[3 + 2] Cycloaddition of Nonstabilized Azomethine Ylides. 8.† An Efficient Synthetic Strategy for Epiboxidine

Ganesh Pandey,* Akhila K. Sahoo, Smita R. Gadre, Trusar D. Bagul, and Usha D. Phalgune

Divison of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune-411 008, India

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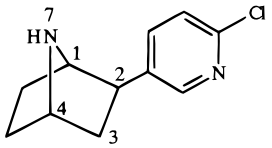
Introduction

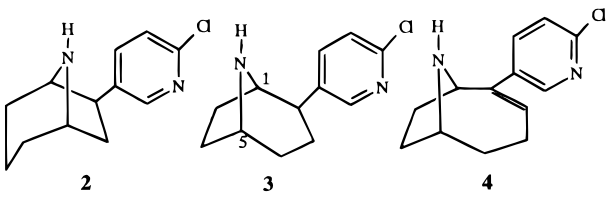
Epibatidine (**1**), isolated by Daly et al.[1a] in 1992, was found to be a member of an entirely new class of alkaloids possessing an organochlorine compound with the 7-azabicyclo[2.2.1]heptane framework. Biological and pharmacological studies exhibited its powerful analgesic properties in a nonopiod fashion[1a] and potent antinociceptive activity via activation of central nicotinic receptors.[1b,2a−c] The various pharmacological properties led researchers to recognize **1** as a therapeutically important drug target. However, due to its high toxicity (causing death in mice at 10 μL/kg scale), its therapeutic development has become a major impediment.[3]



Epibatidine (1)

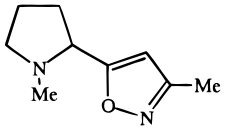
Hence, there has been a renewed interest toward searching for a pharmacophore related to the structure of **1** that exhibits pharmacological properties similar to **1** but with better ratios of pharmacological to toxicological activity. In this context, various groups have begun perceiving compounds analogous to **1** by combining structural features of the known alkaloids having high affinity toward nicotinic receptors with that of **1** and study their activity as well as toxicity. These studies have led to the design and synthesis of various newer analogues such as **2**,[4a,b] **3**,[5] and UB 165[6] (**4**).

Daly et al.[3] designed a pharmacophore by combining the structural features of the known nicotinic receptor



2 **3** **4**

antagonist ABT 418[7a,b] (**5**) and **1** and named it epiboxidine (**6**). Compound **6** was shown[3] to be a potent nicotinic



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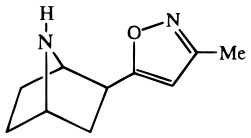

6

receptor agonist and 10-fold less potent antinociceptive agent with 20-fold less toxicity than **1**. Compound **6** was synthesized by them[3] utilizing N-protected-2-*exo*-(carboalkoxy)-7-azabicyclo[2.2.1]heptane **7** as a key precursor. Synthesis of **7** was achieved by the Favorskii rearrangement of tropinone, a strategy reported by Bai et al.[4a] The oxazolidine moiety was later constructed from carbomethoxy moiety of **7** by a known protocol.[7a] Later, Singh and Basmadjian[8] have also reported the synthesis of **7** in four steps by utilizing [4 + 2] cycloaddition of *N*-Boc-pyrrole and methyl 3-bromopropiolate as the key step.

However, both these approaches suffer from poor yield during the azabicyclic formation step itself. Considering the therapeutic potentials of **6** and the lack of synthetically viable strategy, we have devised an attractive approach for the synthesis of **7** by the [3 + 2] cycloaddition of an in situ generated nonstabilized azomethine ylide **9** with ethyl acrylate and its further transformation to **6** in good yield. An alternate approach for the construction of **7** utilizing azanorbornadiene **18**, prepared by a modified [4 + 2]-cycloaddition approach of pyrrole with dimethyl acetylenedicarboxylate (DMAD), has also been described for comparison purposes. Details of both approaches are described herein.

Results and Discussion

[3 + 2]-Cycloaddition Approach. Our synthetic strategy for the synthesis of **6** was envisioned through the retrosynthetic route as shown in Scheme 1. The [3 + 2] cycloaddition of azomethine ylide **9**, where whole of the ylide conjugation is inside the ring of pyrrolidine, with ethyl acrylate was expected to lead to azabicyclic precursor **7** stereoselectively. The in situ generation of **9** from the precursor **10** can be achieved[9a−c] by the sequential one-electron oxidation of **10** employing Ag(I)F as the one-

† For part 7, see ref 9c.

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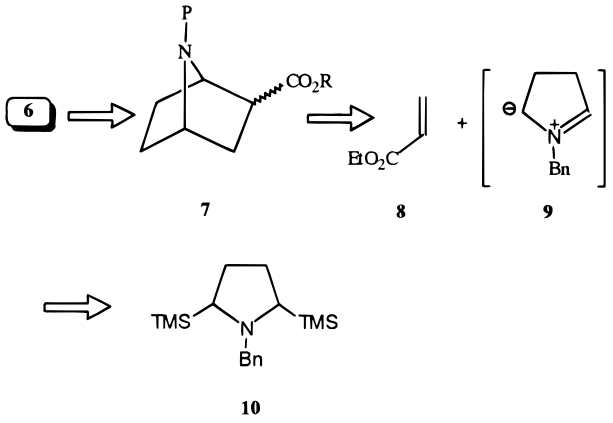
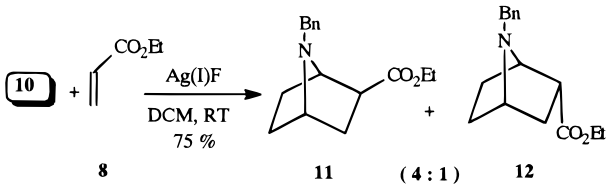
Scheme 1



Scheme 2

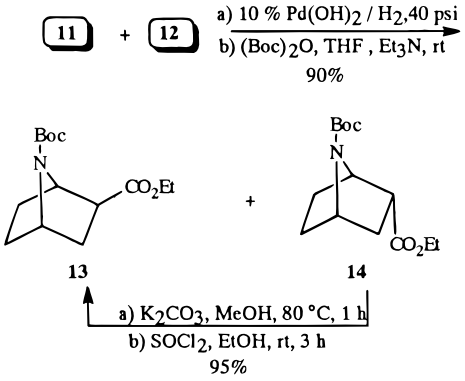


electron oxidant. Ylide precursor **10** is obtained[9c] in 65% yield starting from *N*-Boc-2-(trimethylsilyl)pyrrolidine[10] (Scheme 1).

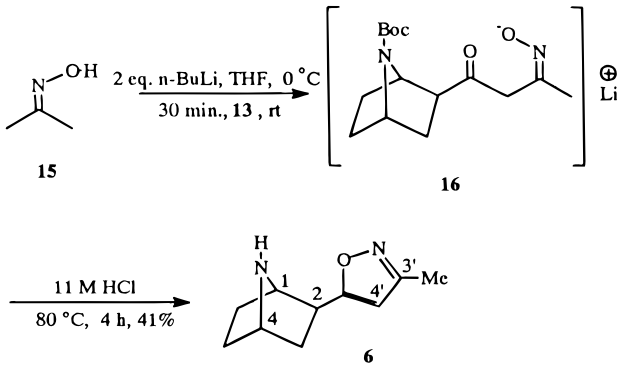
The key [3 + 2]-cycloaddition reaction was carried out at room temperature by the slow addition of a solution of ethyl acrylate in DCM to a stirring suspension of vacuum-dried Ag(I)F and **10** in DCM. The reaction was complete in 8−10 h with concomitant formation of silver mirror on the walls of the reaction flask. Chromatographic purification afforded a mixture of two stereoisomeric cycloadducts **11** and **12** in a 4:1 ratio in 75% yield (Scheme 2). These cycloadducts were further separated by careful column chromatography for spectral analysis and were characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral data. The stereochemistry of the major cycloadduct **11**, indicating exo orientation of the carbethoxy moiety, was determined by detailed ^{1}H NMR decoupling and ^{1}H COSY experiments. For illustration, proton H_2 at δ 2.40 (dd, J = 9.30, 4.90 Hz) was found to couple only with the adjacent two H_{3exo} and H_{3endo} hydrogens at δ 2.25 (m, 1H) and δ 1.50 (dd, J = 12.2, 9.3 Hz, 1H), respectively, but not with the bridgehead proton H_1 at δ 3.63 (bs, 1H). This observation is found to be in conformity with the ^{1}H NMR patterns of the 7-azabicyclo[2.2.1]-heptane systems[1a,11a,b] where no coupling is observed between bridgehead and adjacent endo hydrogens. This confirms the exo orientation for the carbethoxy moiety in major diastereomeric cycloadduct **11.** As expected, in the case of minor cycloadduct **12**, the H_2 hydrogen at δ 3.10 (m, 1H) was found to couple with both H_3 hydrogens at δ 1.90−2.10 (m, 1H) and δ 1.65 (m, 1H), respectively, and also with H_1 at δ 3.55 (t, J = 4.26 Hz), confirming the endo orientation of the carbethoxy moiety.

To carry out further synthetic transformations to accomplish the synthesis of **6**, it was mandatory to cleave the *N*-benzyl moiety from **11** and **12** prior to the construction of oxazolidine moiety to avoid complications at the later stage of the synthesis. In this context, *N*-debenzylation of the cycloadducts (mixture of **11** and **12**) was carried out by hydrogenation over Pearlman's catalyst (10% $Pd(OH)_2$) at 40 psi of hydrogen. The crude mixture was treated with $(Boc)_2O$ in the presence of Et_3N in DCM at room temperature to afford the carbamates **13** and **14**. The undesired endo isomer **14** was epimerized to the required **13**, quantitatively by treating with K_2CO_3 in MeOH at 80 °C[12a, b](Scheme 3).

Scheme 3



Scheme 4



With the key precursor **13** in hand, we transformed its carbethoxy moiety into the 2-methyloxazolidine by treating with the dianion of acetone oxime, obtained by reacting **15** with 2 equiv of *n*-BuLi in THF at 0 °C, followed by treating the reaction mixture with 11 M HCl at 80 °C, which afforded product **6** in 41% yield (Scheme 4). Product **6** was confirmed as epiboxidine by ^{1}H and ^{13}C NMR and mass spectral analysis, which was also found to be in complete agreement with the data reported by Badio et al.[3] The retention of the exo stereochemistry in **6** was once again ascertained by the detailed ^{1}H NMR decoupling and COSY experiments.

[4 + 2]-Cycloaddition as an Alternate Strategy. The synthesis of **6** was also designed alternatively through the azanorbornadiene **18**, easily obtainable by the [4 + 2] cycloaddition of *N*-carbomethoxypyrrole (**19**) and dimethyl acetylenedicarboxylate (**20**) as shown retrosynthetically in Scheme 5.

The known cycloaddition protocol by heating a neat mixture of **19** with **20** afforded **18** in poor yield[13] (42%) due to competing Michael addition and retro-Diels−Alder

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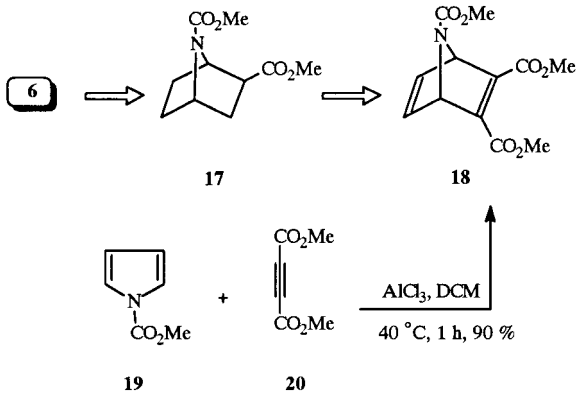
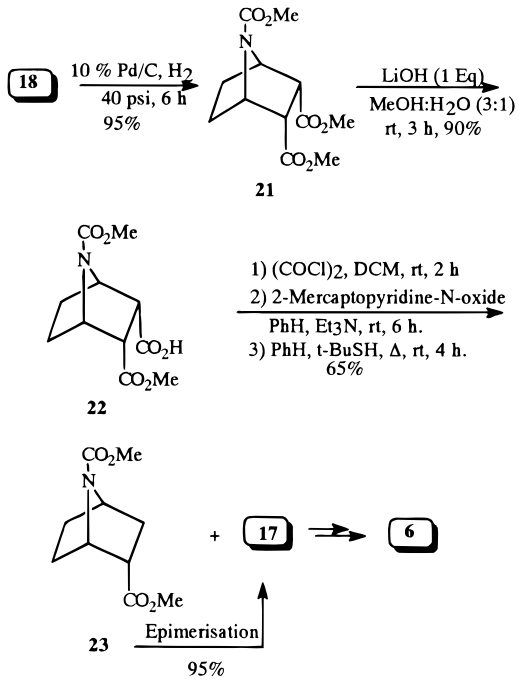
Scheme 5



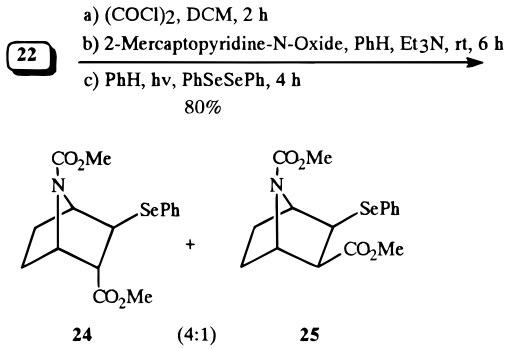
Scheme 6



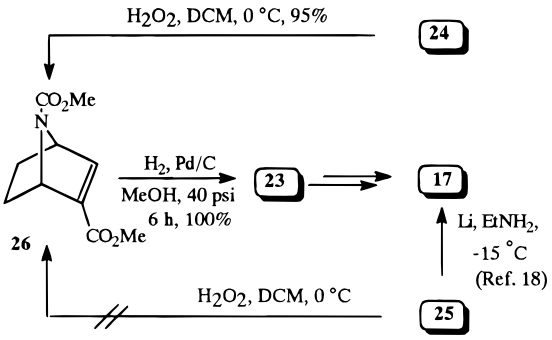
reaction.[14] Therefore, it was decided to carry out this cycloaddition reaction at lower temperatures (40 °C) using $AlCl_3$ as Lewis acid.[15a,b] Stirring of a mixture containing **19** and **20** in DCM at 40 °C in the presence of $AlCl_3$ (1 equiv) afforded **18** in 90% yield. Cycloadduct **18** was hydrogenated at 45 psi using 10% Pd/C as catalyst to yield azanorbornane **21** in 95% yield (Scheme 6). To obtain the required precursor **17**, removal of one of the carboxylate moieties from **21** was essential. Of the various decarboxylation protocols available, the Barton[16] reductive radical decarboxylation route by the pyrrolysis/photolysis of the corresponding thiohydroximate ester in the presence of radical scavengers was selected to achieve the monodecarboxylation of azanorbornane diester **21**.

To this end, the diester **21** was hydrolyzed with 1 equiv of LiOH in MeOH/H_2O (3:1) to obtain monoacid ester **22** in 90% yield. The crude **22** was converted into its corresponding acid chloride by treatment with 5 equiv of oxalyl chloride and was subsequently transformed into the thiohydroximate ester by stirring with 2-mercaptopyridine *N*-oxide in the presence of triethylamine in benzene. Pyrrolysis of the resultant thiohydroximate ester in benzene in the presence of *t*-BuSH affected reductive radical monodecarboxylation to yield the ester intermediates **23** and **17** in 65% yield. The unexpected formation of stereoisomer **17** is possible by the epimerization caused by stirring in the presence of triethylamine for a longer period. Further epimerization of **23** gave exo intermediate **17** quantitatively (Scheme 6).

Scheme 7



Scheme 8



Although we could synthesize **17** by this approach, the moderate yield encountered in the reductive radical decarboxylation step using *t*-BuSH as radical trap prompted us to develop an indirect route. We envisaged the use of PhSeSePh, known[17] to be a better and efficient radical trapping agent than *tert*-butyl mercaptan. Thus, the photolysis (400 W tungsten lamp) of thiohydroximate ester in the presence of PhSeSePh gave selenylated products **24** and **25** in a 4:1 ratio in 80% yield (Scheme 7).

The mixture of these two selenides **24** and **25** was treated with H_2O_2 for deselenylation purposes. As expected, **25** did not undergo oxidative elimination of the phenylselenyl moiety, whereas the selenide **24** afforded **26** in 95% yield. It is possible to reductively remove the phenylselenyl moiety from **25** by the known protocol[18] to afford **17** directly. Hydrogenation of **26** yielded **23** exclusively, which upon epimerization gave key precursor **17** as shown in Scheme 8.

Conclusion. From the above discussions, it appears that the [3 + 2]-cycloaddition approach for the construc-

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tion of the 7-azabicyclo[2.2.1]heptane skeleton, required for the synthesis of **6,** is shorter and high yielding in comparison to the related [4 + 2]-cycloaddition strategy.

Experimental Section

[3 + 2] Cycloaddition of *N*-Benzyl-2,5-bis(trimethylsilyl)pyrrolidine with Ethyl Acrylate. An argon-flushed two-neck flask equipped with a magnetic bar was charged with Ag(I)F (1.87 g, 14.75 mmol) (dried previously under vacuum at 40 °C) and ethyl acrylate (0.78 g, 7.86 mmol) in 30 mL of dry dichloromethane. Compound **10** (2.0 g, 6.56 mmol) dissolved in 30 mL of dry DCM was introduced into the flask dropwise over a period of 15 min. The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the surface of the flask in the form of mirror. The reaction mixture was periodically monitored by GC. After being stirred for 8−10 h, the reaction mixture was filtered through a small plug of Celite, and solvent was evaporated to give a crude brown residue. The crude residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (9:1), to afford 0.25 g of **12** (15%) as a pale yellow oil, and further elution with the same solvent system yielded 1.02 g of **11** (60%) as a pale yellow oil.

7-Benzyl-2-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane (Major Diastereomer) (11). IR (neat): 2958, 2361, 1732, 1451, 1180 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, J = 7.14 Hz, 3H), 1.35 (m, 2H), 1.50 (dd, J = 12.2, 9.3 Hz, 1H), 1.85 (m, 2H), 2.25 (m, 1H), 2.40 (dd, J = 9.3, 4.9 Hz, 1H), 3.35 (bs,1H), 3.40 (d, J = 13.7 Hz, 1H), 3.60 (d, J = 13.7 Hz, 1H), 3.63 (bs, 1H), 4.10 (q, J = 7.14 Hz, 2H), 7.15−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.98, 26.65, 26.82, 33.2, 47.69, 51.24, 59.2, 60.1, 62.98, 126.36, 127.8, 127.93, 140.0, 174.12. MS (*m*/*z*, relative intensity): 259 (M^+, 6), 158 (24), 131 (11), 91 (100). HRMS: calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1569.

7-Benzyl-2-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (Minor Diastereomer) (12). IR (neat): 2961, 2361, 1714, 1442, 1171 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, J = 7.9 Hz, 3H), 1.40 (m, 2H), 1.65−1.90 (m, 3H), 1.90−2.10 (m, 1H), 3.10 (m, 1H), 3.32 (t, J = 4.47 Hz, 1H), 3.55 (t, J = 4.26 Hz, 1H), 3.60 (bs, 2H), 4.15 (q, J = 7.9 Hz, 2H), 7.20−7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.16, 24.09, 28.11, 30.99, 45.66, 51.66, 60.13, 60.21, 62.05, 126.7, 128.12, 128.31, 139.79, 173.89. MS (*m*/*z*, relative intensity): 259 (M^+, 6), 158 (27), 130 (14), 91 (100). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16; N, 5.40. Found: C, 74.26; H, 8.39; N, 5.52.

Transformation of 11 and 12 into 13 and 14. To a mixture of **11** and **12** (0.5 g, 1.93 mmol) in 30 mL of ethanol was added palladium hydroxide (0.1 g), and the resultant suspension was hydrogenated (50 psi, rt) for 2 days. The reaction mixture was filtered, the filtrate was evaporated, and the crude amine was dissolved in 30 mL of DCM and treated with a solution of $(Boc)_2O$ (0.5 g, 2.3 mmol) in DCM followed by triethylamine (0.8 mL) under argon atmosphere. The resulting mixture was stirred for 18 h and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/EtOAc (9:1), to afford 0.09 g of 1**4** (18%) as a colorless oil, and further elution with hexane/EtOAc afforded 0.37 g of **13** (72%) as a colorless oil.

7-(*tert*-Butyloxycarbonyl)-2-*exo*-carbethoxy-7-azabicyclo[2.2.1]heptane (13). IR (neat): 2979, 1738, 1706, 1368, 1156 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 1.50−1.70 (m, 2H), 1.70−1.90 (m, 3H), 2.20−2.35 (m, 1H), 2.57 (dd, J = 8.6, 3.9 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.30 (t, J = 4.31 Hz, 1H), 4.55 (d, J = 4.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.79, 27.81 28.46, 29.12, 32.84, 47.17, 55.45, 58.89, 60.27, 79.03, 154.3, 172.73. MS (*m*/*z*, relative intensity): 269 (M^+, 0.85), 196 (23), 169 (52), 96 (42), 69 (100). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.34; H, 8.85; N, 5.52.

7-(*tert*-Butyloxycarbonyl)-2-*endo*-carbethoxy-7-azabicyclo[2.2.1]heptane (14). IR (neat): 2978, 1734, 1703, 1366, 1156 cm^{-1}.^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 1.40 (s, 9H), 1.45−1.55 (m, 2H), 1.60−1.95 (m, 4H), 2.90−3.05 (m, 1H), 4.05−4.25 (m, 3H), 4.35 (t, J = 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.09, 25.22, 28.12, 29.08, 32.28, 46.35, 57.04, 58.19, 60.46, 79.63, 155.18, 172.42. MS (*m*/*z*, relative intensity): 169 (95), 124 (85), 96 (58), 69 (100). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.24; H, 8.79; N, 5.44.

Epimerization of 14 to 13. A mixture of **14** (0.25 g, 0.93 mmol) and anhydrous K_2CO_3 (0.26 g, 1.86 mmol) in dry methanol (15 mL) was refluxed for 1 h. The reaction mixture was cooled to 0 °C, quenched by the addition of saturated NH_4Cl solution, and finally extracted with CH_2Cl_2. The aqueous layer was acidified by adding 6 N HCl at 0 °C to pH = 2, extracted with DCM, and dried over Na_2SO_4, and the solvent was evaporated. The crude acid was dissolved in methanol and was treated with $SOCl_2$ (0.12 g, 1.02 mmol) at 0 °C. After being stirred for 10 h, the reaction mixture was washed with $NaHCO_3$ solution, extracted with DCM, and dried over Na_2SO_4. The combined organic layer was evaporated to afford **13** (0.24 g, 95%) as a colorless oil.

Transformation of 13 into Epiboxidine (6). A solution of acetone oxime (0.19 g, 2.6 mmol) in 10 mL of dry THF at 0 °C was treated dropwise with *n*-butyllithium (2.1 M in hexane, 2.70 mL, 5.67 mmol), and the reaction mixture was allowed to warm to room temperature over 30 min. A solution of **13** (0.5 g, 1.86 mmol) in 10 mL of THF was introduced dropwise while the reaction mixture was stirred at room temperature. After the reaction mixture was refluxed for 45 min, the THF was removed under argon atmosphere to give a crude residue that was dissolved in 8 mL of concentrated HCl and heated at 80 °C for 4 h. The mixture was cooled, diluted with water, and washed with ethyl acetate (2 × 10 mL). The aqueous layer was basified with saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with ($CHCl_3$/MeOH/NH_3 = 97:2:1), to afford **6** (0.14 g) in 41% yield as a pale yellow oil. IR (neat): 3275, 2967, 2875, 1711, 1600, 1419, 1366, 1059, 1008, 922 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.30−1.45 (m, 2H, H_{5endo}, H_{6endo}), 1.55−1.75 (m, 4H, H_{5exo}, H_{6exo}, H_{3exo}, H-7), 1.90 (dd, J = 12.36, 8.71 Hz, 1H, H_{3endo}), 2.21 (s, 3H, 3′-methyl), 2.95 (dd, J = 8.71, 4.85 Hz, 1H, H_{2endo}), 3.68 (d, J = 4.06 Hz, 1H, H-1), 3.75 (t, J = 4.4 Hz, 1H, H-4), 5.77 (s, 1H, H-4′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.21, 29.14, 29.57, 38.02, 41.07, 56.03, 61.34, 100.58, 159.45, 176.07. MS (*m*/*z*, relative intensity): 179 (M^+, 23), 149 (10), 110 (24), 94 (13), 82 (19), 69 (100). HRMS: calcd for $C_{10}H_{14}N_2O$ 178.1106, found 178.1103.

7-Carbomethoxy-2-*endo*-3-*endo*-di(carbomethoxy)-7-azabicyclo[2.2.1]heptane (21). A solution of **18** (10.0 g, 36.36 mmol) in 70 mL of ethanol containing 10% Pd/C (0.8 g, 20 mol %) was hydrogenated (40 psi, rt) for 8 h. The reaction mixture was filtered, and the filtrate was evaporated and chromatographed over a silica gel column, eluting with hexane/EtOAc (8:2) to afford 8.35 g (85%) of **21** as a colorless oil. IR (neat): 2954, 1716, 1605, 1441, 1078 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.65−1.80 (m, 2H), 1.90−2.05 (m, 2H), 2.25 (bs, 2H), 3.65 (s, 6H), 3.68 (s, 3H), 4.45 (bs, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.95, 47.26, 51.58, 52.56, 59.13, 155.65, 170.83. MS (*m*/*z*, relative intensity): 272 (M^+, 2), 146 (80), 127 (100), 114 (57).

Decarboxylation of 21. A solution of **21** (5.0 g, 18.45 mmol) in methanol−water (3:1, 80 mL) containing LiOH−H_2O (0.77 g, 18.45 mmol) was stirred for 3 h at room temperature. The solvent was evaporated, diluted with water, and washed with CH_2Cl_2 (2 × 10 mL). The aqueous layer was cooled to 0 °C, acidified with 6 N HCl to pH = 2, and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and evaporated to give **22** as a foaming white solid (4.27 g) in 90% yield. The resultant crude acid was dissolved in 100 mL of dry DCM, treated with oxalyl chloride (4.34 mL, 49.8 mmol) and DMF (0.1 mL) under argon atmosphere at room temperature, and further allowed to stir for 2 h. The mixture was evaporated under vacuum to give the corresponding acid chloride as a brown solid. The crude acid chloride was dissolved in dry benzene (100 mL), and to the resultant solution were added DMAP (0.2 g, 1.6 mmol), *N*-hydroxy-2-mercaptopyridine (2.53 g, 19.9 mmol), and triethylamine (4.6 mL, 33.2 mmol) under argon atmosphere. After being stirred for 4 h at room temperature, the solid suspension was allowed to settle and the supernatant solution was syringed out and added to a refluxing solution of *tert*-butyl mercaptan (7.5 mL) in 100 mL of dry benzene. The resultant

mixture was refluxed for 4 h, cooled, washed with aqueous 1 N NaOH solution, water, and brine, and dried over Na_2SO_4. The benzene layer was concentrated, and the crude residue obtained was chromatographed on silica gel, eluting with hexane/ethyl acetate (8:2), to afford **17** (0.46 g, 13%) and **23** (1.84 g, 52%) as colorless oils.

7-Carbomethoxy-2-*exo*-(carbomethoxy)-7-azabicyclo[2.2.1]-heptane (17). IR (neat): 2954, 2879, 1737, 1634, 1367, 1161 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.30−1.55 (m, 2H), 1.63 (dd, J = 12.48, 8.91 Hz, 1H), 1.75−1.95 (m, 2H), 2.17−2.35 (m, 1H), 2.55 (dd, J = 8.91, 4.91 Hz, 1H), 3.63 (s, 3H), 3.67 (s, 3H), 4.35 (t, J = 4.21 Hz, 1H), 4.55 (d, J = 3.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.63, 29.11, 33.29, 47.18, 51.69, 52.0, 55.69, 59.08, 155.53, 173.42. MS (*m*/*z*, relative intensity): 213 (M^+, 16), 184 (13), 154 (39), 126 (100), 82 (17). HRMS: calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.0999.

7-Carbomethoxy-2-*endo*-(carbomethoxy)-7-azabicyclo-[2.2.1]heptane (23). IR (neat): 2954, 1708, 1737, 1633, 1444 cm^{-1}.^1H NMR ($CDCl_3$, 200 MHz): δ 1.40−1.55 (m, 2H), 1.70−2.10 (m, 4H), 2.95−3.15 (m, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 4.28 (t, J = 5.5 Hz, 1H), 4.50 (t, J = 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.49, 29.24, 32.48, 46.35, 51.77, 52.36, 57.08, 58.16, 155.84, 172.72. MS (*m*/*z*, relative intensity): 213 (M^+, 15), 184 (12), 154 (37), 126 (100), 82 (19). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.65; H, 7.21; N, 6.42.

Decarboxylation of 21 in the Presence of PhSeSePh. An identical decarboxylation procedure was adopted using PhSeSePh instead of *tert*-butyl mercaptan. The crude residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (7:3), to afford **24** (64%) and **25** (16%) as pale yellow oils.

7-Carbomethoxy-2-*endo*-(carbomethoxy)-3-*exo*-(phenylseleno)-7-azabicyclo[2.2.1]heptane (24). IR (neat): 2952, 1712, 1577, 1361, 1193 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35−1.60 (m, 2H), 1.65−1.80 (m, 1H), 1.80−1.95 (m, 1H), 3.05 (t, J = 6.5 Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.75 (d, J = 7.1 Hz, 1H), 4.25 (bs, 1H), 4.55 (t, J = 5.1 Hz 1H), 7.20−7.30 (m, 3H), 7.50−7.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.94, 29.65, 45.98, 52.19, 52.55, 55.48, 58.85, 62.76, 127.91, 129.24, 129.49, 134.48, 155.94, 171.39. MS (*m*/*z*, relative intensity): 369 (M^+, 12), 220 (15), 212 (71), 157 (31), 127 (100). HRMS: calcd for $C_{16}H_{19}NO_4Se$ 369.0479, found 369.0487.

7-Carbomethoxy-2-*exo*-(carbomethoxy)-3-*exo*-(phenylseleno)-7-azabicyclo[2.2.1]heptane (25). IR (neat): 2952, 1707, 1578, 1359, 1105 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40−1.55 (m, 2H), 1.65−1.95 (m, 2H), 3.05 (d, J = 10.2 Hz, 1H), 3.50 (d, J = 10.2 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 4.45 (bs, 1H), 4.65 (bs, 1H), 7.25−7.35 (m, 3H), 7.50−7.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.46, 28.77, 48.36, 51.07, 52.06, 53.34, 58.52, 62.67, 127.19, 128.85, 130.79, 133.4, 155.16, 170.55. MS (*m*/*z*, relative intensity): 369 (M^+, 2), 212 (37), 157 (24), 126 (100). Anal. Calcd for $C_{16}H_{19}NO_4Se$: C, 52.18; H, 5.20; N, 3.80. Found: C, 52.34; H, 5.37; N, 3.61.

7-Carbomethoxy-2-(carbomethoxy)-7-azabicyclo[2.2.1]-hept-2-ene (26). To a stirring solution of **24** (2.0 g, 5.43 mmol) in 20 mL of CH_2Cl_2 was added H_2O_2 (30%, 2 mL) dropwise at 0 °C. The resulting reaction mixture was allowed to stir at room temperature for 30 min, washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. The organic layer was concentrated and chromatographed on silica gel, eluting with hexane/EtOAc (9:1), to afford 1.1 g (95%) of **26** as a colorless oil. IR (neat): 2955, 2879, 1721, 1603, 1284, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.15−1.35 (m, 2H), 1.90−2.15 (m, 2H), 3.65 (s, 3H), 3.78 (s, 3H), 4.35 (bs, 1H), 5.05 (bs, 1H), 7.03 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.96, 51.43, 52.36, 59.67, 61.01, 140.63, 144.12, 155.49, 163.11. MS (*m*/*z*, relative intensity): 212 (M^+, 1), 183 (77), 152 (100), 108 (56), 93 (22), 59 (32). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.55; H, 6.35; N, 6.93.

7-Carbomethoxy-2-*endo*-(carbomethoxy)-7-azabicyclo-[2.2.1]heptane (23). A suspension of **26** (1.0 g, 4.74 mmol) and 0.2 g of 10% Pd/C in 15 mL ethanol was hydrogenated (40 psi, rt) for 6 h. The reaction mixture was filtered, concentrated, and chromatographed over silica gel, eluting with hexane/EtOAc (9:1), to afford 1.0 g (100%) of **23**.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of **6**, **11**−**14**, **17**, **21**, and **23**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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