Tetrahedron Letters 50 (2009) 4331–4334

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First dynamic kinetic resolution of selenium-containing chiral amines catalyzed by palladium ($Pd/BaSO_4$) and *Candida antartica* lipase (CAL-B)

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ARTICLE INFO

Article history:
Received 4 April 2009
Revised 7 May 2009
Accepted 11 May 2009
Available online 18 May 2009

ABSTRACT

An efficient method for chemoenzymatic dynamic kinetic resolution of selenium-containing chiral amines (organoselenium-1-phenylethanamines) has been developed, leading to the corresponding amides in excellent enantioselectivities and high isolated yields. This one-pot procedure employs two different types of catalysts: Pd on barium sulphate ($Pd/BaSO_4$) as racemization catalyst and lipase (CAL-B) as the resolution catalyst.

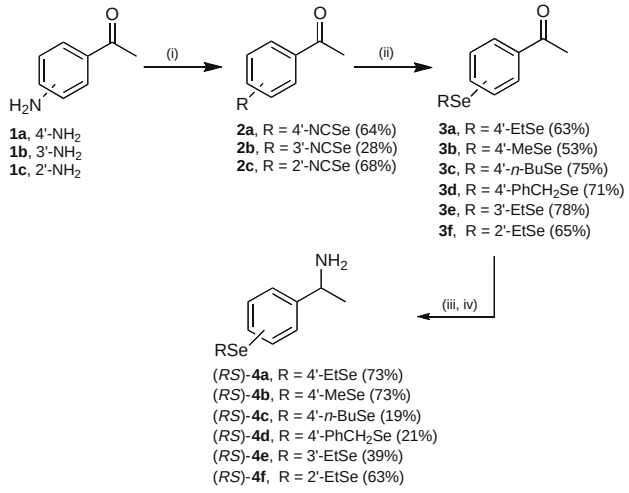
1. Introduction

Chiral organoselenium compounds have demonstrated important applications in organic synthesis, especially as catalysts in asymmetric reactions.[1a–c] Thus, some synthetic tools have been applied to synthesize organoselenium compounds in enantiomerically pure form. Among them, we can mention the use of chiral precursors,[2a,b] and more recently, enantioselective synthesis mediated by enzymes.[3a–c] In the search for practical ways to generate selenium-containing chiral compounds, we turned our attention to bioreduction of organoselenoacetophenones mediated by alcohol dehydrogenases[3a] and kinetic resolution of organoseleno-phenylethanols mediated by lipase.[3b,3c] Encouraged by the excellent results obtained by CAL-B as biocatalyst in the enantioselective acylation of organoseleno-phenylethanols, we decided to study the enzymatic kinetic resolution of organoselenium-1-phenylethanamines through enantioselective acylation. In fact, by using this enzymatic approach, the enantiopure organoselenium amides were obtained in excellent enantiomeric excess (>99%).[4] However, enzymatic kinetic resolution has a drawback, the yield is limited to a maximum 50%. An excellent alternative to achieve 100% yield is the use of a chemoenzymatic protocol, the Dynamic Kinetic Resolution (DKR).[5a,b] This methodology has been shown to be very useful to obtain enantiomerically pure amines and amides in up to 100% yield.[6] This protocol makes use of a catalyst to racemize the amine and a biocatalyst to perform the kinetic resolution. The catalysts usually employed for racemization are ruthenium,[6b–d] iridium,[6e] thiols and AIBN,[6f] palladium[6g–i] and Raney nickel and cobalt.[6j] The kinetic resolution of the amines can be performed by enantioselective acylation mediated by lipases. Therefore, now, we report the first application of the DKR to obtain selenium-containing chiral amides using Pd on barium sulphate ($Pd/BaSO_4$) as racemization catalyst and lipase (CAL-B) as biocatalyst for kinetic resolution through enantioselective acylation.

2. Results and discussion

2.1. Synthesis of the organoselenium-1-phenylethanamines (*RS*-4a–f)

The organoselenium-1-phenylethanamines (*RS*-**4a–f**) were prepared from commercially available *ortho*-, *meta*-, and *para*-aminoacetophenones as described in Scheme 1.



Scheme 1. Reagents and conditions: (i) $NaNO_2$, HCl 2 M, pH 4.3, 0 °C, then KSeCN, 1 h; (ii) RBr, $NaBH_4$, MeOH, 0 °C, 2 h; (iii) $Ti(OCH(CH_3)_2)_4$, NH_3/EtOH (2 M), 12 h; (iv) $NaBH_4$, 12 h, rt.

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doi:10.1016/j.tetlet.2009.05.022

Initially, the in situ preparation of diazonium salts from *ortho*-, *meta*-, and *para*-aminoacetophenones followed by the addition of KSeCN afforded the corresponding selenocyanate acetophenones **2a–c** (up to 68% yield).[4] The next step was the alkylation of the selenium atom using $NaBH_4$ and alkyl halide to give *ortho*-, *meta*-, and *para*-organoselenium acetophenones **3a–f** (up to 78% yield). After the alkylation step, we carried out the reductive amination of the organoselenium acetophenones **3a–f** to afford the organoselenium-1-phenylethanamines **4a–f** (up to 73% yield).

2.2. Evaluation of different acyl donors for the enzymatic kinetic resolution of organoselenium-1-phenylethanamines

Before starting the dynamic kinetic resolution of organoselenium-1-phenylethanamines *RS*-**4a–f**, a screening test was performed to choose the most appropriate acyl donor for the kinetic resolution (KR) via enantioselective acylation catalyzed by lipase (CAL-B).[10] The selected acyl donors for this study were ethyl methoxyacetate, ethyl acetate, dimethyl carbonate, ethyl benzoate, and vinyl benzoate.

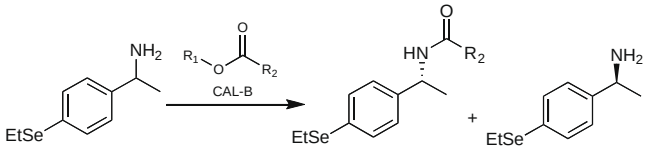
The 1-(4-ethylselenium)phenylethanamine (*RS*-**4a**) was selected as model substrate and hexane as solvent. The results are summarized in Table 1.

As can be seen in Table 1, the use of ethyl methoxyacetate, ethyl acetate, and dimethyl carbonate as acyl donors for the KR of the (*RS*)-**4a** gave the amide (*S*)-**5a** in excellent ee (>99%) and enantiomeric ratio (*E* >200). In relation to the conversion, dimethyl carbonate as acyl donor gave the product (*R*)-**5** with 13% conversion, and with ethyl acetate the conversion value was 18%. When ethyl methoxyacetate was used the conversion increased to 36%, and no reaction was observed with ethyl benzoate and vinyl benzoate as acyl donors.

Encouraged by the results presented in Table 1, we decided to apply ethyl methoxyacetate and ethyl acetate as acyl donors on the kinetic resolution of the organoselenium amines **4e** and **4f** (Table 2). It is worth to mention that dimethyl carbonate is a good acylant agent for amines because the formed carbamate can be easily transformed into the free amine. In spite of this important characteristic, this compound cannot be applied in the DKR because the acylated product (carbamate) is not stable in the racemization conditions required for this process.[8]

In order to evaluate the influence of different acyl donors toward 1-phenylethanamines containing the ethylselenium group attached to the *meta* and *ortho* position of the aromatic ring, we performed the enzymatic kinetic resolution of the compounds **4e** and **4f** with ethyl methoxyacetate and ethyl acetate as acyl donors. The results are summarized in Table 2.

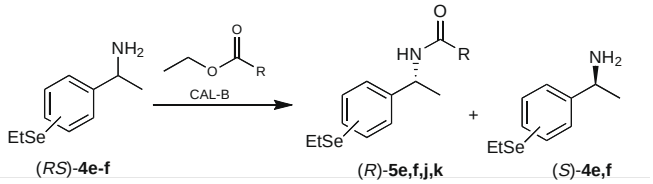
Table 1
Influence of acyl donor on the kinetic resolution of amine (*RS*)-**4a** mediated by CAL-B[a]



Entry	R_1	R_2	(*R*)-**5** ee[b] (%)	(*S*)-**4a** ee[d] (%)	*c*[e]	*E*[f]
1	Et	Me	99	22	18	>200
2	Et	Ph	—	—	—	—
3	Vinyl	Ph	—	—	—	—
4	Me	MeO	99[c]	15	13	>200
5	Et	$MeOCH_2$	99[c]	55	36	>200

[a] Reaction conditions: (*RS*)-**4a** (0.2 mmol), CAL-B (20 mg), acyl donor (0.8 mmol), hexane (1 mL), 30 °C, 48 h.[10]
[b] ee determined by chiral HPLC analysis.[11]
[c] ee determined after hydrolysis and derivatization with acetic anhydride.
[d] ee determined after derivatization with acetic anhydride.
[e] Conversion: $c = ee_s/(ee_s + ee_p)$.
[f] $E = \ln\{(1 - ee_s)/(1 + ee_s/ee_p)\}/\ln\{(1 + ee_s)/(1 + ee_s/ee_p)\}$.[7]

Table 2
Enzymatic kinetic resolution of 1-(ethylselenium)phenylethanamines (*RS*)-**4e–f**[a]



Entry	Substrate	R	(*R*)-**5** ee[b] (%)	(*S*)-**4** ee[d] (%)	*c*[e]	*E*[f]
1	4e, 3′-EtSe	Me	>99	38	38	>200
2	4e, 3′-EtSe	$MeOCH_2$	81[c]	59	42	17
3	4f, 2′-EtSe	Me	>98	8	8	107
4	4f, 2′-EtSe	$MeOCH_2$	70[c]	47	40	9

[a] Reaction conditions: (*RS*)-**4e**, **f** (0.2 mmol), CAL-B (20 mg), acyl donor (0.8 mmol), hexane (1 mL), 30 °C, and 48 h.[10]
[b] ee determined by chiral HPLC analysis.[11]
[c] ee determined after hydrolysis and derivatization with acetic anhydride.
[d] ee determined after derivatization with acetic anhydride.
[e] Conversion: $c = ee_s/(ee_s + ee_p)$.
[f] $E = \ln\{(1 - ee_s)/(1 + ee_s/ee_p)\}/\ln\{(1 + ee_s)/(1 + ee_s/ee_p)\}$.[7]

When ethyl acetate was used as acyl donor the ee values for the products **5e** (98%) and **5f** (99%) were similar to those observed for organoselenium amide **5a** (Table 1, entry 1). In contrast, the conversion value for the *ortho* isomer **4f** (8%) was significantly lower than that for the *meta* isomer **4e** (38%) (Table 2, entries 1 and 3). The low conversion in the kinetic resolution of **4f** can be attributed to the selenium–nitrogen interaction (Se···N).[9] Due to this interaction, the nucleophilicity of the amine group decreases and, consequently, a low conversion can be observed. The same interaction cannot occur when the selenium atom is at the *para* or *meta* position of the aromatic ring.

In comparison with the substrate (*RS*)-**4a** (Table 1, entry 5), we can observe that the KR of (*RS*)-**4e** and (*RS*)-**4f** with ethyl methoxyacetate and CAL-B had lower *E*-values (Table 2, entries 2 and 4) than those reactions with ethyl acetate as acyl donor. In view of these results, we selected ethyl acetate as acyl donor to be employed on the DKR of organoselenium amines.

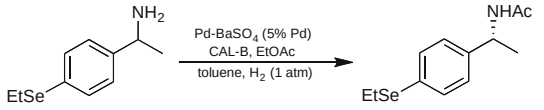
2.3. Dynamic kinetic resolution of organoselenium-1-phenylethanamines (4a–f)

As palladium catalyst, $Pd/BaSO_4$, can be used for racemization of amines,[6g,h] initially, we performed a racemization test with the enantiomerically enriched substrate **4a**. By using the (*S*)-**4a**, 40 mol % of $Pd/BaSO_4$ (5% Pd), toluene at 70 °C under hydrogen (1 atm), and after 48 h, the racemic amine was observed. Thus, we decided to investigate the dynamic kinetic resolution of the amine (*RS*)-**4a** in a more detailed way (Table 3).[12]

As mentioned in Table 3 (entries 1–3), the first reaction condition tested was similar to that used in the kinetic resolution of the 1-(ethylselenium)phenylethanamines (Section 2.2), ethyl acetate as acyl donor, lipase of *Candida antartica* (CAL-B) and toluene at 30 °C under hydrogen atmosphere (1 atm).

Moreover, the effect of the reaction time (24, 48, and 120 h) in the DKR of the (*R,S*)-**4a** was evaluated (Table 3, entries 1–3). The product (*R*)-**5a** was obtained in moderate yield (11–38%) but with excellent enantiomeric excess (91–99%). Then, the same reaction condition was applied to a higher temperature, 50 °C (Table 3, entries 4–6). Indeed, with the increase of the temperature we almost duplicated the yield of the product (*R*)-**5a**. A long reaction time (120 h) for both temperatures (30 and 50 °C) resulted in a decrease

Table 3
Dynamic kinetic resolution of amine (*RS*)-**4a** using Pd/$BaSO_4$ (5% Pd) and CAL-B[a]



(*RS*)-**4a** (*R*)-**5a**

Entry	*T* (°C)	Time (h)	Pd/$BaSO_4$ (mol %)	(*R*)-**5a**	
				ee[b] (%)	Yield (%)
1	30	24	40	>99	11
2	30	48	40	>99	22
3	30	120	40	91	38
4	50	24	40	>99	32
5	50	48	40	>99	39
6	50	120	40	61	61
7	50	48	10	>99	26
8	50	48	30	>99	36
9	50	60	10	>99	47
10	50	60	30	>99	43
11	70	24	40	>99	23
12	70	48	40	>99	57
13	70	120	40	75	22
14	70	48	10	>99	74

[a] Reaction conditions: (*RS*)-**4a** (0.2 mmol), CAL-B (60 mg), ethyl acetate (2 × 0.8 mmol), and toluene (4 mL).[12]
[b] ee determined by chiral HPLC analysis.[11]

of the enantiomeric excess of the (*R*)-**5a**. Based on these results, we decided to study the influence of different amounts of palladium catalyst (Table 3, entries 7–10). Using 10 or 30 mol % of catalyst, after 48 and 60 h reaction time, we obtained the product in up to 47% yield and >99% ee (Table 3, entry 9).

From these results, we expected that an increase in the temperature could lead to a higher yield without compromising the enantioselectivity. In this way, DKR of the (*RS*)-**4a** was performed at 70 °C, in different reaction times 24, 48, and 120 h with 10 and 40 mol % of Pd/$BaSO_4$ (Table 3, entries 11–14). The DKR with 10 mol % of Pd/$BaSO_4$ (48 h, 70 °C) gave (*R*)-**5a** in high yield and excellent enantiomeric excess (Table 3, entry 14: 74% yield, >99% ee).

With the optimized reaction condition in hands, we carried out the DKR of additional organoselenium-1-phenylethanamines (*RS*)-**4b–f** (Table 4).

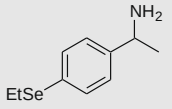
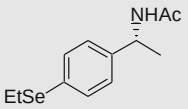
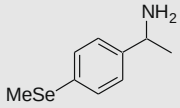
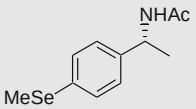
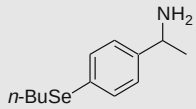
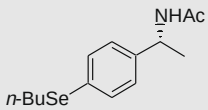
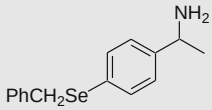
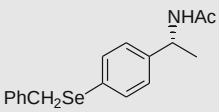
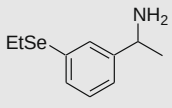
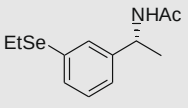
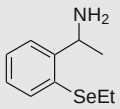
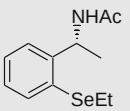
As shown in Table 4, entries 1–5, in spite of the difference of the organoselenium group attached to the aromatic ring, in all cases, the amides (**5a–f**) were obtained in good yield and excellent enantiomeric excess. However, DKR of the compound (*RS*)-**4f**, which contains ethylselenium group attached to the *ortho* position of the aromatic ring, produced the organoselenium amide **5f** in low yield as observed in the KR study (Section 2.2). The unreacted amine (*RS*)-**4f** was recovered. From these results, we also verify that the DKR conditions, which employ palladium, are compatible with the organoselenium compounds and no deselenization was observed.

The absolute configuration of the amides **5a–f** was attributed as follows: The enantiomerically pure organoselenium amides **5a–f** were treated with *n*-butyllithium in THF to afford the enantiomerically pure *N*-(1-phenylethyl)acetamide (Scheme 2). These samples were compared by chiral GC analysis to the (*R*)- and (*S*)-*N*-(1-phenylethyl)acetamide samples prepared from commercially available (*R*)- and (*S*)-1-phenylethanamine.

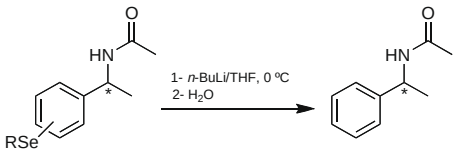
3. Conclusion

In summary, we have demonstrated that the dynamic kinetic resolution mediated by palladium and lipase can be efficiently applied to selenium-containing chiral amines in order to achieve these compounds in high yield and enantioselectivity. The organoselenium groups were compatible with the DKR conditions employed. We expect that this chemoenzymatic protocol will prove to be useful in the synthesis of chiral selenium compounds.

Table 4
Dynamic kinetic resolution of organoselenium-1-phenylethanamines (*RS*)-**4a–f**[a]

Entry	Substrate	Product	% Isolated yield[b] (% ee)	$[\alpha]_D^{25}$
1	 (*RS*)-**4a**	 (*R*)-**5a**	74 (>99)	+102.77 (*c* 0.59, EtOAc)
2	 (*RS*)-**4b**	 (*R*)-**5b**	76 (>99)	+96.39 (*c* 0.78, EtOAc)
3	 (*RS*)-**4c**	 (*R*)-**5c**	77 (>99)	+51.12 (*c* 3.08, EtOAc)
4	 (*RS*)-**4d**	 (*R*)-**5d**	72 (>99)	+65.68 (*c* 1.32, EtOAc)
5	 (*RS*)-**4e**	 (*R*)-**5e**	87 (>99)	+88.67 (*c* 0.21, EtOAc)
6	 (*RS*)-**4f**	 (*R*)-**5f**	30 (>99)	+21.77 (*c* 0.50, EtOAc)

[a] Reaction conditions: (*RS*)-**4a–f** (0.2 mmol), CAL-B (60 mg), ethyl acetate (2 × 0.8 mmol), toluene (4 mL), H_2 (1 atm), 10 mol % Pd/$BaSO_4$ (5% Pd) (42 mg).[12]
[b] ee determined by chiral HPLC analysis.[11]



(*R*) *or* (*S*)-**5a-f** (*R*) *or* (*S*)- *N*-(1-phenylethyl)acetamide

Scheme 2. Deselenization of the organoselenium amides **5a–f** using *n*-BuLi.

Acknowledgments

The authors would like to thank CNPq, CAPES and FAPESP for financial support.

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10. *Representative procedure for kinetic resolution of (RS)-1-((ethylselanyl)phenyl) ethanamines* (**4a**, **4e** *and* **4f**)*:* A suspension containing the organoselenium-1-phenylethanamines (**4a**, **4e**, or **4f**) (0.2 mmol), solvent (1 mL, see tables), CAL-B (Novozym 435) (60 mg), and the acyl donor (see Table 1) was stirred on a rotary shaker for 48 h. After this period, the enzyme was filtered off and washed with CH_2Cl_2 (5 mL). The organic phase was extracted with an aqueous HCl solution (3 × 2 mL, 1 M), affording two solutions: Organic solution (1) containing the amide and aqueous solution (2) containing the amine chloridrate. The organic solution (1) was washed with brine (3 mL) and dried over $MgSO_4$. The solvent was removed in vacuum and the residue, containing the organoselenium amides, was hydrolyzed by reacting the amide with aqueous HCl solution (2 mL, 2 M) at 90 °C for 6 h. After this period, the aqueous phase was extracted with CH_2Cl_2 (5 mL). The organic layer was washed with brine (3 mL) and dried over $MgSO_4$. The organic layer was further acetylated with acetic anhydride for further HPLC analysis.In addition, a saturated aqueous NaOH solution was added to the aqueous solution (2) until pH 10. The resulting solution was extracted with CH_2Cl_2 (3 × 2 mL). The organic phases were combined and washed with brine (3 mL), dried over $MgSO_4$. The solvent was removed in vacuum and the residue, containing the organoselenium amines, was acetylated with acetic anhydride for further HPLC analysis.
11. *HPLC analysis for determination of the enantiomeric excess (ee)*: The enantiomeric purities of the organoselenium amides **5a**–**f** were measured by HPLC analysis. The analysis was carried out on Chiralcel OD-H column and the peaks were detected by a UV detector at 254 nm. Eluent: hexane/isopropanol (95:5), flow rate: 1.0 mL/min. Retention times:(*RS*)-*N*-(1-(4-(Ethylselanyl)phenyl)ethyl) acetamide **(5a)**: (*R*)-**5a** = 20.44 min; (*S*)-**5a** = 24.93 min.(*RS*)-*N*-(1-(4-(Methylselanyl)phenyl)ethyl)acetamide **(5b)**: (*R*)-**5b** = 25.11 min; (*S*)-**5b** = 31.68 min. (*RS*)-*N*-(1-(4-(Butylselanyl)phenyl)ethyl)acetamide **(5c)**: (*R*)-**5c** = 17.56 min; (*S*)-**5c** = 20.87 min.(*RS*)-*N*-(1-(4-(Benzylselanyl)phenyl)ethyl)acetamide **(5d)**: (*R*)-**5d** = 56.46 min; (*S*)-**5d** = 63.76 min.(*RS*)-*N*-(1-(3-(Ethylselanyl)phenyl) ethyl)acetamide **(5e)**: (*R*)-**5e** = 19.19 min; (*S*)-**5e** = 28.29 min.(*RS*)-*N*-(1-(2-(Ethylselanyl)phenyl)ethyl)acetamide (**5f**): (*R*)-**5f** = 16.92 min; (*S*)-**5f** = 44.46 min.
12. *Representative procedure for dynamic kinetic resolution of (RS)-1-((organoselanyl) phenyl) ethanamines* (**4a**–**f**): A suspension containing the organoselenium-1-phenylethanamines (*RS*)-**4a**–**f** (0.2 mmol), Pd-$BaSO_4$ (5% Pd) (42 mg, 10 mol % Pd), CAL-B (60 mg), and ethyl acetate (78 μL and another 78 μL after 24 h) in dry toluene (4 mL) was stirred at 70 °C under hydrogen pressure (1 atm). After 48 h, the reaction mixture was cooled to room temperature and filtered and the remained solid was washed with CH_2Cl_2 (2 × 3 mL). The organic phases were combined and then extracted with an aqueous HCl solution (3 × 3 mL, 1 M), washed with brine (3 mL), and dried over $MgSO_4$. The solvent was removed in vacuum and the residue, containing the (*R*)-organoselenium amides **5a**–**f**, was analyzed by HPLC. In addition, a saturated aqueous NaOH solution was added to the resulting acid aqueous phase until pH 10 and it was then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed once with brine (3 mL) and dried over $MgSO_4$. The solvent was removed in vacuum to give the unreacted organoselenium amines (*RS*)-**4a**–**f**. All the new compounds synthesized were fully characterized. *Selected spectral data*: Compound **5d**: Yield: 72%. IR (KBr) cm^{-1}: 3449, 3342, 2971, 1646, 1538, 1494, 1370, 1138, 819, 697, 539, 463, 425. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.43–7.39 (d, J = 8 Hz, 2H), 7.28–7.17 (m, 7H), 5.68 (s, 1H), 5.12–5.07 (m, 1H), 4.09 (s, 2H), 1.98 (s, 3H), 1.47–1.45 (d, J = 6, 3H). ^{13}C NMR (75 MHz) δ: 169.07, 142.40, 138.47, 133.65, 129.39, 128.83, 128.44, 126.88, 126.84, 48.38, 32.24, 23.46, 21.65. LRMS [EI], *m/z* (relative abundance): 333 (M^+, 29), 318 (1), 274 (4) 200 (4) 120 (3) 91 (100), 65 (5), 43 (4). HRMS [ESI(+)], calcd for $[C_{17}H_{19}NOSe+Na]^+$: 356.053, found 356.0521; calcd for $[C_{17}H_{19}NOSe + K]^+$: 372.0269, found 372.0266.