Tetrahedron Vol. 47, No. 27, pp 4847-4860, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

Free Radical Ring-Expansion Leading to Novel Six- and Seven-Membered Heterocycles

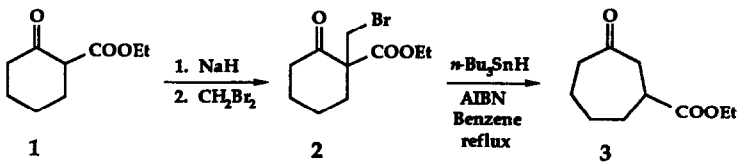
Paul Dowd and Soo-Chang Choi*
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

(*Received in USA* 14 *March* 1991)

Abstract: Free radical promoted ring-expansion of nitrogen-, oxygen- and sulfur-containing heterocyclic β-keto esters is described. Treatment of the derived phenylselenomethyl derivatives with tri-n-butyltin hydride leasds to smooth one-carbon ring expansion.

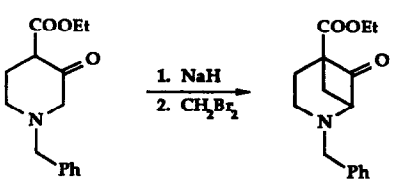
We have begun to explore a new free radical-based reaction sequence for producing unusual, functionalized, medium-size, heterocyclic ring systems. In order to do so it is necessary to establish suitable procedures for approaching the special problems encountered in applying the free radical method to the construction of heterocycles.[1,2]

These aims can be illustrated with a recent carbocyclic example.[3,4,5,6] Cyclohexanone-2-carboxylate **1** was alkylated with dibromomethane, and the bromomethyl adduct **2** treated with tri-*n*-butyltin hydride and AIBN in refluxing benzene to yield the ring-expanded seven-membered γ-keto ester **3** (eq



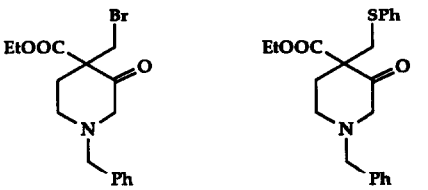
1 **2** **3** (1)

1).[3] When this sequence is applied to heterocycles, the heteroatom reactive center may lead the reactions to take other courses. Thus, treatment of the piperidine β-keto ester **4** with sodium hydride and dibromomethane did not yield the expected bromomethyl adduct **6**. Instead, an apparent internal



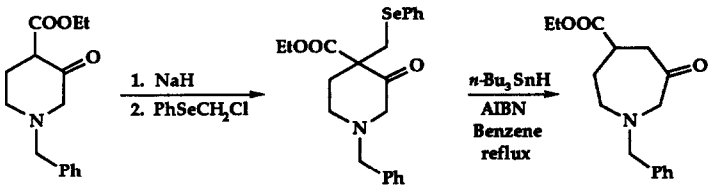
4 **5** (2)

alkylation product, the interesting cyclobutanone **5** (17%), was formed, together with unreacted starting material **4** (20%) (eq 2). None of the desired bromomethyl adduct **6** was observed.



6 **7**

Accordingly, less reactive alkylating agents carrying one nucleofugic group were explored. The thiophenyl derivative **7** was readily prepared but proved to be unreactive in the free radical-directed ring expansion.[7] By contrast, the corresponding selenide **8** was quite satisfactory.

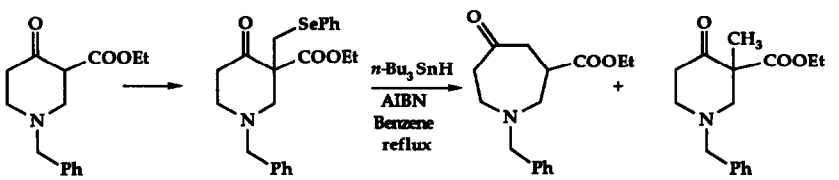


4 **8** **9** 71%

(3)

Alkylation of **4** with chloromethyl phenyl selenide[7] yielded the selenide **8**, which rearranged readily to the corresponding azepine **9** (71%) upon treatment, under free radical generating conditions, with tri-*n*-butyltin hydride and AIBN in refluxing benzene (eq 3).

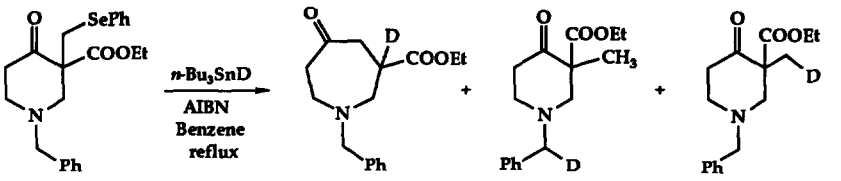
Alkylation of the alternative regioisomer, piperidine β-keto ester **10**, yielded the corresponding phenylselenide **11**. The selenide **11** underwent ring expansion to the azepine **12** (15%), but in this



10 **11** **12** 15% **13** 26%

(4)

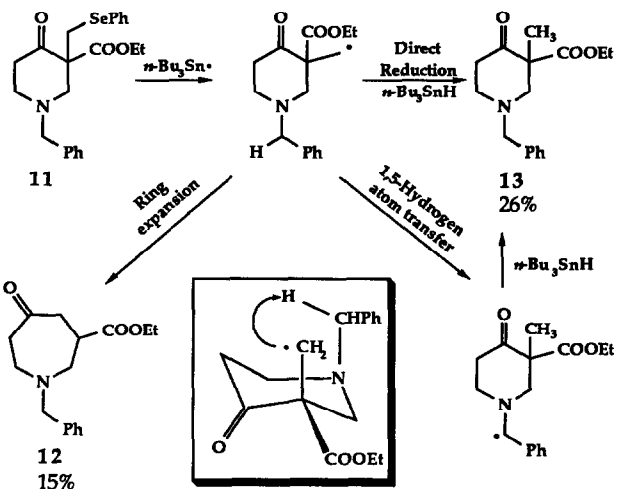
instance, the reaction also produced a greater amount (26%) of the undesired direct, reduction product **13** (eq 4). We suspected that the benzyl protecting group attached to nitrogen might not be an entirely neutral observer. Accordingly, the reaction was repeated using tri-*n*-butyltin deuteride (eq 5). As anticipated, the ring expansion product **12-d** was deuterated at the carbon adjacent to the ester group.



(5)

A combination of nmr and mass spectral analysis of the reduction product **13** demonstrated that deuterium was incorporated at the methyl carbon as shown in **13'-d** and that the benzyl carbon also carried a deuterium as shown in **13-d**. The ratio of **13-d** to **13'-d** was approximately 3:7 according to mass spectral analysis.

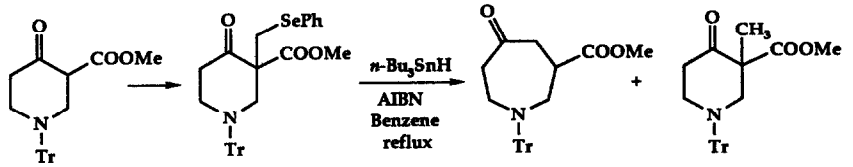
This process may be formulated as an intramolecular hydrogen abstraction by the initially formed methylene radical (Scheme 1). Such a hydrogen transfer requires the axial conformer of the benzylated piperidine (Scheme 1, inset). The ratio of deuterated products **13-d** and **13'-d** changed only



Scheme 1

slightly upon ten-fold dilution, so the free radical-based hydrogen abstraction leading to **13-d** is reasonably ascribed to an intramolecular reaction.

In order to forestall this untoward side reaction, we carried out a parallel sequence employing, instead of benzyl, a trityl protecting group at nitrogen. Treatment of the tritylprotected selenide **15**

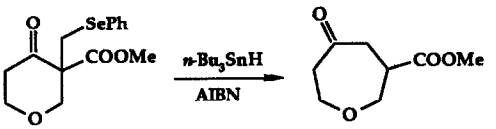


(6)

14 (Tr = trityl) 15 16 66% 17 8%

with tri-*n*-butyltin hydride now gave rearrangement product **16** in 66% yield together with 8% of direct reduction product **17** (eq 6), a substantial improvement over the result obtained with the N-benzyl analogue **11**.

Turning to the oxygen series, the requisite selenide **18** was prepared by alkylation of the corresponding β-keto ester. Ring expansion initiated with tri-*n*-butyltin hydride then yielded the anticipat-

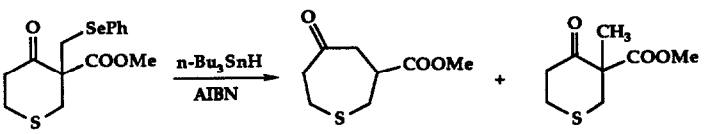


(7)

18 19 66%

ed oxepane **19** (66%) (eq 7).

The sulfur analogue **20** was prepared similarly and yielded the ring-expanded thiapane **21** (46%)

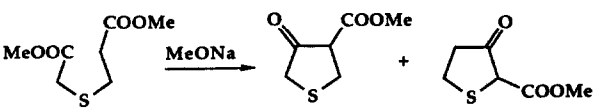


(8)

20 21 46% 22 30%

together with the direct reduction product **22** (30%) upon treatment with tri-*n*-butyltin hydride (eq 8).

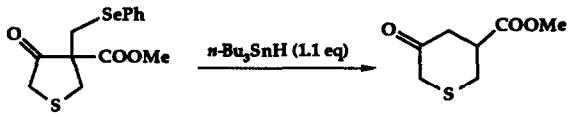
In the five-membered ring series, a mixture of tetrahydrothiophenes **24** and **25** was prepared by Dieckman condensation of the sulfide **23** (eq 9).[8] The minor product **24** was isolated, then it was



(9)

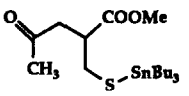
23 24 18% 25 44%

alkylated with chloromethyl phenyl selenide yielding **26**. Treatment of **26** with 1.1 equivalents of tri-*n*-butyltin hydride yielded the ring expanded γ-keto ester **27** (64%) (eq 10). When two equivalents of



26 **27** 64% (10)

tin hydride was employed, the ring-opened tin adduct **28** was obtained together with **27**, in a 2:1 ratio favoring **28**.



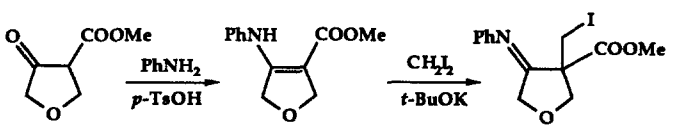
28

In the tetrahydrofuran series it was difficult to alkylate the β-keto ester **29**, prepared from glyco-

29 (11)

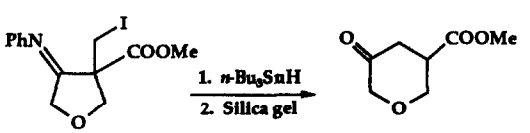
late and acrylate (eq 11),[9] in the presence of sodium hydride because decomposition products were observed.

Accordingly, we had recourse to the enamine anion,[10] a useful device in this series. The β-keto ester **29** was treated with aniline in the presence of p-toluenesulfonic acid and yielded the enamine **30**



29 **30** **31** (12)

(eq 12). Alkylation of the latter with diiodomethane and potassium *tert*-butoxide yielded the iodomethyl adduct **31** (eq 12). We recently demonstrated[3] that Schiff bases rearrange readily under free



31 **32** 44% (13)

radical conditions. Thus, when **31** was treated with tri-*n*-butyltin hydride and the reaction was worked up by mild hydrolysis on silica gel, the product was the tetrahyrdropyranyl β-keto ester **32** obtained in 44% yield (eq 13).

In summary, the free radical-based ring expansion can provide convenient and ready access to functionalized heterocycles otherwise difficult to obtain. Although the examples used here are all one-carbon ring-expansions, it is clear that ring-expansion by three- and four-carbons will also be feasible in the heterocyclic series using the free radical strategy.[3]

Experimental Section

Attempted Alkylation of Ethyl 1-Benzyl-3-oxo-4-piperidinecarboxylate (4) with Dibromomethane. Preparation of 1-Ethoxycarbonyl-4-(benzyl)azabicyclo[3,1,1]heptan-6-one (5). To a suspension of 0.052 g of NaH (1.3 mmoles, 60 % suspension in mineral oil) in 5 mL of dry tetrahydrofuran (THF) containing 0.225 mL (1.3 mmoles) of hexamethylphosphoramide (HMPA) at room temperature under argon, a solution of 0.261 g (1.0 mmoles) of ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate (**4**) in 0.5 mL of THF was added dropwise over 10 min. After completion of the addition, the reaction mixture was stirred at room temperature for 1.5 h, then treated with 0.140 mL (2.0 mmoles) of dibromomethane. After heating at reflux for 27 h, the reaction mixture was cooled to room temperature, poured into 50 mL of ether, and washed with 5 % $Na_2S_2O_3$ (2 x 5 mL) and water (5 x 5 mL). The organic layer was dried over K_2CO_3, filtered, and concentrated *in vacuo*, affording 0.228 g of a brown oil. Flash column chromatography on 1" x 6" column of silica gel (elution with 5:1 hexanes-ethyl acetate) gave 0.077 g (20%) of the starting material **4** and 0.032 g (17%) of the bicyclic compound **5** as a colorless oil, R_f 0.26 (5:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum of **5** ($CDCl_3$) showed δ 7.38-7.25 (m, 5 H), 4.34 (m, 1 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.93 (d, J_{AB} = 12.9 Hz, 1 H), 3.83 (d, J_{AB} =12.9 Hz, 1 H), 3.62-3.54 (m, 1 H), 3.24-3.21 (m, 1 H), 2.71-2.58 (m, 3 H), 2.02-1.98 (m, 1 H), 1.28 (t, J = 7.0 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 14 lines at: δ 208.7 (s), 173.7 (s), 138.0 (s), 128.7 (d, J = 158.5 Hz), 128.14 (d, J = 159.0 Hz), 127.1 (d, J = 160.1 Hz), 85.01 (d, J = 155.5 Hz), 61.2 (t, J = 149.0 Hz), 55.3 (t, J = 134.5 Hz), 53.3 (t, J = 137.3 Hz), 52.2 (t, J = 139.0 Hz), 45.6 (s), 33.3 (t, J = 134.6 Hz), 14.1 (q, J = 127.1 Hz). The IR spectrum (neat) showed bands at: 2980 (w), 2938 (w), 1779 (vs, 4-membered carbonyl), 1728 (vs, -COOEt), and 1280 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 273 (M^+, 0.2), 245 (M^+-CO, 15), 228 (M^+-OEt, 7.5). Exact mass calc'd for $C_{15}H_{19}NO_2$ (M^+-CO): 245.1416. Found: 245.1416.

Ethyl 1-Benzyl-3-oxo-4-phenylthiomethyl-4-piperidinecarboxylate (7). A solution of 0.145 g (0.555 mmoles) of ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate (**4**) in 1.5 mL of THF was added dropwise over 30 min to a suspension of 0.027 g of NaH (0.67 mmoles, 60 % suspension in mineral oil) in 2 mL of dry THF containing 0.125 mL (0.67 mmoles) of HMPA at room temperature under argon . After completion of the addition, the reaction mixture was stirred at room temperature for 1 h, then treated with 0.144 mL (1.1 mmoles) of phenylthiomethyl chloride and 0.167 g of sodium iodide. The reaction mixture was heated at reflux for 1 h, and was judged to be complete by thin layer chromatography (TLC) analysis. The reaction mixture was cooled to room temperature, poured into 50 mL of ether, and washed with water (5 x 5 mL). The organic layer was dried over K_2CO_3, filtered and concentrated *in vacuo*, affording 0.310 g of a brown oil. Flash column chromatography on a 0.5" x 6" column of silica gel (elution with 5:1 hexanes-ethyl acetate) gave 0.0724 g (38%) of the desired phenylthio compound **7** as a colorless oil, R_f 0.35 (5:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum of **7** ($CDCl_3$) showed δ 7.38-7.14 (m, 10 H), 4.10-4.00 (m, 2 H), 3.58-3.43 (m, 2 H), 3.53 (d, J_{AB} = 5.3 Hz, 1 H), 3.45 (d, J_{AB} = 13.4, 1 H), 3.25 (d, J_{AB} = 13.4, 1 H), 3.09 (d, J_{AB} = 5.3 Hz, 1 H), 2.78-2.61 (m, 3 H), 1.86-1.82 (m, 1 H), 1.14 (t, J = 7.1 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 17 lines at: δ 203.1 (s), 169.4 (s), 137.3 (s), 136.9 (s), 130.2, 129.0, 128.5, 127.6, 126.6 (d, J = 160 Hz), 62 5 (t, J = 135.1 Hz), 61.9 (t, J = 134.6 Hz), 61.8 (t, J = 137.9 Hz), 59.04 (s), 49.05 (t, J = 135.8 Hz), 38.7 (t, J = 144.1 Hz), 31.1 (t, J = 131.7 Hz), 14.1 (q, J = 127.2 Hz). The IR spectrum (neat) showed bands at: 3028 (w), 2979 (w), 2961 (w), 2932 (w), 1723 (vs), 1454 (w), and 1144 (w) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 354 (M^+-Et, 0 3) and 91 ($PhCH_2^+$, 100). Exact mass calc'd for $C_{20}H_{20}NO_3S$ (M^+-Et): 354.1164. Found: 354.1160.

Ethyl 1-Benzyl-3-oxo-4-phenylselenomethyl-4-piperidinecarboxylate (8). Following the procedure used for the preparation of **7**, 0.261 g (1.0 mmoles) of ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate (**4**) in 2.0 mL of THF was alkylated, using NaH (0.048 g, 1.2 mmoles), with 0.308 g (1.5 mmoles) of phenylselenomethyl chloride and 0.3 g (2.0 mmoles) of NaI at reflux for 4 h. Standard aqueous workup followed by flash column chromatography on a 1.5" x 6" column of silica gel (elution with 6:1 hexanes-ethyl acetate) gave 0.0824 g (18%) of the desired phenylseleno compound **8** as a colorless oil, R_f 0.39 (6:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum of **8** ($CDCl_3$) showed δ 7.51-7.49 (m, 2 H), 7.32-7.22 (m, 8 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.57 (d, J_{AB} = 13.1 Hz, 1 H), 3.51 (d, J_{AB} = 13.1 Hz, 1 H), 3.28 (d, J_{AB} = 12.5 Hz, 1 H), 3.22 (d, J_{AB} = 12.5 Hz, 1 H), 3.16 (d, J_{AB} = 15.7 Hz, 1 H), 3.06 (d, J_{AB} = 15.7 Hz, 1 H), 2.76-2.61 (m, 3 H), 1.97-1.87 (m, 1 H), 1.14 (t, J = 7.1 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 17 lines at: δ 203.0 (s), 169.4 (s), 136.8 (s), 132.5 (s) 131.0, 128.7, 128.5, 128.0, 127.1, 126.7, (d, J = 161 Hz), 61.9 (t, J = 135.0 Hz), 61.3 (t, J = 153.9 Hz), 61.2 (t, J = 141.5 Hz), 58.1 (s), 48.5 (t, J = 135.0 Hz), 31.7 (t, J = 146.9 Hz), 31.4 (t, J = 121.9 Hz), 13.7 (q, J = 127.4 Hz). The IR spectrum (neat) showed bands at: 3060 (w), 3028 (w), 2979 (w), 2958 (w) 1722 (vs), and 1189 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 431 (M^+, 6), 386 (M^+-EtO, 1.5), 260 (M^+-$PhSeCH_2$, 20), 91 ($PhCH_2^+$, 100). Exact mass calc'd for $C_{22}H_{25}NO_3Se$ (M^+): 431.0999. Found: 431.1000.

Reaction of Ethyl 1-Benzyl-3-oxo-4-phenylselenomethyl-4-piperidinecarboxylate (8) with Tri-n-butyltin Hydride and AIBN. Under argon, a solution of tri-*n*-butyltin hydride (0.101 mL, 0.42 mmoles) and AIBN (0.0138 g, 0.084 mmoles) in 4.2 mL of benzene was added dropwise over 7 h, using a syringe pump, to a refluxing solution of the phenylseleno compound **8** (0.046 g, 0.106 mmoles) in 1 mL of benzene. After heating at reflux for an additional 1 h, the reaction mixture was cooled to room temperature and evaporated on the rotary evaporator yielding an oil, which was dissolved in 25 ml of dichloromethane and washed with 10% potassium fluoride solution (5 x 1 mL). The organic layer was dried over K_2CO_3, filtered, and concentrated. The resulting oil was taken up in 25 mL of acetonitrile, washed with hexanes (4 x 5 mL), and concentrated *in vacuo*, affording 0.0683 g of light brown oil. Column chromatography on 2 g of silica gel (elution with 6:1 hexanes-ethyl acetate) afforded 20.8 mg (71%) of the rearranged product **9** as a colorless oil, R_f 0.26 (6:1 hexanes-ethyl acetate). The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 7.33-7.24 (m, 5 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.68 (s, 2 H), 3.35 (d, J_{AB} =18.3 Hz, 1 H), 3.28 - 3.20 (m, 1 H), 3.10 (d, J_{AB} = 18.3 Hz, 1 H), 2.97-2.90 (m, 1 H), 2.78 - 2.67 (m, 2 H), 2.59-2.51 (m, 1 H), 2.04-1.95 (m, 2 H), 1.25 (t, J = 7.2 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 14 lines at: δ 212 (s), 174 (s), 138 (s), 128.7 (d, J = 159.0 Hz), 128.4 (d, J = 160.0 Hz), 127.4 (d, J = 160.3 Hz), 66.4 (t, J = 127.0 Hz), 61.9 (t, J = 124.0 Hz), 60.9 (t, J = 148.0 Hz), 54.3(t, J = 132.0 Hz), 43.9 (t, J = 132.0 Hz), 39.8 (d J = 132.4 Hz), 31.8 (t, J = 130.0 Hz), 14.2 (q, J = 128.0 Hz). The IR spectrum (neat) showed bands at: 2935 (m), 2930 (m), 2805 (m), 1735 (vs, COOEt), 1714 (vs, CO), and 1182 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 275 (M^+, 20), 246 (M^+-Et, 20), 230 (M^+-OEt, 11), 156 (M^+-$PhCH_2^+$-CO, 60), 91 ($PhCH_2^+$, 100). Exact mass calc'd for $C_{16}H_{21}NO_3$ (M^+): 275.1521. Found: 275.1521.

Ethyl 1-Benzyl-4-oxo-3-phenylselenomethyl-3-piperidinecarboxylate (11). Following the procedure used for the preparation of **8**, 0.261 g (1.0 mmoles) of ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate **10** in 2.0 mL of THF was alkylated, using NaH (0.048 g, 1.2 mmoles), 0.308 g (1.5 mmoles) of phenylselenomethyl chloride and 0.3 g (2.0 mmoles) of NaI at reflux for 3 h. Flash column chromatography on a 1.5" x 6" column of silica gel (elution with 6:1 hexanes-ethyl acetate), after standard aqueous work-up, gave 0.235 g (55%) of the desired phenylseleno compound **11** as a colorless oil, R_f 0.38 (5:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 7.52-7.48 (m, 2 H), 7.33-7.20 (m, 8 H), 4.11 (q, J = 7.2 Hz, 2 H), 3.59 (d, J_{AB} = 13.2 Hz, 1 H), 3.49 (d, J_{AB} =13.2 Hz, 1 H), 3.41 (dd, J_{AB} = 12.5, 2.0 Hz, 1 H), 3.27 (d, J_{AB} = 12.2 Hz, 1 H), 3.11 (d, J_{AB} = 12.2 Hz, 1 H), 2.97-2.84 (m, 2 H), 2.57-2.42 (m, 3 H), 1.14 (t, J = 7.2 Hz, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 17 lines at: δ 205.4.0 (s), 170.3 (s), 137.6 (s), 132.9, (s) 131.8, 128.9, 128.7, 128.2, 127.3, 127.0, (d, J = 162 Hz) 62.7 (s), 61.6 (overlapped two t, J = 137.0 Hz), 60.8 (t, J = 141 Hz), 53.1 (t, J = 134.7 Hz), 40.0 (t, J = 129.8 Hz), 29.8 (t, J = 145.1 Hz), 13.9 (q, J = 127.0 Hz). The IR spectrum (neat) showed bands at: 3028 (w), 2979 (m), 2811 (m), 1725 (vs), 1717 (vs), and 1239 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 386 (M^+-EtO, 0.8), 274 (M^+-PhSe, 50), 91 ($PhCH_2^+$, 100). Exact mass calc'd for $C_{16}H_{20}NO_3$ (M^+-PhSe): 274.1443. Found: 274.1442.

Reaction of Ethyl 1-Benzyl-4-oxo-3-phenylselenomethyl-3-piperidinecarboxylate (11) with Tri-*n*-butyltin Hydride

(a) Under Standard Conditions: 100 mM in 11. Following the same procedure used for the reaction of **8** with *n*-Bu_3SnH and AIBN, a refluxing solution (100 mM) of the phenylseleno compound **11** (0.092 g, 0.21 mmoles) in 2.1 mL of benzene, under argon, was added dropwise over 7 h to a solution of tri-*n*-butyltin hydride (0.222 mL, 0.83 mmoles) and AIBN (0.048 g, 0.166 mmoles) in 6.0 mL of benzene. The reaction was heated at reflux for an additional 17 h . After standard aqueous workup,

column chromatography on 2 g of silica gel (elution with 4:1 hexanes-ethyl acetate) afforded 0.009 g (15%) of the rearranged product **12** and 0.015 g (26%) of the reduced product **13** as colorless oils, R_f 0.29 and 0.52 (4:1 hexanes-ethyl acetate), respectively.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the rearranged produced **12** showed peaks at δ 7.32-7.26 (m, 5 H), 4.17-4.09 (m, 2 H), 3.68 (s, 2 H), 3.08 - 2.59 (m, 9 H), 1.23 (t, J = 7.1 Hz, 3 H). The IR spectrum (neat) showed bands at: 2925 (s), 2854 (m), 1730 (vs), 1454(w), and 1175 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 275 (M^+, 6), 230 (M^+-OEt, 8), 202 (M^+-COOEt, 4), 184 (M^+-$PhCH_2$, 6), 91 ($PhCH_2^+$, 100). Exact mass calc'd for $C_{16}H_{21}NO_3$ (M^+): 275.1521. Found: 275.1521.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the reduced product **13** showed δ 7.35-7.24 (m, 5 H), 4.27-4.12 (m, 2 H), 3.60 (d, J_{AB} = 13.3 Hz, 1 H), 3.57 (d, J_{AB} =13.3, 1 H), 3.46 (dd, J_{AB} = 11.5, 2.7 Hz, 1 H), 3.09-3.02 (m, 1 H), 2.97-2.85 (m, 1 H), 2.43-2.35 (m, 2 H), 2.13 (d, J_{AB} = 11.5 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.21 (s, 3 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 17 lines at: δ 206.4 (s), 172.6 (s), 137.9 (s), 128.8 (d, J = 158.2 Hz), 128.3 (d, J = 159.6 Hz), 127.4 (d, J = 160.1 Hz), 62.7 (t, J = 139.7 Hz), 61.8 (t, J = 131.9 Hz), 61.3 (t, J = 148.4 Hz), 53.7 (t, J = 135.1 Hz), 40.3 (t, J = 130.1 Hz), 17.8 (q, J = 130.2 Hz), 14.1 (q, J = 127.3 Hz). The IR spectrum (neat) showed bands at: 2982 (w), 2898 (w), 1721 (vs), 1454 (w),and 1231 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 275 (M^+, 10), 230 (M^+-OEt, 15), 202 (M^+-COOEt, 40), 184 (M^+-$PhCH_2$, 11), 91 ($PhCH_2^+$, 100). Exact mass calc'd for $C_{16}H_{21}NO_3$ (M^+): 275.1521. Found: 275.1521.

(b) Under Dilute Condition; 10 mM in 11 The procedure was repeated with a 10-fold diluted solution of **11** (0.0184 g, 0.0424 mmoles) in 4.24 mL of benzene. Gas-liquid chromatography analysis of the reaction mixture on a SPB-1, fused silica, 30-m capillary column) showed the rearrangement product **12** and the reduced product **13** formed in a ratio of 47:53, little changed from the more concentrated conditions.

Reaction of Ethyl 1-Benzyl-4-oxo-3-phenylselenomethyl-3-piperidinecarboxylate (11) with Tri-*n*-butyltin Deuteride and AIBN. A solution of tri-*n*-butyltin deuteride (0.262 g, 0.9 mmoles) and AIBN (0.015 g) in 9.0 mL of benzene was added dropwise over 6 h to a refluxing solution of the phenylseleno compound **11** (0.129 g, 0.30 mmoles) in 3 mL of benzene under argon. The reaction was heated at reflux for an additional 12 h. After standard aqueous workup, column chromatography on 2 g of silica gel (elution with 2:1 hexanes-ethyl acetate) afforded 0.011 g (13%) of the rearranged product **12-d** together with 0.028 g (33%) of the reduced product as a 3:7 mixture of **13-d** and **13'-d**, based on the relative intensities of the base peaks at m/e 92 and 91 in the mass spectrum (*vide infra*).

The 300 MHz proton nmr spectrum ($CDCl_3$) of the rearranged produced **12-d** showed δ 7.32-7.26 (m, 5 H), 4.17-4.09 (m, 2 H), 3.68 (s, 2 H), 3.08 (d, J_{AB} = 12.9 Hz, 1 H), 2.97 (d, J_{AB} = 12.9 Hz, 1 H), 2.86 (d, J_{AB} = 16.2 Hz, 1 H), 2.80-2.56 (m, 5 H), 1.23 (t, J = 7.1 Hz, 3 H). The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 276 (M^+, 7), 231 (M^+-OEt, 9), 203 (M^+-COOEt, 4), 185 (M^+-$PhCH_2$, 7), 92 (10.8), 91 ($PhCH_2^+$, 100). Exact mass calc'd for $C_{16}DH_{20}NO_3$ (M^+): 276.1584. Found: 276.1584.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the mixture of the reduced product **13-d** and **13'-d** showed δ 7.35-7.24 (m), 4.27-4.12 (m, 2 H), 3.61-3.50 (m), 3.46 (dd, J_{AB} = 11.5, 2.7 Hz), 3.05-3.02 (m), 2.97-2.85 (m), 2.43-2.35 (m), 2.13 (d, J_{AB} = 11.5 Hz), 1.25-1.16 (m). The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 276 (M^+, 12), 231 (M^+-OEt, 18), 203 (M^+-COOEt, 55), 202 (3.6), 185 (M^+-$PhCH_2$, 11), 92 ($PhCDH^+$, the base peak of **13-d**, 49), 91 ($PhCH_2^+$, the base peak of **13'-d**, 100). Exact mass calc'd for $C_{16}DH_{20}NO_3$ (M^+): 276.1584. Found: 276.1584. The peaks at m/z 92 and 91 had an intensity ratio of 49 : 100 corresponding to a 3 : 7 ratio of **13-d** to **13'-d**.

Methyl 4-Oxo-1-triphenylmethyl-3-piperidinecarboxylate (14). A mixture of methyl 4-oxo-3-piperidinecarboxylate hydrochloride (1.93 g, 10.0 mmoles, Aldrich), triphenylmethyl chloride (2.5 g, 9.1 mmoles) and *N, N*-diisopropylethyl amine (3.47 mL, 20 mmoles) in dry dichloromethane(40 mL) was stirred at room temperature under argon for 12 h . The reaction was poured into 60 mL of dichloromethane, washed with water (2 x 3 mL), dried over Na_2SO_4, and evaporated *in vacuo* to 5.5 g of brown oil. Flash column chromatography on a 2"x 6" column of silica gel (6:1 hexanes-ethyl acetate containing 0.5% Hunig's base) afforded 1.68 g (42%) of the title compound **14** as a mixture of keto and enol forms, R_f 0.44 (6 :1 hexanes-ethyl acetate). The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 11.9 (br. s, enol OH), 7.50-7.48 (m, Ar), 7 29-7.14 (m, Ar), 3.77 (s, -$COOCH_3$), 3.66 (s, -$COOCH_3$), 3.10-2.90 (m), 2.85-2.65 (m), 2.60-2.30 (m), 2.17 (s). The IR spectrum (neat) showed bands at: 3058 (w), 3021 (w), 2952 (w), 2824 (w), 1744 (m), 1720 (m), 1666 (vs),1622 (m), 1312 (s), and 1225 (vs) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 399 (M^+, 0.2), 322 (M^+-Ph, 2), 290 (M^+-MeOH-Ph, 1.5), 243 (Ph_3C^+, 100). Exact mass calc'd for $C_{20}H_{20}NO_3$ (M^+-Ph): 322.1443. Found: 322.1444.

Methyl 4-Oxo-3-phenylselenomethyl-1-triphenylmethyl-3-piperidinecarboxylate (15). Following the procedure used for the preparation of **7**, 0.399 g (1.0 mmoles) of methyl 4-oxo-1-triphenylmethyl-3-piperidinecarboxylate (**14**) in 2.0 mL of THF was alkylated, using NaH (0.048 g, 1.2 mmoles) with 0.308 g (1.5 mmoles) of phenylselenomethyl chloride and 0.3 g (2.0 mmoles) of NaI at reflux for 2 h . Flash column chromatography on a 1.5" x 6" column of silica gel (elution with 6:1 hexanes-ethyl acetate), after standard aqueous work-up, gave 0.107 g (19%) of the desired phenylseleno compound **15** as a colorless oil, R_f 0.35 (6:1 hexane-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 7.47-7.18 (m, 20 H, Ar), 3.80 (s, 3 H), 3.67 (dd, J_{AB} = 11.5, 2.5 Hz, 1 H), 3.40-3.20 (m, 2 H), 3.11 (d, J_{AB} =12.3 Hz, 1 H), 2.99 (d, J_{AB} = 12.3 Hz, 1 H), 2.44-2.39 (m, 1 H), 1.95 (d, J_{AB} = 11.5 Hz, 1 H), 1.63-1.60 (m, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 20 lines at: δ 205.6 (s), 171.4 (s), 133.5 (s), 133.1, 132.1, 129.2, 128.9, 127.9, 127.7, 127.3, 127.1, 126.5, 126.2, (d, J = 161 Hz) 68.1 (s), 62.8 (s), 56.8 (t, J = 138.4 Hz), 52.3 (q, J = 147.0 Hz), 49.1 (t, J = 137.2 Hz), 41.2 (t, J = 133.2 Hz), 30.4 (t, J = 145.7 Hz). The IR spectrum (neat) showed bands at: 3057 (w), 3029 (w), 3020 (w), 2950 (w), 1732 (vs), 1721 (vs), 1717 (vs), 1448 (m), and 1217 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 569 (M^+, 0.22), 492 (M^+-Ph, 0.44), 243 (Ph_3C^+, 100). Exact mass calc'd for $C_{33}H_{31}NO_3Se$ (M^+): 569.1469. Found: 569.1467.

Reaction of Methyl 4-Oxo-3-phenylselenomethyl-1-triphenylmethyl-3-piperidinecarboxylate (15) with Tri-*n*-butyltin Hydride and AIBN. Following the procedure used for the reaction of **8** with *n*-Bu_3SnH and AIBN, a refluxing solution of the phenylseleno compound **15** (0.057 g, 0.1 mmoles) in 1 mL of benzene under argon was added dropwise over 6 h to a solution of tri-*n*-butyltin hydride (0.074 mL, 0.28 mmoles) and AIBN (0.092 g, 0.056 mmoles) in 2.0 mL of benzene. The reaction was heated at reflux for an additional 1 h. After standard aqueous workup, column chromatography on 2 g of silica gel (elution with 4:1 hexanes-ethyl acetate) afforded 0.027 g (66%) of the rearranged product **16** and 0.003 g (8%) of the reduced product **17** as colorless oils, R_f 0.21 and 0.42 (4:1 hexanes-ethyl acetate), respectively.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the rearranged product **16** showed δ 7.50-7.30 (m, 6 H), 7.29-7.25 (m, 6 H), 7.19-7.10 (m, 3 H), 3.67 (s, 3 H), 3.11-3.04 (m, 2 H), 2.88-2.65 (m, 5 H), 2.49-2.39 (m, 2 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 13 lines at: δ 210.4 (s), 173.4 (s), 142.7 (s), 129.1 (d, J = 159 Hz), 127.5 (d, J = 155 Hz), 126.4 (d, J = 154 Hz), 79.4 (s), 56.6 (t, J = 139.3 Hz), 52.1 (q, J = 146.8 Hz), 48.1 (t, J = 127.5 Hz), 44.7 (two overlapped t, J = 127.3 Hz), 42.2 (d, J = 125.4 Hz). The IR spectrum (neat) showed bands at: 3031 (w), 3020 (w), 2967 (vs), 2930 (w), 1738 (vs), 1709 (vs), and 1448 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 413 (M^+, 0.05), 336 (M^+-Ph, 3), 243 (Ph_3C^+, 100). Exact mass calc'd for $C_{21}H_{22}NO_3$ (M^+-Ph): 336.1600. Found: 336.1600.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the reduced product **17** showed δ 7.60-7.38 (m, 6 H), 7.40-7.15 (m, 9 H), 3.90 (s, 3 H), 3.60 (br. d, J = 11.6 Hz, 1 H), 3.3-3.1 (m, 2 H), 2.48-2.40 (m, 1 H), 1.83 (br. d, J = 11.6 Hz, 1 H), 1.80-1.60 (m, 1 H), 1.23 (s, 3 H). The IR spectrum (neat) showed bands at: 3029 (w), 3022 (w), 2825 (w), 1735 (vs), 1720 (vs), and 1244 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 413 (M^+, 0.1), 336 (M^+-Ph, 2.1), 260 (M^+-2Ph, 2.0), 243 (Ph_3C^+, 100). Exact mass calc'd for $C_{21}H_{22}NO_3$ (M^+-Ph): 336.1600. Found: 336.1601.

Methyl tetrahydro-4*H*-pyran-4-one-3-carboxylate. A solution of 0.743 g (7.43 mmoles) of tetrahydro-4*H*-pyran-4-one in 10 mL of benzene was added dropwise over 5 h to a refluxing slurry of 0.823 g (14.9 mmoles) of NaH (60% dispersion in mineral oil), 0.134 g (1.16 mmoles) of potassium hydride (KH) (35% in mineral oil), and 1.42 mL (14.86 mmoles) of dimethyl carbonate in 10 mL of benzene. After refluxing for an additional 1 h, the reaction was cooled to room temperature and cautiously quenched with 6.0 mL (96 mmoles) of acetic acid in 10 mL of ice water. The product was extracted with benzene (5 x 10 mL), washed with cold water (3 x 10 mL), dried over Na_2SO_4, and evaporated *in vacuo*; giving 1.0 g of brown oil. Flash column chromatography on 1.5" x 6" (2:1 hexanes-ethyl acetate containing 0.5% Hunig's base) gave 0.093 g (8%) of the title compound as an oily mixture of enol and keto forms, R_f 0.50 (3:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 11.8 (br. s, enol O*H*), 4.28 (s), 4.22 (dd, J_{AB} = 11.7, 7.1 Hz, 1 H), 4.12 (dd, J_{AB} = 11.7, 4.8 Hz, 1 H), 4.07-3.83 (m), 3.77 (s, 3H), 3.76 (s, 3H), 3.57-3.47 (m), 2.72-2.51 (m), 2.41-2.39 (m). The ^{13}C nmr spectrum ($CDCl_3$) showed 14 lines at: δ 201.4 (s), 170.4 (s), 168.9 (s), 168.3 (s), 97.3 (s), 69.6 (t, J = 153.4 Hz), 68.2 (t, J = 146.6 Hz), 63.9 (t, J = 144.5 Hz), 62.9 (t, J = 147.7 Hz), 57.7 (d, J = 131.9 Hz), 52.5 (q, J = 148.3 Hz), 51.4 (q, J = 147.9 Hz), 42.0 (t, J = 131.3 Hz), 28.7 (t, J = 129.3 Hz). The IR spectrum (neat) showed bands at: 2857 (w), 1747 (vs), 1722 (vs), 1668 (vs), 1633 (vs) cm^{-1}.

Methyl 1-Oxa-3-phenylselenomethylcyclohexan-4-one-3-carboxylate (18). Following the procedure used for the preparation of **8**, 0.124 g (0.78 mmoles) of methyl tetrahydro-4*H*-pyran-4-one-3-carboxylate in 2.5 mL of THF was alkylated, using NaH (0.038 g, 0.94 mmoles) with 0.248 g (1.2 mmoles) of phenylselenomethyl chloride and 0.24 g (1.6 mmoles) of NaI at reflux for 6 h. Flash column chromatography on a 0.8" x 6" column of silica gel (elution with 150 : 3 : 0.15 CH_2Cl_2-CH_3CN-

Hunig's base), after standard aqueous work-up, gave 0.065 g (25%) of the desired phenylseleno compound **18** as a colorless oil, R_f 0.45 (6:0.25 CH_2Cl_2-CH_3CN).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 7.53-7.46 (m, 2 H, Ar), 7.30-7.25 (m, 3 H, Ar), 4.50 (dd, J_{AB} = 10.7, 1.2 Hz, 1 H), 4.18-4.14 (m, 1 H), 3.78 (dt, J_{AB} =10.7, 3.7 Hz, 1 H), 3.71 (d, J_{AB} =12.7 Hz, 1 H), 3.66 (s, 3 H, -COOC*H*$_3$), 3.26 (d, J_{AB} = 12.6 Hz, 1 H), 3.14 (d, J_{AB} =12.6 Hz, 1 H), 2.89-2.81 (m, 1 H), 2.50 (dt, J = 14.8, 3.5 Hz, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 12 lines at: δ 202.7 (s), 169.9(s), 133.1 (d, J = 162.0 Hz), 130.9 (s), 129.2 (d, J = 158.8 Hz), 127.4 (d, J = 161.3 Hz), 74.1 (t, J = 145.2 Hz), 68.6 (t, J = 145.2 Hz), 63.7 (s), 52.7 (q, J = 148.6 Hz), 41.0 (t, J = 131.0 Hz), 28.1 (t, J = 145.8 Hz). The IR spectrum (neat) showed bands at: 3056 (w), 2958 (w), 2853 (w), 1732 (vs), 1716 (vs), 1437 (m), and 1258 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 328 (M^+, 74), 171 (M^+-PhSe, 25), 157 (M^+-PhSeCH_2, 30), 139 (M^+-PhSeCH_2-CO, 100). *Exact mass calc'd for* $C_{14}H_{16}O_4Se$ (M^+): 328.0214. *Found:* 328.0199.

Reaction of Methyl tetrahydro-4*H*-pyran-3-phenylseleno-4-one-3-carboxylate (18) with Tri-*n*-butyltin Hydride and AIBN. Following the procedure for the reaction of **8** with *n*-Bu_3SnH and AIBN, a refluxing solution of the phenylseleno compound **18** (0.058 g, 0.18 mmoles) in 5 mL of benzene, under argon, was added dropwise over 6 h to a solution of tri-*n*-butyltin hydride (0.142 mL, 0.53 mmoles) and AIBN (0.01 g, 0.035 mmoles) in 3.0 mL of benzene. The reaction was heated at reflux for an additional 2 h. Column chromatography on 2 g of silica gel (elution with 2:1 hexanes-ethyl acetate), after standard aqueous workup, afforded 0.018 g (61%) of the rearranged product **19** as a colorless oil, R_f 0.31 (2:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) of **19** showed δ 4.21 (ddd, J = 12.1, 6.1, 0.7 Hz, 1 H), 3.99 (dd, J = 12.1, 2.4, 1 H), 3.91 (ddd, J = 10.5, 6.8, 3.9 Hz, 1 H), 3.79 (ddd, J = 10.5, 7.6, 3.1 Hz, 1 H), 3.74 (s, 3 H), 3.01 (dd, J = 15.3, 7.8 Hz, 1 H), 2.91-2.87 (m, 1 H), 2.83-2.74 (m, 2 H), 2.67 (ddd, J = 9.9, 6.6, 3.3 Hz, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 8 lines at: δ 209.4 (s), 172.5 (s), 74.7 (t, J = 147.7 Hz), 67.1 (t, J = 144.0 Hz), 52.5 (q, J = 147.7 Hz), 46.6 (t, J = 127.6 Hz), 44.7 (t, J = 127.5 Hz), 42.9 (d, J = 129.9 Hz). The IR spectrum (neat) showed bands at: 2961 (s), 1716 (vs), 1699 (vs), and 1260 (vs) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 172 (M^+, 4), 141 (M^+-OMe, 21), 113 (M^+-COOMe-H, 31). Exact mass calc'd for $C_8H_{12}O_4$ (M^+): 172.0736. Found: 172.0737.

Dimethyl 4-thiaheptanedioate. Methyl acrylate (3.6 g, 42 mmoles) was added dropwise over 20 min to a stirred solution of methyl 2-mercaptopropionate (4.8 g, 40 mmoles) and piperidine (0.05 mL) at room temperature. When half of the acrylate had been introduced, more piperidine (0.05 mL) was added. After completion of the addition of the acrylate, the reaction mixture was heated for 10 min in a 80 °C bath, cooled and diluted with 150 mL of ether. The ether layer was washed with water (4 x 40 mL), dried over K_2CO_3, filtered, evaporated *in vacuo*, and distilled under reduced pressure to yield 5.87 g (73%) of the title compound as a colorless oil, b. p. 125-128 °C (0.3 mm Hg).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed peaks at δ 3.71 (s, 6 H), 2.82 (t, J = 7.5 Hz, 4 H), 2.63 (t, J = 7.5 Hz, 4 H). The IR spectrum (neat) showed bands at: 2953 (m), 1738 (vs), 1438 (m), and 1173 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 206 (M^+, 58), 175 (M^+-OMe, 11), 146 (M^+-COOMe-H, 73), 119 (M^+-CH_2CH_2COOMe, 56). Exact mass calc'd for $C_8H_{14}O_4S$ (M^+): 206.0613. Found: 206.0605.

Methyl 1-Thiacyclohexan-4-one-3-carboxylate. A solution of 0.60 g (3 mmoles) of dimethyl 4-thiaheptanedioate in 30 mL of THF was added dropwise over 1 h to a stirred slurry of 0.144 g (3.6 mmoles) of NaH (60% dispersion in mineral oil) and 0.644 g(3.6 mmoles) of HMPA in 30 mL of THF at room temperature. After heating at reflux for 17 h, the reaction mixture was concentrated *in vacuo* to a volume of about 10 mL, then diluted with 150 mL of ether. The ether layer was washed with water (5 x 5 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*; giving 0.89 g of a light yellow oil. Flash column chromatography on a 1.5" x 6" column of silica gel (5:1 hexanes-ethyl acetate) gave 0.066 g (13%) of the title compound as an oily mixture of enol and keto forms, R_f 0.50 (5:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 12.5 (br. s, enol O*H*), 3.79 (s, -COOC*H*$_3$), 3.78 (s, -COOC*H*$_3$), 3.71-3.67 (m), 3.36 (s), 3.10-2.74 (m), 2.62-2.58 (m). The ^{13}C nmr spectrum ($CDCl_3$) showed 14 lines at: δ 203.4 (s), 172.4 (s), 171.8 (s), 169.1 (s), 97.6 (s), 58.6 (d, J = 131.5 Hz), 52.5 (q, J = 147.9 Hz), 51.8 (q, J = 147.4 Hz), 43.5 (t, J = 131.4 Hz), 32.5 (t, J = 146.0 Hz), 30.8 (t, J = 129.7 Hz), 30.4 (t, J = 142.9 Hz), 24.7 (t, J = 140.9 Hz), 23.5 (t, J = 141.9 Hz). The IR spectrum (neat) showed bands at: 3003 (w), 2954 (w), 2904 (w), 1745 (vs), 1714 (vs), 1657 (vs), 1614 (vs), 1441 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 174 (M^+, 100), 142 (M^+-OMe, 40), 115 (M^+-COOMe, 52). Exact mass calc'd for $C_7H_{10}SO_3$ (M^+): 174.0350. Found: 174.0351.

Methyl 3-Phenylselenomethyl-1-thiacyclohexan-4-one-3-carboxylate (20). Following the procedure for the preparation of **8**, 0.087 g (0.5 mmoles) of methyl 1-thiacyclohexan-4-one-3-carboxylate in 1.0 mL of THF was alkylated, using

NaH (0.024 g, 0.6 mmoles) with 0.154 g (0.75 mmoles) of phenylselenomethyl chloride and 0.15 g (1.0 mmoles) of NaI at reflux for 4 h. Flash column chromatography on a 0.8" x 6" column of silica gel (elution with 5 : 1 hexanes-ethyl acetate), after standard aqueous work-up, gave 0.040 g (23%) of the desired phenylseleno compound **20** as a colorless oil, R_f 0.24 (5 : 1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 7.54-7.51 (m, 2 H, Ar), 7.29-7.24 (m, 3 H, Ar), 3.64 (s, 3 H), 3.40-3.30 (m, 3 H), 3.16-2.8 (m, 5 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 12 lines at: δ 204.6 (s), 170.2(s), 133.5 (d, J = 162.0 Hz), 131.1 (s), 129.1 (d, J = 158.0 Hz), 127.4 (d, J = 161.0 Hz), 64.2 (s), 52.6 (q, J = 148.0 Hz), 42.7 (t, J = 130.0 Hz), 38.2 (t, J = 142.0 Hz), 31.9 (t, J = 145.8 Hz), 30.6 (t, J = 143.3 Hz). The IR spectrum (neat) showed bands at: 2952 (w), 1735 (vs), 1712 (vs), 1436 (m), and 1285 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 344 (M^+, 67), 187 (M^+-PhSe, 44), 173 (M^+-$PhSeCH_2$, 21), 155 (M^+-PhSe-MeOH, 100). Exact mass calc'd for $C_{14}H_{16}SO_3Se^{80}$ (M^+): 343.9985. Found: 343.9987.

Reaction of Methyl 3-Phenylselenomethyl-1-thiacyclohexan-4-one-3-carboxylate (20) with Tri-*n*-butyltin Hydride and AIBN. A solution of tri-*n*-butyltin hydride (0.078 mL, 0.29 mmoles) and AIBN (0.006 g, 0.004 mmoles) in 3.0 mL of benzene was added dropwise over 3 h to a refluxing solution of the phenylseleno compound **20** (0.023 g, 0.065 mmoles) in 0.7 mL of benzene under argon. After completion of the addition of the tin hydride, the reaction was heated at reflux for an additional 1 h. Column chromatography on 2 g of silica gel (elution with 3:1 hexanes-ethyl acetate), after standard aqueous workup, afforded 0.006 g (46%) of the rearranged product **21** and 0.004 g (30%) of the reduced product **22** as colorless oils, R_f 0.23 and 0.50 (3:1 hexanes-ethyl acetate), respectively.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the rearranged product **21** showed δ 3.73 (s, 3 H), 3.03-2.75 (m, 9 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 8 lines at: δ 208.7 (s), 173.1 (s), 52.4 (q, J = 147.4 Hz), 47.3 (t, J = 129.0 Hz), 44.4 (d, J = 128.3 Hz), 43.9 (t, J = 130.7 Hz), 36.9 (t, J = 141.8 Hz), 27.3 (t, J = 141.7 Hz), . The IR spectrum (neat) showed bands at: 2944 (m), 1732 (vs), 1706 (vs), and 1436 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 188 (M^+, 57), 129 (M^+-COOMe, 28). Exact mass calc'd for $C_8H_{12}SO_3$ (M^+): 188.0507. Found· 188.0507.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the reduced product **22** showed δ 3.78 (s, 3 H), 3.32 (dd, J = 13.2, 3.29 Hz, 1 H), 3.00-2.78 (m, 4 H), 2.70 (d, J = 13.2 Hz, 1 H), 1.40 (s, 3 H). The IR spectrum (neat) showed bands at: 2954 (m), 2938 (m), 1732 (vs), 1714 (vs), 1454 (m), and 1205 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 188 (M^+, 30), 173 (M^+-Me, 23), 156 (M^+-MeOH, 15), 129 (M^+-COOMe, 100). Exact mass calc'd for $C_8H_{11}SO_3$ (M^+): 188.0507. Found: 188.0515.

Dimethyl 3-thiahexanedioate (23).[6] Methyl acrylate (9.0 g, 105 mmoles) was added dropwise over 20 min to a stirred solution of methyl thioglycolate (10.6 g, 100 mmoles) and piperidine (0.10 mL) at room temperature. When about half of the acrylate had been introduced, more piperidine (0.10 mL) was added. After completion of the addition of the acrylate, the reaction mixture was heated for 10 min in an 80 °C bath, and diluted with 100 mL of ether. The ether layer was washed with water (5 x 5 mL), dried over Na_2SO_4, filtered, evaporated *in vacuo*, and distilled under reduced pressure to yield 14.2 g (74%) of the title compound **23** as a colorless oil, b. p.120-125 °C (0.2 mm Hg).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 3.75 (s, 3 H), 3.70 (s, 3 H), 3.26 (s, 2 H), 2.92 (t, J = 7.2 Hz, 2 H), 2.66 (t, J = 7.2 Hz, 2 H). The IR spectrum (neat) showed bands at: 2999 (w), 2954 (m), 1738 (vs), and 1253 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 192 (M^+, 20), 160 (M^+-MeOH, 40), 133 (M^+-COOMe, 27). Exact mass calc'd for $C_7H_{12}O_4S$ (M^+): 192.0456. Found: 192.0456.

Methyl tetrahydrothiophen-3-one-4-carboxylate (24).[6] To a stirred slurry of 0.777 g (14.3 mmoles) of sodium methoxide in 4 mL of dry ether at room temperature, 1.8 g (9.4 mmoles) of dimethyl 3-thiahexanedioate **(23)** was added dropwise over 20 min. The reaction was heated at reflux for 3 h, cooled to room temperature and cautiously quenched with a solution of 1 mL of acetic acid in 4 mL of ice-water. The product was extracted with ether (4 x 2 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*; giving 1.3 g of a light yellow oil. Flash column chromatography on a 1.5" x 6" column of silica gel (2:1 hexanes-ether) gave 0.260 g (18%) of the title compound **24** as a mixture of enol and keto form along with 0.660 g (44%) of the regioisomer, methyl tetrahydrothiophen-3-one-2-carboxylate **(25)** as a colorless oil, of R_f 0.38 and 0.50 (2:1 hexanes-ether), respectively.

The 300 MHz proton nmr spectrum ($CDCl_3$) of **24** showed δ 10.9 (br. s, enol O*H*), 3.85-3.67 (m), 3.81 (s, -$COOCH_3$), 3.80 (s, -$COOCH_3$), 3.56-3.52 (m), 3.44-3.35 (m), 3.23-3.14 (m). The ^{13}C nmr spectrum ($CDCl_3$) showed 12 lines at: δ 204.9 (s), 171.7 (s), 168.8(s), 167.5 (s), 98.5 (s), 54.7 (d, J = 137.0 Hz), 51.9 (q, J = 148.1 Hz), 50.8 (q, J = 147.9 Hz), 36.7 (t, J = 144.4 Hz), 35.3 (t, J = 144.3Hz), 30.7 (t, J = 146.0 Hz), 28.3 (t, J = 146.9 Hz). The IR spectrum (neat) showed bands at: 3024 (w), 3003 (w), 2954 (w), 1753 (s), 1732 (s), 1668 (s), 1628 (s), 1445 (s), and 1237 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 160 (M^+, 77), 128 (M^+-MeOH, 31), 101 (M^+-COOMe, 28). Exact mass calc'd for $C_6H_8SO_3$ (M^+): 160.0194. Found: 160.0193.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the regioisomer **25** showed δ 4.04 (s, 1 H), 3.78 (s, 3 H), 3.37-3.27 (m, 1 H), 3.18-2.95 (m, 1 H), 2.94-2.80 (m, 1 H), 2.74-2.59 (m, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 6 lines at: δ 206.6 (s), 168.6 (s), 52.5 (q, J = 147.0 Hz), 51.4 (d, J = 149.0 Hz), 38.2 (t, J = 132.0 Hz), 24.9 (t, J = 145.0 Hz). The IR spectrum (neat) showed bands at: 2955 (w), 1749 (vs), 1732 (vs), 1656 (w), 1653 (w), 1436 (m), and 1296 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 160 (M^+, 60), 128 (M^+-MeOH, 25), 101 (M^+-COOMe, 35). Exact mass calc'd for $C_6H_8SO_3$ (M^+): 160.0194. Found: 160.0193.

Methyl 4-Phenylselenomethyl-1-thiacyclopentan-3-one-4-carboxylate (26). A solution of 0.320 g (2.0 mmoles) of methyl tetrahydrothiophene-3-one-4-carboxylate (**23**) in 4.0 mL of THF was alkylated, using NaH (0.096 g, 2.4 mmoles) as base, with 0.616 g (4.0 mmoles) of chloromethyl phenyl selenide and 0.6 g (4.0 mmoles) of NaI at reflux for 6 h. After standard aqueous work-up, flash column chromatography on a 1.5" x 6" column of silica gel (elution with 3 : 1 hexanes-ethyl acetate containing Hunig's base (0.1%)), gave 0.277 g (42%) of the desired phenylseleno compound **26** as a colorless oil, R_f 0.43 (3 : 1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 7.55-7.53 (m, 2 H), 7.28-7.26 (m, 3 H), 3.68 (s, 3 H), 3.54 (d, J_{AB} =12.1 Hz, 1 H), 3.49 (d, J_{AB} =12.8 Hz, 1 H), 3.47 (d, J_{AB} =18.2 Hz, 1 H), 3.32 (d, J_{AB} =18.2 Hz, 1 H), 3.29 (d, J_{AB} =12.8 Hz, 1 H), 3.20 (d, J_{AB} =12.1 Hz, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 11 lines at: δ 206.0 (s), 169.0(s), 132.9 (d, J = 162.0 Hz), 130.0 (s), 128.9 (d, J = 161.0 Hz), 127.4 (d, J = 162.0 Hz), 62.6 (s), 53.0 (q, J = 148.0 Hz), 37.5 (t, J = 145.0 Hz), 34.7 (t, J = 147.0 Hz), 30.5 (t, J = 145.0 Hz). The IR spectrum (neat) showed bands at: 2999 (w), 2952 (m), 1745 (vs), 1728 (vs), and 1251 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 330 (M^+, 25) and 173 (M^+-PhSe, 42). Exact mass calc'd for $C_{13}H_{14}O_3SSe$ (M^+): 329.9829. Found: 329.9813.

Reaction of Methyl 4-Phenylselenomethyl-1-thiacyclopentan-3-one-4-carboxylate (26) with Tri-*n*-butyltin Hydride and AIBN.

(a) Reaction with 2 equiv. of n-Bu_3SnH: A solution of tri-*n*-butyltin hydride (0.204 mL, 0.6 mmoles) and AIBN (0.010 g, 0.007 mmoles) in 36 mL of benzene was added dropwise over 6 h to a refluxing solution of the phenylseleno compound **26** (0.099 g, 0.3 mmoles) in 42 mL of benzene under argon. After completion of the addition of the tin hydride, the reaction was heated at reflux for an additional 12 h. Column chromatography on 2 g of silica gel (elution with 3:1 hexanes-ethyl acetate), after standard aqueous workup, afforded 0.009 g (17%) of the rearranged product **27** and 0.048 g (39%) of the open-chain product **28** as colorless oils, R_f 0.31 and 0.40 (3:1 hexanes-ethyl acetate), respectively.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the rearranged product **27** showed δ 3.73 (s, 3 H), 3.39-3.35 (m, 1 H), 3.32 (d, J_{AB} =13.3 Hz, 1 H), 3.08 (d, J_{AB} =13.3 Hz, 1 H), 3.02 (dd, J_{AB} =13.9, 9.2 Hz, 1 H), 2.99 (dd, J_{AB} =13.9, 4.0 Hz, 1 H), 2.69 (dd, J_{AB} =14.0, 4.8 Hz, 1 H), 2.64 (dd, J_{AB} =14.0, 10.2 Hz, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 7 lines at: δ 200.6 (s), 171.5 (s), 52.1 (q, J = 147.8 Hz), 48.4 (d, J = 133.4 Hz), 42.7 (t, J = 129.4 Hz), 37.9 (t, J = 141.2 Hz), 29.8 (t, J = 140.4 Hz). The IR spectrum (neat) showed bands at: 1736 (vs), 1716 (vs), 1573 (m), and 1417 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 174 (M^+, 25), 156 (M^+-CO, 25), 142 (M^+-MeOH, 10). Exact mass calc'd for $C_7H_{10}O_3S$ (M^+): 174.0351. Found: 174.0351.

The 300 MHz proton nmr spectrum ($CDCl_3$) of the open-chain product **28** showed δ 3.72-3.68 (m, 1 H), 3.69 (s, 3 H), 3.08-2.82 (m, 4 H), 2.18 (s, 3 H), 1.59-1.52 (m, 6 H), 1.33 (sextet, J =7.4 Hz, 6 H), 1.15 (t, J = 7.9 Hz, 6 H), 0.91 (t, J = 7.3 Hz, 9 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 11 lines at: δ 206.5 (s), 173.8 (s), 51.8 (q, J = 147.1 Hz), 43.6 (d, J = 132.0 Hz), 43.1 (t, J = 125.0 Hz), 28.5, 28.4, 27.8, 26.9, 13.5, 13.4. The IR spectrum (neat) showed bands at: 2957(s), 2926 (vs), 2872 (m), 2854 (m), 1738 (vs), 1722 (vs), and 1194 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 409 (M^+-*n*-Bu, 18), 291 (*n*-Bu_3Sn, 5), 175 (M^+-*n*-Bu_3Sn, 27). Exact mass calc'd for $C_{15}H_{29}O_3S^{120}Sn$ (M^+-*n*-Bu): 409.0859. Found: 409.0856.

(b) Reaction with 1.1 equiv. of n-Bu_3SnH; The procedure above was repeated with 1.1 equivalents of *n*-Bu_3SnH (0.056 mL, 0.165 mmoles) and **26** (0.050 g, 0.15 mmoles). The rearranged product **27** was obtained in 64% yield (0.016 g) while the open-chain product **28** was not observed.

Methyl tetrahydrofuran-3-one-4-carboxylate (29) To a stirred slurry of 1.76 g (44 mmoles) of NaH in 40 mL of dry ether at room temperature, 3.6 g (40 mmoles) of methyl glycolate was added dropwise over 15 min. After stirring at room temperature for 30 min, the reaction was concentrated *in vacuo*. The resulting white solid was treated with 4.17 g (48 mmoles) of methyl acrylate in 20 mL of dimethyl sulfoxide at 0 °C and stirred for 15 min. The cooling bath was removed and stirring was continued for an additional 45 min. The reaction was quenched by pouring slowly into 50 mL of 5% H_2SO_4. The product was extracted with ether (6 x 40 mL), washed with brine (3 x 5 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*;

giving 8.0 g of a light yellow oil. Flash column chromatography on a 1.5" x 6" column of silica gel (3:1 hexanes-ethyl acetate) gave 4.46 g (69%) of the title compound **29** as a colorless oil of R_f 0.34 (3:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 4.47 peaks at δ 4.48 (apparent sextet, J_{AB} = 10, $J_{AX,BX}$ = 8.3 Hz), 4.08 (d, J_{AB} =17.0 Hz, 1 H), 3.93 (d, J_{AB} =17.0 Hz, 1 H), 3.79 (s, 3 H), 3.54 (t, J = 8.3 Hz, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 6 lines at: δ 207.3 (s), 166.8(s), 70.5 (t, J = 149.0 Hz), 69.2 (t, J = 153.0 Hz), 52.9 (d, J = 137.0 Hz), 52.6 (q, J = 148.0 Hz). The IR spectrum (neat) showed bands at: 3002 (w), 2957 (w), 2887 (w), 1774 (vs), 1735 (vs), 1436 (m), and 1211 (m) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 144 (M^+, 17), 113 (M^+-MeO, 19), 85 (M^+-COOMe, 23). Exact mass calc'd for $C_6H_8O_4$ (M^+): 144.0423. Found: 144.0422.

Methyl 3-Phenylamino-2,4-dihydrofuran-4-carboxylate (30). A solution of methyl 1-oxacyclopentan-3-one carboxylate (**29**) (0.72 g, 5 mmoles), aniline (0.55 g, 6 mmoles), and *p*-toluenesulfonic acid (0.1 g, 0.052 mmoles) in 12.5 mL of benzene was heated at reflux for 12 h. The water generated was removed using a Soxhlet extractor containing calcium hydride. The reaction was concentrated *in vacuo* to 0.885 g of a brown oil, which was purified by flash column chromatography on a 1.5" x 6" column of silica gel, eluting with 6:1 hexanes-ethyl acetate containing Hunig's base (0.1%), and yielding 0.783 g (72%) of the title compound **30**, R_f 0.44 (6:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 9.10 (br. s, 1 H, NH), 7.36-7.27 (m, 2 H), 7.07 (t, J = 7.5 Hz, 1 H), 6.93 (d, J = 7.8 Hz, 2 H), 4.94 (t, J =3.0 Hz, 2 H), 4.80 (t, J =3.0 Hz, 2 H), 3.75 (s, 3 H). The IR spectrum (neat) showed bands at: 2905 (w), 2864 (w), 1677 (s), 1674 (s), 1670 (s), 1665 (s), and 1278 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 219 (M^+, 100). Exact mass calc'd for $C_{12}H_{13}NO_3$ (M^+): 219.0895. Found: 219.0896.

Methyl 4-Iodomethyl-3-phenylimino-tetrahydrofuran-4-carboxylate (31). To a suspension of 0.124 g (1.11 mmoles) of potassium *t*-butoxide in 1.2 mL of dry benzene at room temperature under argon, a solution of 0.202 g (0.92 mmoles) of **30** and 0.292 g (1.11 mmoles) of 18-crown-6 in 1.2 mL of benzene was added dropwise, but rapidly, over 1 min. The reaction mixture was stirred at room temperature for 0.5 h, and treated with 0.222 mL (2.76 mmoles) of diiodomethane. After further stirring at room temperature for 12 h, the reaction mixture was poured into 100 mL of ether, washed with 5% $Na_2S_2O_3$ (3 x 3mL) and saturated KCl (5x5 mL), dried over K_2CO_3, filtered and concentrated *in vacuo*, affording 0.240 g of a brown oil. Flash column chromatography on a 1.5" x 6" column of silica gel (elution with 6:1 hexanes-ethyl acetate containing Hunig's base (0.5%)) gave 0.087 g (26%) of the desired iodomethyl compound **31** as colorless oil, R_f 0.25 (6:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 7.34 (t, J = 7.8 Hz, 2 H), 7.13 (t, J = 7.6 Hz, 1 H), 6.81 (d, J = 7.4 Hz, 2 H), 4.60 (d, J_{AB} = 9.7 Hz, 1 H), 4.28 (d, J_{AB} =15.7 Hz, 1 H), 4.20 (d, J_{AB} = 15.7 Hz, 1 H), 4.17 (d, J_{AB} = 9.7 Hz, 1 H), 3.86 (s, 3 H), 3.79 (d, J_{AB} = 10.3 Hz, 1 H), 3.62 (d, J_{AB} = 10.3 Hz, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 11 lines at: δ 173.9 (s), 169.2 (s), 149.7 (s), 129.2 (dd, J = 161.0, 8.8 Hz), 125.2 (dd, J = 166.0, 7.6 Hz), 119.0 (dd, J = 159.0, 6.7 Hz), 76.3 (t, J = 152.0 Hz), 67.9 (t, J = 151.0 Hz), 58.1 (s), 53.3 (q, J = 148.0 Hz), 6.3 (t, J = 157.0 Hz). The IR spectrum (neat) showed bands at: 2952 (w), 2885 (w), 1738 (vs), 1698 (m), and 1593 (w) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 359 (M^+, 11), 232 (M^+-I, 24), 173 (M^+-I-$COOCH_3$, 3). Exact mass calc'd for $C_{13}H_{14}NO_3I$ (M^+): 359.0018. Found: 359.0019.

Reaction of Methyl 4-Iodomethyl-3-phenylimino-1-tetrahydrofuran-4-carboxylate (31) with Tri-*n*-butyltin Hydride and AIBN. A solution of tri-*n*-butyltin hydride (0.149 mL, 0.544 mmoles) and AIBN (0.010 g, 0.007 mmoles) in 20 mL of benzene was added dropwise over 3 h to the refluxing solution of the iodomethyl compound **31** (0.132 g, 0.37 mmoles) in 15 mL of benzene under argon After completion of the addition of the tin hydride, the reaction was heated at reflux for an additional 2 h. Column chromatography on 2 g of silica gel (elution with 1:1 hexanes-ethyl acetate), after standard aqueous workup, afforded 0.026 g (44%) of the rearranged and hydrolyzed product **32** as colorless oil, R_f 0.33 (1:1 hexanes-ethyl acetate).

The 300 MHz proton nmr spectrum ($CDCl_3$) showed δ 4.07 (dd, J_{AB} = 12.3, 4.2 Hz, 1 H), 4.04 (s, 2 H), 4.01 (dd, J_{AB} =12.3, 6.0 Hz, 1 H), 3.75 (s, 3 H, $COOCH_3$), 3.20-3.16 (m, 1 H), 2.83 (dd, J_{AB} =17.4, 7.2 Hz, 1 H), 2.70 (dd, J_{AB} =17.4, 6.3 Hz, 1 H). The ^{13}C nmr spectrum ($CDCl_3$) showed 7 lines at: δ 205.0 (s), 172.0 (s), 74.6 (t, J = 145.2 Hz), 67.2 (t, J = 146.6 Hz), 52.4 (q, J = 146.8 Hz), 41.3 (d, J = 131.7 Hz), 39.0 (t, J = 132.7 Hz). The IR spectrum (neat) showed bands at: 2957 (w), 2866 (w), 1735 (vs), 1728 (vs), 1437 (m), and 1103 (s) cm^{-1}. The mass spectrum (70 eV) showed peaks at m/z (rel. int.): 158 (M^+, 52), 126 (M^+-MeOH, 18), 99 (M^+-COOMe, 15). Exact mass calc'd for $C_7H_{10}O_4$ (M^+): 158.0579. Found: 158.0580.

Acknowledgement This work was generously supported by the Institute for General Medical Sciences of the National Institutes of Health under grant GM 39825.

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