Decarbonylative Radical Cyclization of α-Amino Selenoesters upon Electrophilic Alkenes. A General Method for the 6-Azabicyclo[3.2.1]octane Synthesis

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α-Amino selenoester-tethered electronically poor alkenes on treatment with tributyltin hydride or TTMSS undergo intramolecular radical cyclization to provide 6-azabicyclo[3.2.1]octanes through 1-aminomethyl radical intermediates.

Introduction

The 6-azabicyclo[3.2.1]octane nucleus is the backbone of peduncularine[1] and actinobolamine[2] and appears as a structural subunit in several alkaloids such as sarain A,[3] aphanorphine,[4] hetisine,[5] and some of the securinega group.[6] Additionally, several 6-azabicyclo[3.2.1]octane compounds are pharmacologically interesting; e.g., azaprophen[7] is a muscarinic antagonist and the 6-methyl-6-azabicyclo[3.2.1]octan-3*β*-ol benzoate has potent binding affinities to the cocaine site on the dopamine transporter.[8]

Despite the availability of many synthetic methods to prepare the 6-azabicyclo[3.2.1]octane skeleton,[9,10] so far there has been little use of radical chemistry to build this bridged framework. Apart from the studies on *N*-centered radicals coming from either *N*-chloramines[11] or amidyl radical precursors,[12] only the procedure reported in this paper[13] and that recently described by Weinreb[6e] using ketyl radicals have been developed to achieve this azabicyclic structure by means of carboradical species.

In our approach to the 6-azabicyclo[3.2.1]octane nucleus, we chose to explore the decarbonylative radical cyclization of α-amino selenoesters upon deactivated alkenes (Scheme 1). Acyl radicals can be generated by hydride treatment of selenoesters, and their reactions can be classified into three types: (i) the atom or group transfer reaction on the acyl carbon, as exemplified by hydrogen abstraction to give the corresponding aldehydes; (ii) the addition to unsaturated bonds; and (iii) the decarbonylation process by a fragmentation to give carbon monoxide and an alkyl radical.[14] We considered that the third pathway would be favored in an α-aminoacyl radical, since the stability of an α-amino-substituted radical is enhanced as a result of the interaction of the nitrogen lone pair with the radical center.[15] Thus, the tributyltin hydride treatment of α-amino selenoesters could be a new entry to α-aminoalkyl radicals. Crich,[16] Boger,[17] and Renaud[18] in their studies on acyl radicals came across decarbonylation analogue processes providing a nitrogen-stabilized radical in lactam or carbamate functionalities, but the reaction with amino compounds is unprecedented.

Several procedures have been reported for the generation of α-aminoalkyl radicals:[19] (a) tin hydride treatment

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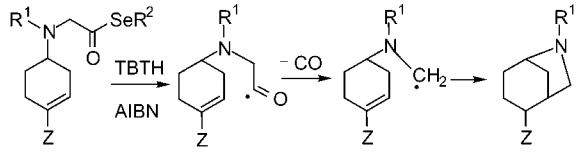
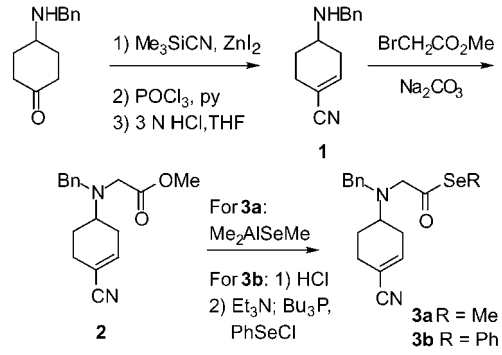
Scheme 1. Proposed Intramolecular Radical Cyclization of α-Amino Selenoesters



Scheme 2. Synthesis of Selenoester-Tethered Nitriles



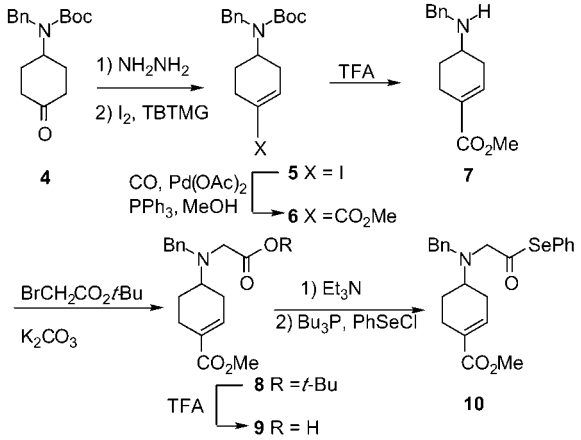
of *N*,*S*-acetals, which in turn are prepared from iminium salts and thiols;[20] (b) treatment of iminium ions with SmI_2;[21] (c) photoinduced single electron transfer from α-trimethylsilylamines;[22] and (d) 1,5-hydrogen transfer in *N*-*o*-halobenzyl or -allyl derivatives.[23]

In this paper we describe a procedure to generate α-aminoalkyl radicals consisting of treatment of α-amino selenoesters with the hydride reagents Bu_3SnH (TBTH) or $(Me_3Si)_3SiH$ (TTMSS), and we report a synthetic entry to valuable functionalized 6-azabicyclo[3.2.1]octanes based on an α-aminoalkyl radical cyclization.

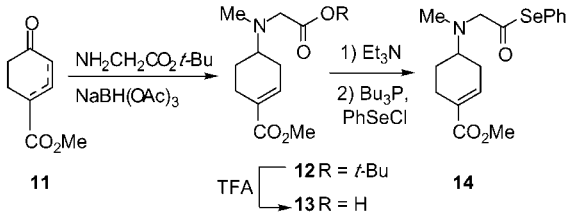
Results and Discussion

Efficient routes to the synthesis of α-amino ester-tethered alkenes **2**, **8**, **12**, and **18** were developed (Schemes 2−5), and these esters served as precursors of the required selenoesters for the radical cyclizations. For the series in which an α,*β*-unsaturated nitrile acts as the radical acceptor, amino ester **2** was prepared by alkylation with methyl bromoacetate of the known secondary amine **1**[24] (Scheme 2). The synthesis of **1**, starting from 4-benzylaminocyclohexanone,[24] was improved by the following synthetic sequence: formation of the corresponding *O*-trimethylsilylcyanohydrin, dehydration with $POCl_3$, and hydrolysis of the generated phosphoramide

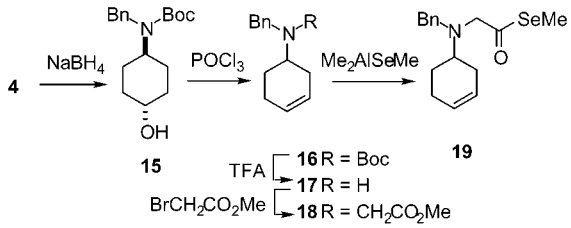
Scheme 3. Synthesis of Selenoester-Tethered Esters



Scheme 4. Straightforward Synthesis of Selenoester-Tethered Esters



Scheme 5. Synthesis of Selenoester-Tethered Alkenes



(50% overall yield for the three steps). From **2** the methylselenoester **3a** was synthesized following the Kozikowski protocol,[25] in which dimethylaluminum methylselenolate reacts directly with the methyl ester **2**, while the Crich protocol[26] was used for the phenylselenoester **3b**, treating the corresponding carboxylic acid with benzeneselanyl chloride in the presence of Bu_3P in a basic medium.

In the series in which an α,*β*-unsaturated ester is the radical acceptor (Schemes 3 and 4), we needed intermediates with an ester group at the side chain that could be converted chemoselectively to the required carboxylic acids (**9** or **13**). For this reason, the *tert*-butyl ester **8** was synthesized, starting from the known ketone **4**.[24] Treatment of **4** with hydrazine monohydrate, followed by oxidative cleavage of the formed hydrazone with iodine in the presence of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine, gave the vinyl iodide **5**, which furnished the compound **8** upon palladium-mediated methoxycarbonylation[27] followed by a deprotection step and alkylation of the secondary amine **7**.[24] Cleavage of *tert*-butyl ester in

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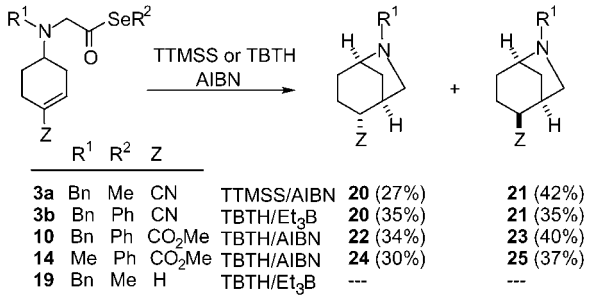
Scheme 6. Synthesis of 6-Azabicyclo[3.2.1]octanes



	R^1	R^2	Z			
3a	Bn	Me	CN	TTMSS/AIBN	**20** (27%)	**21** (42%)
3b	Bn	Ph	CN	TBTH/Et_3B	**20** (35%)	**21** (35%)
10	Bn	Ph	CO_2Me	TBTH/AIBN	**22** (34%)	**23** (40%)
14	Me	Ph	CO_2Me	TBTH/AIBN	**24** (30%)	**25** (37%)
19	Bn	Me	H	TBTH/Et_3B	---	---

8 was followed by the conversion of carboxylic acid **9** into the proradical phenyl selenoester **10**.

A more straightforward synthesis for the *N*-methyl analogue was achieved using our recently reported procedure to obtain 4-alkylaminocyclohex-1-enecarboxylates. This method is based on the reductive amination of the cyclohexenones **11** obtained from the conversion of the Diels−Alder adduct formed by reaction of Danishefsky's diene with methyl acrylate.[28] The application of this procedure, using the *tert*-butyl ester of sarcosine and $NaBH(OAc)_3$ in acetic acid medium in the reductive amination step, led to the tertiary amine **12**, from which the selenoester **14** was prepared (Scheme 4).

In the alkene series in which the radical acceptor lacks an electron-withdrawing group, we prepared the methylselanyl ester **19** from the aminocyclohexene **16** following the sequence depicted in Scheme 5. Compound **16** is available from ketone **4** through three procedures: (a) sodium borohydride reduction, followed by dehydration of the resulting alcohol using $POCl_3$; (b) formation of the tosylhydrazone and its cleavage with K-*t*-BuO in a Shapiro-type process; or (c) formation of the corresponding enol triflate and reduction with Et_3SiH.

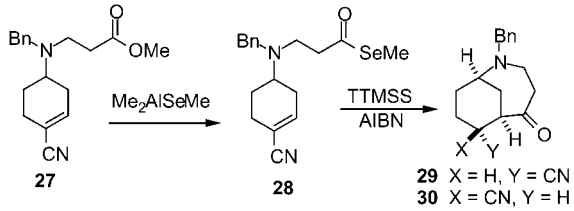
We now turned our attention to the behavior of 1-methylamino radical-tethered alkenes generated from the selenoesters **3**, **10**, **14**, and **19** (Scheme 6). Treatment of **3a**[29] or **3b** with TTMSS/AIBN gave the 6-azabicyclo[3.2.1]octane derivatives **20** and **21** in 2:3 ratio and 69% combined yield. When the reaction was carried out from **3b** at room temperature using TBTH/Et_3B, an equimolecular ratio of both epimers was formed.

Treatment of **10** with TTMSS/AIBN also gave the normorphan nucleus and, as in the above series, a mixture of epimers was formed (**22** and **23**, 45:55 ratio determined by MS−GC). Working from the *N*-methyl derivative **14** and promoting the reaction with TBTH, the bicyclic compounds **24** and **25** were obtained in the same 45:55 ratio.

The stereochemistry of azabicyclic compounds **20**−**25** was proven by NMR techniques. Compounds with the substituent group at C-2 in an equatorial disposition (**21**, **23**, **25**) showed more deshielded signals for C-4 and C-8 than compounds **20**, **22**, and **24**, with the electron-withdrawing group at C-2 (CN or CO_2Me) axially located.

We next attempted to carry out the cyclization process from the selenoester **19**, since there are examples of cyclization of α-amino radicals upon alkenes,[23b] although it is true that several attempts to promote the cyclization

Scheme 7. Synthesis of 2-Azabicyclo[4.3.1]decanes



27 **28** **29** X = H, Y = CN; **30** X = CN, Y = H

of α-amino radicals with tethered nonconjugated alkenes have failed owing to their reduced radicaloid character, due to the nitrogen lone pair interference.[20a,30] In our case, the reaction of **19** either with TTMSS/AIBN at 80 °C or TBTH/Et_3B at room temperature was fruitless, the noncyclized compound **26** being the only product isolated.[31]

Finally, we studied how the β-aminoselenoester **28** reacted in the radical conditions previously used. Unsurprisingly, the radical process occurs via a different pathway (Scheme 7). Thus, the generated acyl radical formed by treatment of **28** with TTMSS/AIBN did not suffer decarbonylation, as this would lead to a β-aminoalkyl radical without any increase in the radical intermediate's stability, but instead reacted intramolecularly with the double bond furnishing the 2-azabicyclo[4.3.1]decanes **29** and **30** in 71% yield (5:2 ratio). The relative configuration at C-7 was inferred from the NMR data. Hence, the isomer **29** that showed C-9 (δ 26.0) and C-10 (δ 28.3) more upfield than isomer **30** (δ 29.1 for C-9 and δ 31.6 for C-10) was assigned to the compound having the cyano group with an axial disposition. The synthetic entry here reported for the homomorphan skeleton present in compounds **29** and **30** constitutes one of the few that have been described for this heterocycle.[33]

In summary, from a strategic viewpoint, the use of α-aminoalkyl radicals, generated by decarbonylation from α-amino selenoesters, tethered with electronically poor double bonds constitutes an attractive entry to 6-azabicyclo[3.2.1]octane compounds. Under other structural circumstances, the initially formed acyl radical suffers only a decarbonylative-reductive process without formation of a new C−C bond. When the radical process is

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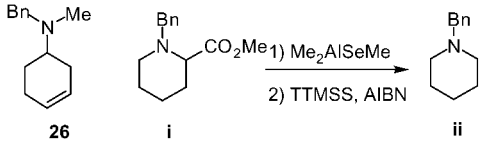
(30) For some interesting observations about the modification of behavior of α-aminoalkyl radicals when the stabilizing influence of the nitrogen lone pair is removed, allowing cyclization processes upon alkenes, see: (a) Rios, L. A.; Dolbier, W. R., Jr.; Paredes, R.; Lusztyk, J.; Ingold, K. U.; Jonsson, M. *J. Am. Chem. Soc.* **1996**, *118*, 11313−11314. (b) Della, E. W.; Smith, P. A. *J. Org. Chem.* **1999**, *64*, 1798−1806. (c) Pandey, G.; Kapur, M. *Synthesis* **2001**, 1263−1267. See also ref 21a

(31) Considering the overall transformation (**18** → **26**), this protocol could be useful as a new procedure for decarboxylation of α-amino acids and their derivatives.[32] For example, α-amino ester **i** was converted into the amino compound **ii** in two steps (60% yield).



26 **i** **ii**

(32) For a radical decarboxylation of *N*-protected amino acids, see: Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2000**, *65*, 4930−4937 and references therein.

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carried out upon β-amino selenoesters, the pathway changes and the cyclization allows a carbonylative process to give an azabicylic ketone through a surviving acyl radical.

Experimental Section[34]

4-[*N*-Benzyl-*N*-(methoxycarbonylmethyl)amino]cyclohex-1-enecarbonitrile (2). To a solution of **1**[24] (1.8 g, 8.6 mmol) in CH_3CN (258 mL) were added Na_2CO_3 (2.7 g, 25.7 mmol) and methyl 2-bromoacetate (1.6 mL, 17.2 mmol). The reaction mixture was heated at reflux for 4 h, concentrated, and partitioned between water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried and concentrated to leave a residue, which was purified by chromatography (CH_2Cl_2) to give ester **2** (2.3 g, 96%) as a yellow oil: IR (NaCl) 2225, 1739−1749; ^{1}H NMR 1.54 (dddd, J = 13, 11.5, 11, 6, 1H), 2.06 (dm, J = 12, 1H), 2.14−2.51 (m, 4H), 3.00 (m, 1H), 3.36 (s, 2H), 3.66 (s, 3H), 3.80 and 3.86 (2 d, J = 14, 1H each), 6.56 (br s, 1H), 7.21−7.37 (m, 5H); ^{13}C NMR 25.0 (t), 27.2 (t), 29.7 (t), 51.0 (t), 51.5 (q), 54.5 (t), 54.8 (d), 112.1 (s), 119.2 (s), 127.1(d), 128.4 (2 d), 139.2 (s), 143.9 (d), 172.4 (s). Anal. Calcd for $C_{17}H_{20}N_2O_2 \cdot {}^1/_4H_2O$: C, 70.69; H, 7.15; N, 9.69. Found: C, 70.92; H, 7.22; N, 9.35.

4-{*N*-Benzyl-*N*-[2-(methylselanyl)-2-oxoethyl]amino}cyclohex-1-enecarbonitrile (3a). Dimethylaluminum methylselenolate (2 M in toluene, 15 mL, 30 mmol) was added to a cooled (0 °C) solution of ester **2** (1.4 g, 5 mmol) in degassed CH_2Cl_2 (54 mL), and the mixture was stirred at 0 °C for 1 h and at room temperature for 3 h. The mixture was concentrated and the residue was taken up with EtOAc and washed with aqueous saturated Na_2CO_3 and brine. The organic extracts were dried and concentrated, and the residue was purified by chromatography (hexane/CH_2Cl_2 1:3) to give selenoester **3a** (1.6 g, 83%) as a yellow solid: mp 85−86 °C (CH_2Cl_2); IR (KBr) 2213, 1694; ^{1}H NMR (500 MHz, COSY) 1.52 (qd, J = 12, 6, 1H, H-5$_{ax}$), 2.07 (s, 3H, $SeCH_3$), 2.00−2.60 (m, 5H), 2.88 (m, 1H, H-4$_{ax}$), 3.25 and 3.32 (2d, J = 17, 1H each, CH_2N), 3.73 and 3.80 (2d, J = 13.5, 1H each, CH_2Ar), 6.56 (br s, 1H, H-2), 7.26−7.40 (m, 3H, ArH), 7.46 (d, J = 7, 2H, ArH); ^{13}C NMR (HMQC) 3.9 ($SeCH_3$), 23.3 (C-5), 27.4 (C-6), 28.6 (C-3), 53.7 (C-4), 55.5 (CH_2Ar), 61.9 (CH_2N), 112.2 (C-1), 119.0 (CN), 127.6, 128.5, 128.9 (Ar), 137.7 (C-ipso), 143.7 (C-2), 207.6 (CO). Anal. Calcd for: $C_{17}H_{20}N_2OSe$: C, 58.79; H, 5.80; N, 8.07. Found: C, 58.58; H, 6.04; N, 7.91.

4-{*N*-Benzyl-*N*-[2-(phenylselanyl)-2-oxoethyl]amino}cyclohex-1-enecarbonitrile (3b). Ester **2** (1.8 g, 6.4 mmol) in 6 N HCl (47 mL) was heated at 60 °C for 7 h. The mixture was concentrated and the resulting solid was triturated with Et_2O. After removing the solvent, ***N*-benzyl-*N*-carboxymethyl-N-[4-cyanocyclohexen-3-en-1-yl]ammonium chloride**, structure not shown, was isolated as a white solid (1.70 g, 88%): IR (KBr) 2200, 1731. ^{1}H NMR 2.01 (m, 1H), 2.43 (dm, J = 13, 1H), 2.51−3.02 (m, 4H), 3.89 (m, 1H), 4.22 (br s, 2H), 4.62 and 4.67 (2 d, J = 13, 1H each), 6.74 (br s, 1H), 7.50−7.75 (m, 5H); ^{13}C NMR 24.2 (t), 28.3 (t), 51.0 (t), 59.5 (t), 62.5 (d), 114.1 (s), 120.1 (s), 131.2, 132.3, 133.4 (d), 143.0 (d), 169.5 (s). To a stirred solution of the obtained carboxylic acid (800 mg, 2.61 mmol) in CH_2Cl_2 (15 mL) was added a solution of Et_3N (0.83 mL, 6 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 30 min and concentrated to give the crude triethylammonium carboxylate as a yellow oil. To a solution of PhSeCl (0.84 g, 4.42 mmol) in THF (22 mL) was added PBu_3 (1.1 mL, 4.42 mmol) with stirring at room temperature. After 15 min the above triethylammonium salt in THF (18 mL) was added to the reaction mixture and stirred at room temperature for 24 h. The resulting solution was poured into EtOAc and aqueous 2 N NaOH solution. The aqueous layer was further extracted with EtOAc, and the combined organic extracts were washed with water and brine. The concentrated dried organic extracts were purified by chromatography (CH_2Cl_2) to give **3b** (754 mg, 70%) as a yellow solid: IR (KBr) 2200, 1710; ^{1}H NMR 1.54 (qd, J = 11.5, 5.5, 1H), 2.12 (dm, J = 12, 1H), 2.15−2.53 (m, 4H), 2.96 (m, 1H), 3.38 and 3.42 (2 d, J = 17, 1H each), 3.80 and 3.88 (2 d, J = 13.5, 1H each), 6.58 (br s, 1H), 7.20−7.65 (m, 10H); ^{13}C NMR 23.5 (t), 27.4 (t), 28.7 (t), 53.9 (d), 55.9 (t), 62.1 (t), 112.3 (s), 119.0 (s), 127.2, 127.7, 128.3, 128.6, 129.0, 129.1, 135.8 (d), 137.4 (s), 143.6 (d), 205.6 (s). Anal. Calcd for $C_{22}H_{22}N_2OSe$: C, 64.55; H, 5.38; N, 6.83. Found: C, 64.42; H, 5.42; N, 6.87.

Methyl 4-[*N*-Benzyl-*N*-(tert-butoxycarbonylmethyl)-amino]cyclohex-1-enecarboxylate (8). To a solution of amine **7** (480 mg, 2.23 mmol) in CH_3CN (67 mL) were added *tert*-butyl bromoacetate (0.66 mL, 4.46 mmol) and Na_2CO_3 (0.71 g, 6.69 mmol). The mixture was heated at reflux for 24 h and concentrated. The residue was partitioned between water and CH_2Cl_2 and the aqueous phase was extracted with CH_2Cl_2. Concentration of the dried organic extracts gave a residue, which was purified by chromatography (CH_2Cl_2), to yield diester **8** as an orange oil (678 mg, 85%): IR (NaCl) 1717; ^{1}H NMR 1.40−1.60 (m, 1H), 1.45 (s, 9H), 2.00−2.60 (m, 5H), 3.00 (m, 1H), 3.26 (s, 2H), 3.72 (s, 3H), 3.83, 3.89 (2 d, J = 14, 1H each), 6.91 (br s, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR 24.8 (t), 25.6 (t), 28.1 (q), 29.8 (t), 51.6 (d), 52.0 (t), 54.7 (t), 55.6 (q), 80.7 (s), 126.8, 128.2, 128.4 (s), 129.8 (s), 138.4 (d), 139.8 (s), 167.5 (s), 171,5 (s). HRMS calcd for $C_{21}H_{29}NO_4$ 359.2097. Found 359.2099. Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.28; H, 8.23; N, 3.88.

***N*-Benzyl-*N*-carboxymethyl-N-(4-methoxycarbonylcyclohex-3-en-1-yl)ammonium Trifluoroacetate (9).** TFA (8.11 mL, 105 mmol) was added dropwise to an ice-cooled solution of **8** (620 mg, 1.73 mol) in CH_2Cl_2 (2.3 mL), and the mixture was stirred for 45 min at room temperature and concentrated. The residue was triturated with Et_2O to give the trifluoroacetate salt **9** as a white solid (653 mg, 91%): mp 152−153 °C (Et_2O); IR (KBr) 3425, 1706, 1687; ^{1}H NMR (CD_3OD) 1.80 (m, 1H), 2.25−2.40 (m, 2H), 2.50−2.85 (m, 3H), 3.70 (m, 1H), 3.72 (s, 3H), 4.04 (s, 2H), 4.56, 4.51 (2 d, J = 13, 1H each), 6.89 (br s, 1H), 7.40−7.55 (m, 3H), 7.55−7.65 (m, 2H); ^{13}C NMR (CD_3OD) 24.1 (t), 25.1 (t), 27.2 (t), 50.3 (t), 52.3 (q), 58.4 (t), 62.2 (d), 130.3, 131.3, 132.3 (d), 130.5, 131.2 (s), 135.9 (d), 167.9 (s), 168.8 (s). Anal. Calcd for $C_{19}H_{22}F_3NO_6$: C, 54.68; H, 5.31; N, 3.36. Found: C, 54.78; H, 5.50; N, 3.43.

Methyl 4-{Benzyl-[2-(phenylselanyl)-2-oxoethyl]amino}cyclohex-1-enecarboxylate (10). Following the above procedure to prepare **3b** using carboxylic acid **9** (300 mg, 0.72 mmol), the crude product was purified by chromatography (hexane/EtOAc, 8:2) to give the phenylselanyl ester **10** (226 mg, 70%) as a white solid: mp 95−97 °C; IR (KBr) 1719; ^{1}H NMR 1.49 (qd, J = 12, 6, 1H), 2.10−2.65 (m, 5H), 2.95 (m, 1H), 3.38, 3.44 (2 d, J = 18, 1H each), 3.71 (s, 3H), 3.82, 3.88 (2 d, J = 10, 1H each), 6.93 (br s, 1H), 7.10−7.40 (m, 10H); ^{13}C NMR 23.9 (t), 24.9 (t), 28.5 (t), 51.6 (q), 54.8 (d), 55.9 (t), 62.2 (t), 127.5, 128.4, 129.0, 135.8 (d), 130.0 (s), 137.7 (s), 138.0 (d), 167.3 (s), 206.1 (s). Anal. Calcd for $C_{23}H_{25}NO_3Se$: C, 62.44; H, 5.70; N, 3.17. Found: C, 62.09; H, 5.71; N, 3.23.

Methyl 4-(*N*-tert-Butoxycarbonylmethyl-*N*-methylamino)cyclohex-1-en-1-carboxylate (12). Triethylamine (1.39 mL, 14 mmol) was added to a solution of *tert*-butyl methylaminoacetate hydrochloride (2.41 g, 13.3 mmol) in 1,2-dichloroethane (15 mL), to which sequentially was added a solution of enones **11** (1.13 g, 7.34 mmol) in 1,2-dichloroethane (10.5 mL), $NaBH(OAc)_3$ (2.34 g, 11.0 mmol), and AcOH (0.52 mL, 9.1 mmol). The mixture was stirred at room temperature for 24 h and concentrated. The residue was taken up in CH_2Cl_2 (40 mL) and washed with 10% aqueous K_2CO_3 solution. After evaporation of the organic solvent, the residue was purified by chromatography (98:2, CH_2Cl_2:MeOH) to give **12** (1.17 g, 56%) as a yellow oil: IR (film) 1714; ^{1}H NMR 1.41 (qd, J = 11, 5, 1H), 1.46 (s, 9H), 1.90−2.60 (m, 5H), 2.43 (s, 3H), 2.80 (m, 1H), 3.26 (s, 2H), 3.73 (s, 3H), 6.92 (br s, 1H); ^{13}C NMR 24.5 (t), 25.1 (t), 28.0 (q), 28.9 (t), 38.6 (q), 51.4 (q), 55.8 (t), 57.4 (d), 80.7 (s), 129.7 (s), 137.9 (d), 167.2 (s), 170.4 (s). Anal. Calcd for $C_{15}H_{25}NO_4 \cdot {}^1/_4H_2O$: C, 62.59; H, 8.93; N, 4.87. Found: C, 62.89; H, 8.92; N, 4.94.

***N*-Methyl-*N*-carboxymethyl-*N*-(4-methoxycarbonylcyclohex-3-en-1-yl)ammonium Trifluoroacetate (13).** TFA

(34) For general procedures, see Supporting Information.

(129 mL, 1.68 mol) was added dropwise to an ice-cooled solution of **12** (7.8 g, 27.6 mol) in CH_2Cl_2 (37 mL) and the mixture was stirred for 45 min at room temperature and concentrated. The residue was triturated with Et_2O to give the trifluoroacetate salt **13** as a white solid (8.05 g, 86%): mp 132−133 °C (Et_2O); IR (KBr) 3425, 1709; ^{1}H NMR (CD_3OD) 1.76 (qd, J = 12, 5, 1H), 2.15−2.80 (m, 5H), 2.95 (s, 3H), 3.62 (m, 1H), 3.72 (s, 3H), 4.11 (s, 2H), 6.88 (br s, 1H); ^{13}C NMR (CD_3OD) 23.8 (t), 25.0 (t), 26.9 (t), 38.8 (q), 52.3 (q), 54.4 (t), 63.0 (d), 131.2 (s), 135.8 (d), 168.0 (s), 168.5 (s). Anal. Calcd for $C_{13}H_{18}F_3NO_6$: C, 45.75; H, 5.32; N, 4.10. Found: C, 45.49; H, 5.47; N, 4.27.

Methyl 4-{*N*-Methyl-*N*-[2-(phenylselanyl)-2-oxoethyl]-amino}cyclohex-1-enecarboxylate (14). Following the above procedure to prepare **3b** using carboxylic acid **13** (7.48 g, 22 mmol), the crude product was treated with hexane to give the phenylselanyl ester **14** (5.2 g, 65%) as a yellowish solid: mp 68−70 °C; IR (KBr) 1717, 1702; ^{1}H NMR 1.51 (qd, J = 12, 6, 1H), 2.00−2.70 (m, 5H), 2.51 (s, 3H, NMe), 2.87 (m, 1H), 3.32 (s, 2H), 3.74 (s, 3H), 6.95 (br s, 1H), 7.30−7.40 (m, 3H), 7.40−7.50 (m, 2H); ^{13}C NMR 24.8 (t), 24.9 (t), 28.5 (t), 39.4 (q), 51.6 (q), 59.0 (d), 65.5 (t), 128.0 (d), 128.3 (d), 129.0 (d), 130.0 (s), 135.7 (s), 137.8 (d), 167.3 (s), 206.9 (s). Anal. Calcd for $C_{17}H_{21}NO_3Se$: C, 55.74; H, 5.78; N, 3.83. Found: C, 55.74; H, 5.89; N, 3.71.

Radical Cyclization of Selenoester 3a with TTMSS and AIBN. A solution of **3a** (150 mg, 0.43 mmol) and AIBN (14 mg, 0.08 mmol) in benzene (85 mL) was heated at reflux. TTMSS (0.29 mL, 0.95 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 3 h. Concentration of the solvent gave a residue, which was partitioned between EtOAc and 1 N HCl. The aqueous phase was basified with saturated Na_2CO_3 and extracted with EtOAc. The dried organic extracts were concentrated and purified by chromatography (CH_2Cl_2/MeOH 98:2). The first eluate gave 26 mg (27%) of **(1*RS*,2*RS*,5*RS*)-6-Benzyl-6-azabicyclo[3.2.1]-octane-2-carbonitrile (20)** as a white solid: mp 173−175 °C; IR (NaCl) 2250; ^{1}H NMR (500 MHz, COSY) 1.55 (td, J = 13, 5, 1H, H-4$_{ax}$), 1,71 (m, 1H, H-4$_{eq}$), 1.80−1.90 (m, 2H, H-3$_{eq}$, H-8$_{eq}$), 1.92 (d, J = 12, 1H, H-8$_{ax}$), 2.07 (m, 1H, H-3$_{ax}$), 2.62 (m, 1H, H-1$_{eq}$), 2.75 (m, 1H, H-2$_{eq}$), 2.77 (d, J = 10.5, 1H, H-7$_{endo}$), 2.85 (dd, J = 10.5, 5.5 Hz, 1H, H-7$_{exo}$), 3.17 (m, 1H, H-5$_{eq}$), 3.80 (s, 2H, CH_2Ph), 7.20−7.40 (m, 5H, ArH); ^{13}C NMR (HMQC) 23.0 (C-3), 28.9 (C-4), 31.2 (C-2), 32.7 (C-8), 38.3 (C-1), 57.5 (C-7), 58.4 (C-5), 59.5 (CH_2Ar), 122.4 (CN), 126.9, 128.1, 128.2 (Ar), 140.0 (C-ipso). Anal. Calcd for $C_{15}H_{18}N_2 \cdot {}^1/_2 H_2O$: C, 76.56; H, 8.14; N, 11.90. Found: C, 76.68; H, 8.09, N, 11.58. The second eluate gave 42 mg (42%) of **(1*RS*,2*SR*,5*RS*)-6-benzyl-6-azabicyclo[3.2.1]octane-2-carbonitrile (21)** as a white solid: IR (NaCl) 2250; ^{1}H NMR (500 MHz, COSY) 1.19 (m, 1H, H-4$_{ax}$), 1.28 (d, J = 11.5, 1H, H-8$_{ax}$), 1.67 (dm, J = 12.5, 1H, H-4$_{eq}$), 1.81−1.98 (m, 3H, H-8$_{eq}$, H-3), 2.54 (br s, 1H, H-1$_{eq}$), 2.55 (dm, J = 10.5, 1H, H-2$_{ax}$), 2.77 (dd, J = 10.5, 5.5, 1H, H-7$_{exo}$), 2.99 (d, J = 11, 1H, H-7$_{endo}$), 3.04 (m, 1H, H-5$_{eq}$), 3.73 (s, 2H, CH_2Ph), 7.12−7.30 (m, 5H, ArH); ^{13}C NMR (HMQC) 23.7 (C-3), 30.4 (C-4), 31.9 (C-2), 35.5 (C-8), 39.0 (C-1), 55.5 (C-7), 57.5 (C-5), 59.1 (CH_2Ar), 122.3 (CN), 126.8, 128.1, 128.2 (Ar), 144.0 (C-ipso). HRMS calcd for $C_{15}H_{18}N_2$: 226.1477, found 226.1469.

Radical Cyclization of Selenoester 3b with TBTH and Et$_3$B. Acyl selenide **3b** (130 mg, 0.32 mmol) was dissolved in benzene (64 mL) and stirred under an atmosphere of dry air using a drying tube packed with Drierite. A 15% solution of Et_3B in hexane (3.7 mL, 0.38 mmol) was added, followed by TBTH (0.13 mL, 0.48 mmol), and the mixture was stirred at room temperature for 15 h. Then, additional Et_3B (3.17 mL) was added and stirring was maintained for 6 h. The reaction mixture was concentrated, and the residue was taken up in EtOAc and treated with aqueous saturated KF solution. The precipitated Bu_3SnF was removed by filtration through Celite and the filtrate separated and dried. Removal of the solvent yielded a mixture of **20** and **21** (51 mg, 70%) in a ratio 1:1 ratio (estimated by ^{1}H NMR and GC−MS).

Radical Cyclization of 10 with TBTH and AIBN. A solution of selenoester **10** (132 mg, 0.30 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (61 mL) was heated at reflux. Then, TBTH (178 μL, 0,66 mmol) was added dropwise, and the reaction mixture was stirred at this temperature for 3 h. After evaporation of the solvent, the residue was dissolved in EtOAc and extracted with aqueous 1 N HCl. The aqueous phase was basified with saturated Na_2CO_3 and extracted with EtOAc. Evaporation of the dried organic extracts afforded a residue, which was purified by chromatography (Al_2O_3, hexane/EtOAc 98:2) to give a mixture of epimers **22** and **23** (57 mg, 74%) as a yellow oil in a 45:55 ratio (estimated by ^{1}H NMR and GC−MS): IR 1732. **(1*RS*,2*RS*,5*RS*) Methyl 6-benzyl-6-azabicyclo-[3.2.1]octane-2-carboxylate (22)**: ^{1}H NMR (500 MHz, COSY) 1.44 (d, J = 11.5, 1H, H-8$_{ax}$), 1.50 (tdd, J = 13.5, 6, 1.5, 1H, H-4$_{ax}$), 1.62−1.68 (m, 1H, H-4$_{eq}$), 1.68−1.75 (m, 1H, H-8$_{eq}$), 1.76−1.80 (m, 1H, H-3), 1.93−1.97 (m, 1H, H-3), 2.54 (m, 1H, H-2$_{eq}$), 2.72 (q, J = 5, 1H, H-1$_{eq}$), 2.75 (d, J = 10.5, 1H, H-7$_{endo}$), 2.90 (dd, J = 10, 6, 1H, H-7$_{exo}$), 3.10 (q, J = 5, 1H, H-5$_{eq}$), 3.63 (s, 3H, OCH_3), 3.79, 3.83 (2 d, J = 14, 1H each, CH_2Ph), 7.20−7.40 (m, 5H, ArH); ^{13}C NMR (HMQC): 20.6 (C-3), 28.8 (C-4), 32.8 (C-8), 38.2 (C-1), 44.8 (C-2), 51.5 (OCH_3), 58.2 (C-7), 58.8 (C-5), 59.0 (CH_2Ph), 126.5, 128.1, 128.2 (C-*o*, C-*m*, C-*p*), 175.4 (CO). **(1*RS*,2*SR*,5*RS*) Methyl 6-benzyl-6-azabicyclo[3.2.1]-octane-2-carboxylate (23)**: ^{1}H NMR (500 MHz, COSY) 1.30 (tdd, J = 14, 6, 1,5, 1H, H-4$_{ax}$),1.40 (d, J = 11, 1H, H-8$_{ax}$), 1.76−1.80 (m, 1H, H-4$_{eq}$), 1.80−1.87 (m, 2H, H-3), 1.89−1.95 (m, 1H, H-8$_{eq}$), 2.49 (ddd, J = 12, 5.5, 1.5, 1H, H-2$_{ax}$), 2.65 (t, J = 5, 1H, H-1$_{eq}$), 2.76 (dd, J = 11, 5.5, 1H, H-7$_{exo}$), 2.85 (d, J = 11, 1H, H-7$_{endo}$), 3.10 (q, J = 5, 1H, H-5$_{eq}$), 3.68 (s, 3H, OCH_3), 3.80 (s, 2H, CH_2Ph), 7.20−7.40 (m, 5H, ArH). ^{13}C NMR (HMQC) 22.1 (C-3), 30.3 (C-4), 36.6 (C-8), 38.2 (C-1), 45.6 (C-2), 51.5 (OCH_3), 55.3 (C-7), 58.1 (C-5), 58.6 (CH_2Ph), 126.5, 128.1, 128.2 (C-*o*, C-*m*, C-*p*), 175.2 (CO). Anal. Calcd for $C_{16}H_{21}NO_2 \cdot {}^1/_5 H_2O$: C, 73.08; H, 8.20; N, 5.33. Found: C, 73.38; H, 8.06; N, 5.60.

(1*RS*,2*RS*,5*RS*)- and (1*RS*,2*SR*,5*RS*)-Methyl 6-Methyl-6-azabicyclo[3.2.1]octane-2-carboxylate (24 and 25). Following the above procedure for the radical cyclization with TBTH and AIBN, phenylselanyl ester **14** (1 g, 2.73 mmol) in benzene (550 mL) was treated with AIBN (186 mg, 1.14 mmol), and TBTH (1.25 mL, 4.64 mmol) was added dropwise at reflux temperature, which was maintained for 3 h. The crude material obtained after the workup was purified by chromatograpy (Al_2O_3, CH_2Cl_2) to give a mixture of epimers **24** and **25** (300 mg, 60%) as a yellow oil in a 45:55 ratio (estimated by GC−MS); working on a 0.27 mmol scale, the yield increased up to 67%: IR 1729. Compound **24**: ^{1}H NMR ($CDCl_3$, 500 MHz, COSY) 1.42 (d, J = 11.5, 1H, H-8$_{ax}$), 1.60 (m, 1H, H-4$_{ax}$), 1.60−1.71 (m, 3H, H-4$_{eq}$, H-3, H-8$_{eq}$), 1.90 (m, 1H, H-3), 2.44 (s, 3H, NMe), 2.50 (m, 1H, H-2$_{eq}$), 2.70 (q, J = 5, 1H, H-1$_{eq}$), 2.75 (d, J = 10.5, 1H, H-7$_{endo}$), 2.86 (dd, J = 10.5, 6, 1H, H-7$_{exo}$), 2.98 (t, J = 4.5, 1H, H-5$_{eq}$), 3.63 (s, 3H, OCH_3); ^{13}C NMR (HMQC) 20.2 (C-3), 27.9 (C-4), 32.4 (C-8), 38.5 (C-1), 41.8 (NMe), 44.6 (C-2), 51.5 (OCH_3), 59.5 (C-7), 60.9 (C-5), 175.1 (CO). Compound **25**: ^{1}H NMR (500 MHz, COSY) 1.32 (tdd, J = 14, 6, 1,5, 1H, H-4$_{ax}$), 1.38 (d, J = 11, 1H, H-8$_{ax}$), 1.60−1.71 (m, 1H, H-3), 1.72−1.81 (m, 1H, H-4$_{eq}$), 1.80 (m, 1H, H-3), 1.90 (m, 1H, H-8$_{eq}$), 2.42 (s, 3H, NMe), 2.45 (ddd, J = 12.5, 5, 2, 1H, H-2$_{ax}$), 2.62 (t, J = 5.5, 1H, H-1$_{eq}$), 2.74 (dd, J = 10.5, 5.5, 1H, H-7$_{exo}$), 2.83 (d, J = 10, 1H, H-7$_{endo}$), 2.98 (t, J = 5, 1H, H-5$_{eq}$), 3.68 (s, 3H, OCH_3), ^{13}C NMR (HMQC) 21.7 (C-3), 29.4 (C-4), 36.3 (C-8), 38.5 (C-1), 41.0 (NMe), 45.4 (C-2), 51.5 (OCH_3), 56.5 (C-7), 60.0 (C-5), 175.1 (CO). HRMS calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1260.

(1*RS*,6*RS*,7*RS*)- and (1*RS*,6*RS*,7*SR*)-2-Benzyl-5-oxo-2-azabicyclo[4.3.1]decane-7-carbonitrile (29 and 30). Following the general procedure for the radical cyclization with TTMSS and AIBN, methylselanyl ester **28** (70 mg, 0.19 mmol) in benzene (38 mL) was treated with AIBN (6 mg, 0.034 mmol) and TTMSS (0.12 mL, 0.41 mmol), and the crude material was chromatographed (CH_2Cl_2/MeOH 99:1). The first eluate gave **29 (**26 mg, 50%) as a white solid: IR (NaCl) 2240, 1710; ^{1}H NMR (500 MHz, COSY) 1.60 (dm, J = 14.5, 1H, H-8$_{eq}$), 1,77 (tm, J = 15.5, 1H, H-9$_{ax}$), 1.96 (dt, J = 14.5, 3, 1H, H-9$_{eq}$), 2.29 (tt, J = 14.5, 5, 1H, H-8$_{ax}$), 2.31 (ddd, J = 15.4, 2.5, 1H, H-10), 2.51 (m, $W_{1/2}$ = 8.5, 1H, H-6$_{eq}$), 2.57 (ddd, J = 13.5, 11.5,

5.5, 1H, H-4), 2.67 (dm, J = 15.5, 1H, H-10), 2.75 (ddd, J = 13.5, 9, 3, 1H, H-4), 2.81 (td, J = 13, 2.5, 1H, H-3), 2.84 (m, 1H, H-1_{eq}), 2.92 (ddd, J = 13.5, 9, 5, 1H, H-3), 3.22 and 3.93 (2 d, J = 15, 1H each, CH_2Ar), 3.73 (m, $W_{1/2}$ = 10, 1H, H-7_{eq}), 7.18 (d, J = 8, 2H, ArH), 7.24 (t, J = 7, 1H, ArH), 7.33 (t, J = 7.5, 1H, ArH); ^{13}C NMR (HMQC) 20.5 (C-8), 26.0 (C-9), 27.2 (C-7), 28.3 (C-10), 41.2 (C-4), 44.9 (C-3), 46.0 (C-6), 56.5 (C-1), 58.3 (CH_2Ar), 122.3 (CN), 127.0, 127.8, 128.6 (Ar), 139.0 (C-ipso), 206.7 (CO). HRMS calcd for $C_{17}H_{20}N_2O$ 268.1575, found 268.1574. The second eluate gave **30** (11 mg, 21%) as a white solid: IR (NaCl) 2240, 1712; ^{1}H NMR (500 MHz, COSY) 1.42 (tm, J = 14, 1H, H-9_{ax}), 1.77 (dm, J = 13.5, 1H, H-8_{eq}), 1.83 (ddd, J = 15, 3.5, 2, 1H, H-10), 2.04 (dm, J = 14.5, 1H, H-9_{eq}), 2.42 (qd, J = 13.5, 4, 1H, H-8_{ax}), 2.54 (ddd, J = 13.25, 11.5, 6, 1H, H-4), 2.65 (m, 1H, H-6_{eq}), 2.69−2.76 (m, 3H, H-4, H-7_{ax}, H-10), 2.77 (m, 1H, H-1_{eq}), 2.82 (dd, J = 11.25, 3, 1H, H-3), 2.87 (ddd, J = 13.5, 9.5, 6, 1H, H-3), 3.20, 3.14 (2 d, J = 15, 1H each, CH_2Ar), 7.19−7.34 (m, 5H, ArH); ^{13}C NMR 21.8 (C-8), 29.1 (C-9), 29.9 (C-7), 31.6 (C-10), 41.4 (C-4), 44.9 (C-3 and C-6), 56.1 (C-1), 58.5 (CH_2Ar), 121.4 (CN), 127.0, 127.9, 128.6 (Ar), 139.0 (C-*ipso*), 206.3 (CO). HRMS calcd. for $C_{17}H_{20}N_2O$ 268.1575, found 268.1570.

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Supporting Information Available: Experimental procedures and NMR data for compounds **1**, **4**−**7, 15**−**19**, and **26**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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