5, 28.8, 47.9, 50.6, 70.9, 107.6, 110.1, 141.5, 154.5 and 172.2.

General procedure for the conversion of 3a into the amide–Baylis–Hillman adduct. *N-tert*-Butyl-3-hydroxy-3-phenyl-2-methylenepropionamide 5a

Aqueous hydrogen peroxide (*ca*. 30%, 0.55 g, 0.49 mmol) was added to a solution of **3a** (0.118 g, 0.30 mmol) in THF (3 cm^3) at room temperature. The reaction mixture was allowed to stir for 12 hours. THF was removed *in vacuo* and the residue was subjected to flash chromatography (silica gel, hexane then hexane–ethyl acetate 2:1 v/v) to give **5a** (0.066 g, 94%) as a white solid; mp 89 °C (Found: C, 71.70; H, 8.18; N, 5.99. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–3300, 3000, 1650 and 1600; δ_H(270 MHz, $CDCl_3$) 1.27 (s, 9 H), 3.94 (d, *J* 5.3, 1 H), 5.36 (s, 1 H), 5.50 (d, *J* 5.0, 1 H), 5.96 (br, 1 H) and 7.24–7.40 (m, 5 H); δ_C(67.5 MHz, $CDCl_3$) 28.5, 51.3, 74.9, 119.9, 126.0, 127.5, 128.3, 141.0, 146.2 and 167.4.

***N-tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-3-(4-chlorophenyl)-2-methylenepropionamide 5b.** The title compound **5b** was prepared from **3b** (0.279 g, 0.52 mmol) as a white solid (0.185 g, 93%); mp 93 °C (Found: C, 62.57; H, 8.36; N, 3.65. $C_{20}H_{32}ClNO_2Si$ requires C, 62.88; H, 8.44; N, 3.67%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3350, 3000–2850, 1660 and 1620; δ_H(270 MHz, $CDCl_3$) 0.08 (s, 3 H), 0.10 (s, 3 H), 0.93 (s, 9 H), 1.15 (s, 9 H), 5.48 (s, 1 H), 5.49 (s, 1 H), 6.01 (d, *J* 1.3, 1 H), 6.49 (br, 1 H) and 7.26 (s, 4 H); δ_C(67.5 MHz, $CDCl_3$) −4.9, 18.1, 25.7, 28.5, 50.8, 75.0, 121.6, 126.8, 128.2, 132.9, 140.2, 145.8 and 164.6.

***N-tert*-Butyl-3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropionamide 5c.** The title compound **5c** was prepared from **3c** (0.221 g, 0.53 mmol) as a white solid (0.107 g, 77%); mp 85 °C (Found: C, 68.09; H, 7.78; N, 5.37. $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300–3200, 3000, 1650 and 1580; δ_H(270 MHz, $CDCl_3$) 1.24 (s, 9 H), 3.78 (s, 3 H), 4.58 (br, 1 H), 5.31 (s, 1 H), 5.41 (s, 1 H), 5.77 (s, 1 H), 6.42 (br, 1 H), 6.85 (d, *J* 8.7, 2 H) and 7.26 (d, *J* 8.9, 2 H); δ_C(67.5 MHz, $CDCl_3$) 28.9, 51.6, 55.6, 74.7, 114.0, 120.6, 127.7, 133.7, 146.9, 159.3 and 167.7.

***N-tert*-Butyl-3-(*tert*-butyldimethylsilyloxy)-3-(2-furyl)-2-methylenepropionamide 5d.** The title compound **5d** was prepared from **3d** (0.223 g, 0.45 mmol) as a colourless oil (0.129 g, 85%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 3350, 3000–2850, 1660 and 1620; δ_H(270 MHz, $CDCl_3$) 0.11 (s, 3 H), 0.14 (s, 3 H), 0.93 (s, 9 H), 1.29 (s, 9 H), 5.52 (s, 1 H), 5.53 (s, 1 H), 6.09 (d, *J* 1.3, 1 H), 6.22 (t, *J* 1.3, 1 H), 6.32 (dd, *J* 2.0, 3.3, 1 H), 6.83 (br, 1 H) and 7.34 (t, *J* 1.0, 1 H); δ_C(67.5 MHz, $CDCl_3$) 18.1, 25.6, 28.6, 50.8, 70.7, 106.5, 110.1, 122.5, 141.9, 143.5, 154.2 and 164.7.

Crystal structure determination of 2b and 2d

Single crystals of **2b** and **2d** were recrystallised from CH_2Cl_2–hexane.

Crystal data for 2b. $C_{20}H_{25}NO_2S$, $M = 343.48$, monoclinic, $a = 10.917(4)$, $b = 21.278(5)$, $c = 9.367(7)$ Å, $U = 1948(1)$ Å^3, $T = 294.2$ K, space group Cc (no. 9), $Z = 4$, μ(Mo-Kα) = 0.169 mm^{-1}, 7543 reflections measured, 932 unique ($R_{int} = 0.054$) which were used in all calculations. The final $wR(F^2)$ was 0.0482 (all data).

Crystal data for 2d. $C_{22}H_{29}NO_2S$, $M = 371.54$, orthorhombic, $a = 16.09(1)$, $b = 16.19(1)$, $c = 8.298(7)$ Å, $U = 2163(2)$ Å^3, $T = 294.2$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, μ(Mo-Kα) = 0.156 mm^{-1}, 2845 reflections measured, 1179 unique ($R_{int} = 0.063$) which were used in all calculations. The final $wR(F^2)$ was 0.0551 (all data). CCDC reference number 207/490. See http://www.rsc.org/suppdata/p1/b0/b004721j/ for crystallographic files in .cif format.

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