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Intermolecular Conjugate Addition of Alkyl Radicals on Solid Phase†

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The conjugate addition of alkyl radicals, generated photolytically from the corresponding Barton esters, to acrylate immobilized on solid-phase was investigated. Using cross-linked polystyrene, acrylic acid was loaded with either the Wang or Rink linkers, and the reactions were carried out with 10 equiv of Barton ester. The yields following resin cleavage by trifluoroacetic acid were comparable to Barton's solution-phase results. TentaGel resins gave approximately 15% poorer yields, possibly due to radical quenching by the poly(ethylene glycol) spacer. With the Barton ester from cyclopent-2-enylacetic acid, the initial product of conjugate addition is capable of further intramolecular cyclization followed by attack of a second acrylate chain, resulting in polymer cross-linking.

Introduction

The solid-phase synthesis [or more accurately, gel-phase synthesis] of peptides was pioneered by Merrifield[1] over 30 years ago. This approach lends itself particularly well to peptide and oligonucleotide synthesis, where a small number of operations [monomer activation, coupling, and deprotection] are repetitively employed. In recent years, the popularity of high-throughput screening for drug discovery applications has triggered the extension[2] of solid-phase techniques beyond oligomeric molecules. The added complexity of such synthetic targets requires the whole gamut of organic reactions to be adapted to solid-phase conditions.

Carbon−carbon bond formation is the fundamental means by which organic compounds are assembled. The solid phase is not always inert to the reactive intermediates of such processes. For example, commonly used polystyrene-based resins undergo transmetalation with organolithium compounds. However, the kinetics are sufficiently slow that a variety of strongly basic organometallic reagents have been successfully used[3] to preferentially react with resin-bound substrates. A more serious limitation is the propensity of polystyrene for aromatic electrophilic substitution. Thus, it is unlikely that Friedel−Crafts reactions of loaded substrates will be efficient, as the polymer contains a multitude of competing sites. We decided to investigate if radical reactions, another powerful route to carbon−carbon bond formation,[4] suffer from any solid-phase limitations. The facile nature of radical−radical recombination as well as radical addition reactions also provides an opportunity to address issues[5,6] of site isolation versus site interaction when radical intermediates are formed on cross-linked polymers.

When we began this work, there was only one published example of a solid-phase carbon−carbon bond forming radical reaction. The Cambridge group[7] cyclized aryl radicals, generated from halides by tributyltin hydride, with a pendant alkene or alkyne (Figure 1a). A stoichiometric amount of radical initiator (AIBN) was needed with polystyrene resin but not with TentaGel, suggesting quenching effects from the polystyrene backbone. Similar cyclizations were recently reported[8] by a group at Novartis, while Armstrong's group[9] (Figure 1b) used SmI_2 for radical generation. The organosamarium intermediate was also trapped by an electrophile in solution, with TentaGel performing better than polystyrene−Rink amide resin. This was attributed to TentaGel's superior swelling properties or anion quenching by the Rink amide proton rather than inherent reactivity of polystyrene.

The above examples demonstrate the feasibility of *intramolecular* carbon−carbon bond forming radical reactions on solid phase. However, they benefit from the tremendous entropic acceleration imposed by intramolecularity, disfavoring undesired bimolecular pathways. We believe that an *intermolecular* process is a more stringent test of solid-phase radical reactions. The first example was recently disclosed by Sibi and Chandramouli,[10] who trapped α-carboxyl radicals on Wang resin with allylstannanes (Figure 1c). Formation of the radicals required a noncatalytic amount (3−4 equiv) of AIBN. A second example[11] (Figure 1d) involved the combination of intramolecular halide cyclization followed by intermolecular allylstannane trapping. Here, we report our studies on another intermolecular reaction, conjugate addition, in which the radicals are in solution and the acceptor is immobilized.

Results and Discussion

Among the various methods for producing alkyl radicals, the esters of *N*-hydroxy-2-thiopyridone developed by Barton appeared most suitable for practical reasons. These Barton esters are readily prepared[12] from the corresponding carboxylic acid. Upon irradiation with an ordinary tungsten lamp, fragmentation occurs without the need for elevated temperatures. Furthermore, the fragmentation itself generates

† Dedicated to the memory of Sir D. H. R. Barton (1918−1998), a grandmaster at the art of chemical invention.

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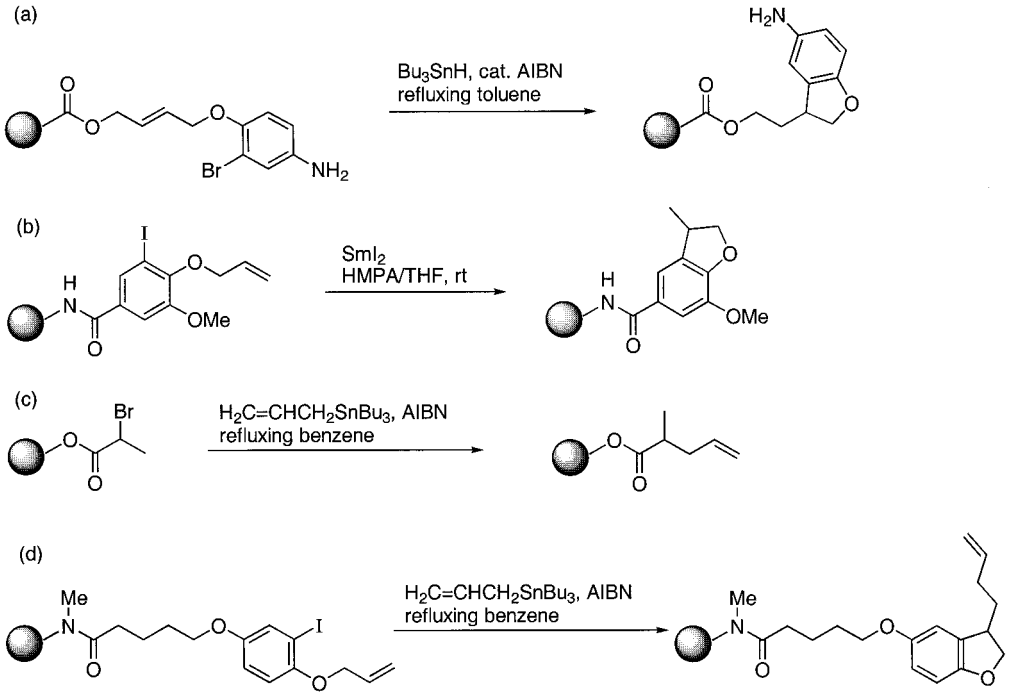
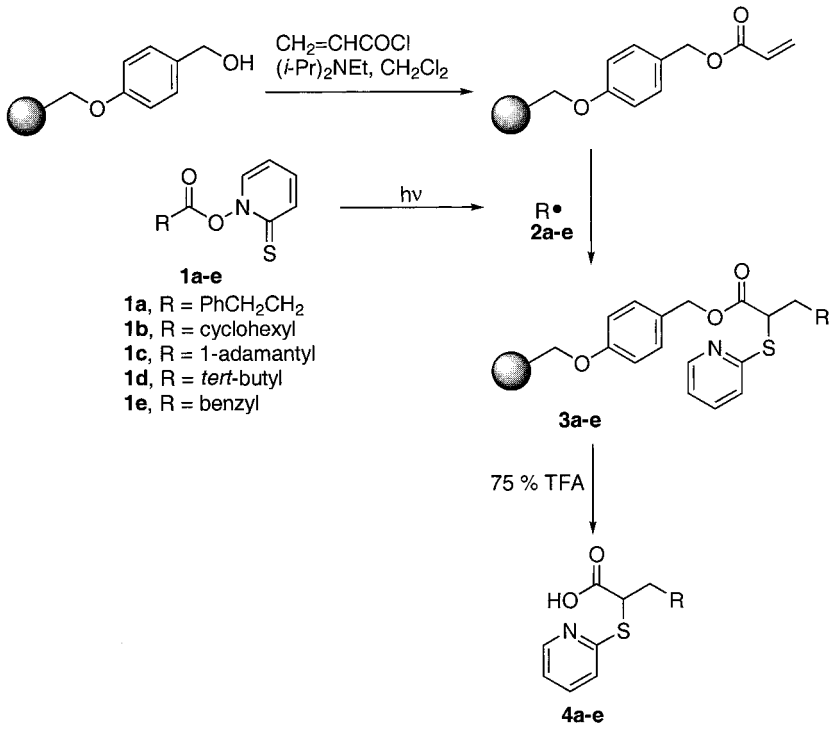


Figure 1. Examples of solid-phase radical reactions.

Scheme 1. Solid-Phase Intermolecular Conjugate Radical Additions



the chain transfer species, unlike the case with organotin methods leading to a trialkyltin radical. Finally, in solution phase, Barton has shown that the radicals can be efficiently trapped by conjugate addition to acrylonitriles,[13] acrylate esters,[14] and acrylamide.[15]

For the solid-phase version, we attached acrylic acid to the Wang linker. To examine polymer backbone effects, we used both polystyrene−Wang and TentaGel−Wang resins. These were then reacted (Scheme 1) with a set of five Barton esters **1a**−**e** which would give rise to primary, secondary, tertiary, or stabilized (benzyl) radicals **2a**−**e**. In these reactions, 10 equiv of Barton ester was employed. Yields were lower when this was reduced to 5 equiv.

The conjugate addition products **3a**−**e** were cleaved from the resin by trifluoroacetic acid (TFA) treatment, and the yield of acids **4a**−**e** was determined after chromatography (Table 1). From the results, the conjugate addition of nonstabilized radicals **2a**−**c** gives high yields on solid phase. The yield of **4a** and **4b** is comparable to Barton's results with methyl acrylate, while addition of the 1-adamantyl radical **2c** was somewhat less efficient. The benzyl radical **2e** performed poorly, but this is likely due to its stabilized

Scheme 2. Conjugate Radical Additions with the Rink Amide Linker

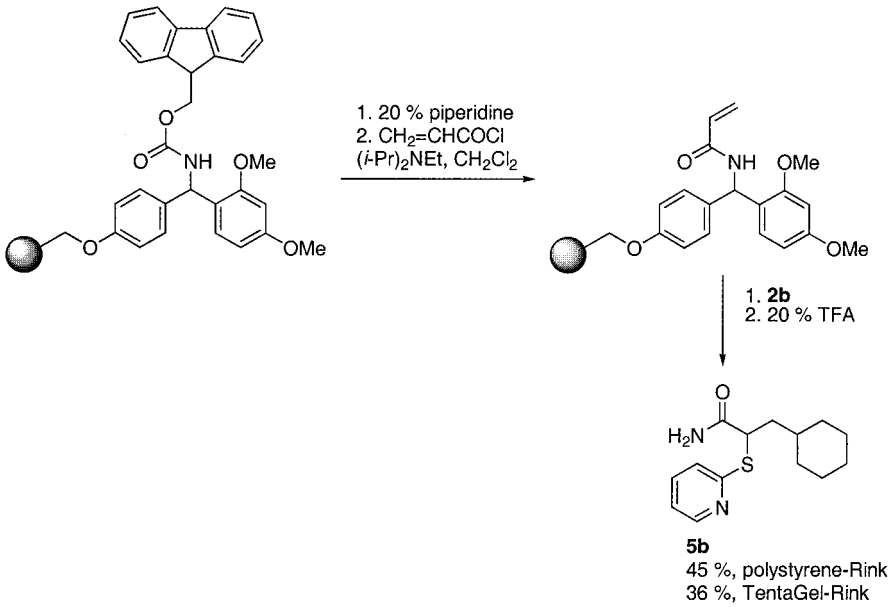


Table 1. Solid-Phase Intermolecular Conjugate Radical Addition Reactions

	isolated yield (%)[a]		
product	polystyrene−Wang resin	TentaGel−Wang resin	solution-phase precedent[b]
4a	94	76	98
4b	91	76	95
4c	63	45	94
4d	91	78	
4e	32	17	

[a] Yield of chromatographically purified product, based on manufacturer's loading of Wang resin. [b] Solution-phase yields of radical addition to methyl acrylate reported by Barton et al.[14]

nature rather than the solid-phase conditions (this radical was not included in Barton's study).

The TentaGel−Wang resin gave consistently lower yields by approximately 15%. It is possible the resins differed in loading efficiency, but this could not be directly compared due to the difficulty of isolating acrylic acid after TFA cleavage. Instead, the two resins were reacted with phenylacetyl chloride under the same conditions used for acrylate attachment. After TFA cleavage, ^{1}H NMR with a known amount of *p*-anisaldehyde as internal standard quantified the crude yield of phenylacetic acid. The loading for both resins was found to closely match the manufacturer's specifications. Thus, the lower yield appears to arise from the radical reaction itself on TentaGel resin. As hydrogen atom abstraction from ethers is well precedented,[16] it is possible that this is due to interference from the poly(ethylene glycol) linker. Depending on the age of the resin and exposure to oxygen and light, TentaGel resins are also susceptible to peroxide formation, which is likely to be detrimental to these reactions.

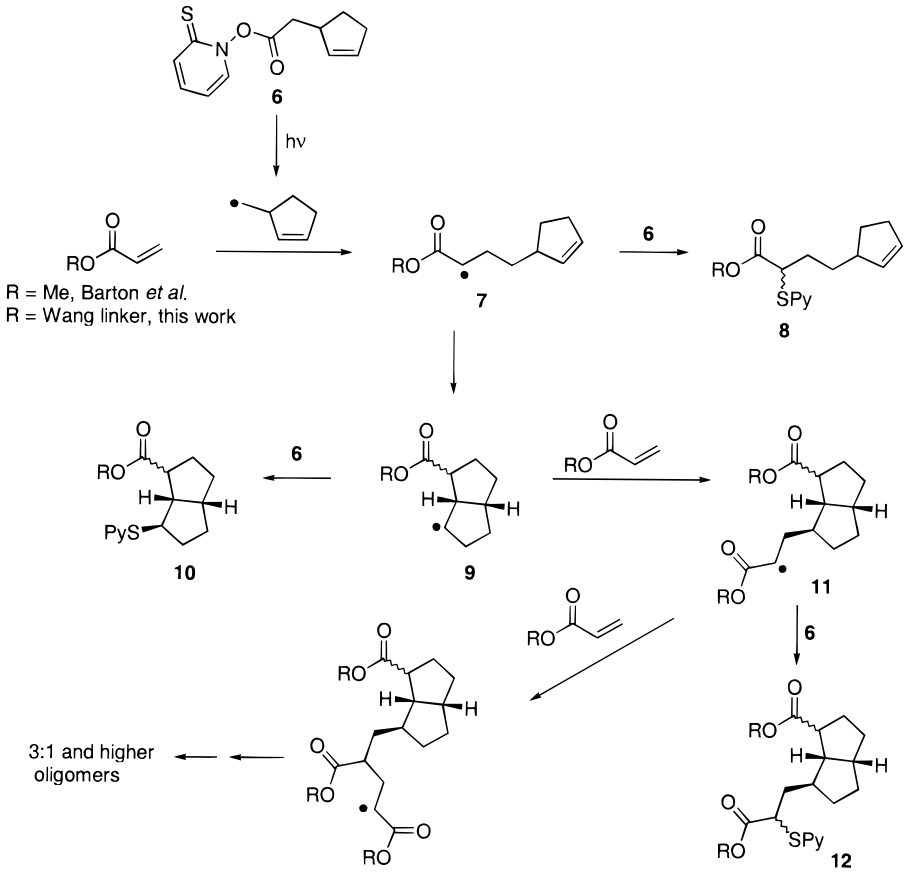
We have also examined the conjugate addition to acrylic acid immobilized by the Rink amide linker. The yield was lower than that with the ester linkage (as illustrated by the product **5b** of cyclohexyl radical addition, Scheme 2), a result which parallels Barton's solution-phase observations with acrylamide relative to acrylate esters.

Barton, da Silva, and Zard have demonstrated[17] that the intermediate α-carboxymethyl radical can undergo further reactions. For example, irradiation of the Barton ester **6** derived from cyclopent-2-enylacetic acid with methyl acrylate affords the conjugate addition product radical **7** (Scheme 3). Rather than immediate chain transfer to give **8**, the major reaction pathway of this electrophilic acyl-substituted radical is intramolecular cyclization to yield bicyclic radical **9**, as a mixture of epimers. As a nucleophilic alkyl radical, **9** is not only capable of chain transfer (leading to **10**) but a competing second conjugate addition, resulting in electrophilic radical **11**. The fate of **11** is either chain transfer (to **12**) or further conjugate additions, leading to oligomers. Despite the complexity of this system, experimentally **12** was isolated as the major product in 43% yield (as a mixture of diastereomers) from the reaction.

We were interested in comparing this reaction on solution and solid phase, since immobilization of the acrylate chains might simulate high-dilution conditions and hinder the formation of 2:1 or higher adducts. In our hands, the solution-phase experiment (with limiting Barton ester and 2 equiv of methyl acrylate) also afforded **12** as the major product, in 35% yield. In addition, we isolated 8% of 1-(2-thiopyridyl)-methyl-2-cyclopentene (the result of direct chain transfer with the cyclopentenylmethyl radical), 7% of **8**, a trace amount (<5%) of **10**, and 18% of a 3:1 adduct of methyl acrylate and cyclopentenylmethyl radical.

We then performed the reaction with polystyrene−Wang bound acrylate under our solid-phase conditions (10 equiv of Barton ester). After TFA cleavage, the free carboxylic acids in the crude product mixture were converted to methyl esters ($SOCl_2$, MeOH) for ease of purification. The 2:1 adduct **12** was still the major product (36%) based on consumption of acrylate. We also isolated **8** (13%) and **10** (24%). Both **10** and **12** were obtained as a mixture of two diastereomers whose structures were assigned on the basis of nuclear Overhauser effect (NOE) experiments (Figure 2). In the case of **10**, the assignment was supported by the fact that the major diastereomer **10b** (**10a**:**10b** approximately 1:4)

Scheme 3. Conjugate Addition with the 2-Cyclopentenylmethyl Radical



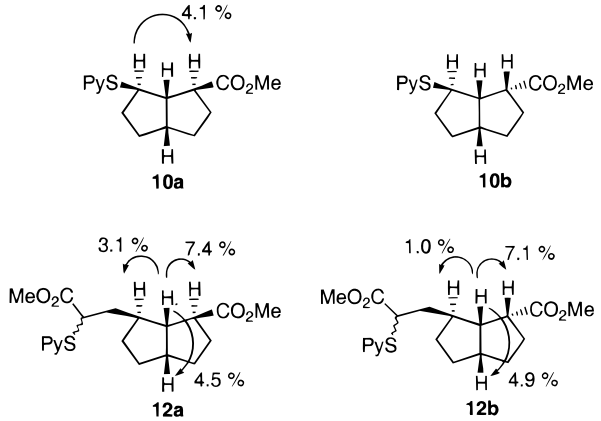


Figure 2. Diagnostic NOEs used in stereochemical assignment of **10** and **12**.

could be epimerized (1,8-diazabicyclo[5.4.0]undec-7-ene, refluxing MeOH, 1 day) to **10a**.

The major difference in product ratio for these two experiments is the significantly higher amount of **10** formed on solid phase. This could be due to intrinsic differences between the solution- and solid-phase reactions or reflect the concentration of Barton ester (10:1 on solid phase relative to acrylate, compared to the solution phase 1:2). It is difficult to distinguish these alternatives on solid phase, as an excess of Barton ester is needed to ensure good yields. Instead, we repeated the solution-phase experiment with 10 equiv of Barton ester. Under these conditions, we isolated 13% of **8**, 43% of **10** (approximately 1:4 diastereomeric mixture), and 35% of **12** (approximately 1:1 diastereomeric mixture).

These results show that the fate of radical **9** is mainly determined by the concentration of Barton ester. When this is high, chain transfer resulting in **10** effectively competes with further conjugate additions of acrylate. The slower kinetics on solid phase relative to homogeneous conditions are probably responsible for the lower accumulation of **10** (24 versus 43%). Our work also shows that site isolation of radical **9** on solid phase is not significant, enabling relatively free access to a second acrylate chain, leading to **12**. This is consistent with previous studies of chain flexibility and cross-linking when two mutually reactive functional groups are on the resin. To quote Merrifield,[18] "It is now well recognized that the apparent isolation effects, when they occur, are a result of kinetically controlled competing reactions. There is actually very significant polymer chain motion, even in the cross-linked resins, that allows large amounts of intermolecular reactions to occur if other very rapid reactions are not present."

Conclusions

Our solid-phase conditions [limiting acrylate immobilized on resin] are quite different from Barton's original solution-phase work with an excess of conjugate acceptor. Nevertheless, the yields obtained are similar, a tribute to the reliability and adaptability of this reaction. Our results show that radical conjugate addition is a viable synthetic process on solid phase. The mildness of the reaction conditions [compared to organometallic reagents such as organocuprates] and the diversity of alkyl groups accessible from commercial carboxylic acids are noteworthy features. The comparison between resins indicates that polystyrene is preferable to TentaGel. Besides the possibility of quenching reactions with

the latter, recent work by others[19,20] has helped clarify differences between the two supports. Polystyrene appears to be a generally suitable resin when used with solvents that promote efficient swelling, especially when highly polar or ionic species are not involved. Under such conditions, reactions can often be kinetically faster on polystyrene relative to TentaGel.

As in the solution-phase precedent, an ester linkage gave better yields than an amide. Our initial concerns about interference from the benzylic ether functionality of the Wang linker also proved to be unfounded. Finally, we have shown that the product of conjugate addition is capable of further intramolecular and intermolecular reactions (Scheme 3). The results reveal a good degree of site interaction on the resin, with an intermediary radical capable of cross-linking a second acrylate chain.

Experimental Section

General. All chemicals obtained commercially were used without further purification. Dichloromethane was distilled from CaH_2 immediately before use. Wang resin (capacity: 1.08 mmol/g) and Rink amide resin (capacity: 0.56 mmol/g) were obtained from Calbiochem-Novabiochem Corp. TentaGel HL PHB (capacity: 0.42 mmol/g) and TentaGel HL RAM (capacity: 0.38 mmol/g) were obtained from Rapp Polymere GmbH. All water- and air-sensitive reactions were performed under nitrogen atmosphere in oven-dried glassware. Analytical TLC was performed on precoated glass plates (Merck, silica gel 60F-254) and visualized with UV light. Preparative TLC was carried out on 20×20 cm^2 glass plates precoated with 1 mm silica (Aldrich). Column chromatography was performed with silica (Merck, 70−230 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solutions with a Bruker Avance-400 instrument. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were obtained on a VG7035 analytical spectrometer. Infrared spectra were recorded on a BIO-RAD Win-IR spectrometer ($CHCl_3$ thin film, KBr liquid cell).

Preparation of 1a−e and Acrylate Attachment to Resins. *N*-Hydroxypyridine-2-thione and *N*,*N*-dicyclohexylcarbodiimide (1 equiv) were dissolved in dry CH_2Cl_2 under N_2 atmosphere. The solution was protected from light and cooled to 0 °C, followed by dropwise addition of a carboxylic acid dissolved in dry CH_2Cl_2. The reaction mixture was warmed to room temperature, stirred overnight, and rapidly filtered (while protected from light), and the precipitates were washed with CH_2Cl_2. The combined filtrates were concentrated to give the crude Barton ester, which was purified by passage through a short silica column, eluting with CH_2Cl_2/hexanes. The Barton esters were stored in the dark until further use. Resins were loaded with acrylate by agitation (4 h, room temperature) with acryloyl chloride (10 equiv) and diisopropylethylamine (10 equiv), followed by washing (CH_2Cl_2, CH_3OH) and drying in vacuo.

Solid-Phase Radical Reactions. The loaded resins (200 mg for polystyrene resins, 500 mg for TentaGel resins) were agitated in CH_2Cl_2 at 0 °C with 10 equiv of a Barton ester. Photolysis was initiated by irradiation with two commercial 100 W tungsten lamps. After 4 h, the resin was filtered, washed (CH_2Cl_2, CH_3OH), and dried in vacuo. Cleavage from Wang linkers was carried out by treatment with TFA/CH_2Cl_2/triethylsilane (75:20:5) for 90 min. After the resin was washed, the combined filtrate was evaporated and the crude product purified using preparative TLC with ethyl acetate/hexanes/acetic acid as the developing solvent. Cleavage of **5b** from the Rink amide linkers was accomplished by treatment with 20% TFA/CH_2Cl_2/5% Et_3SiH (20 min).

5-Phenyl-2-(2-pyridinylthio)pentanoic Acid (4a): IR ν_{max} 2401, 1732, 1589, 1561 cm^{-1}; ^{1}H NMR δ 1.77−1.92 (m, 3H), 2.18−2.24 (m, 1H), 2.55−2.74 (m, 2H), 3.87 (t, 1H, J = 7.0 Hz), 7.10−7.27 (m, 6H), 7.40 (d, 1H, J = 8.1 Hz), 7.67 (m, 1H), 8.40 (d, 1H, J = 5.0 Hz); ^{13}C NMR δ 28.8, 29.7, 35.4, 47.8, 121.2, 124.1, 125.9, 128.3, 128.3, 138.1, 141.6, 147.8, 158.0, 172.8; MS (EI) *m*/*z* 287 (M$^+$), 269, 243, 182, 164, 111, 91, 51, 39; HRMS calcd for $C_{16}H_{17}NO_2S$ 287.09799, found 287.09919.

3-Cyclohexyl-2-(2-pyridinylthio)propionic Acid (4b): IR ν_{max} 2401, 1730, 1589 cm^{-1}; ^{1}H NMR δ 0.88−0.96 (m, 2H), 1.10−1.28 (m, 3H), 1.52−1.74 (m, 7H), 2.04 (m, 1H), 3.99 (t, 1H, J = 7.5 Hz), 7.22 (m, 1H), 7.40 (d, 1H, J = 7.9 Hz), 7.69 (m, 1H), 8.42 (d, 1H, J = 4.5 Hz); ^{13}C NMR δ 26.0, 26.1, 26.4, 32.7, 33.2, 34.9, 37.3, 45.2, 121.2, 124.1, 138.1, 147.8, 158.3, 172.9; MS (EI) *m*/*z* 265 (M$^+$), 247, 221, 182, 164, 125, 111, 55; HRMS calcd for $C_{14}H_{19}NO_2S$ 265.11365, found 265.11492.

3-(Adamantyl-1-yl)-2-(2-pyridinylthio)propionic Acid (4c): IR ν_{max} 2401, 1728, 1589 cm^{-1}; ^{1}H NMR δ 1.40−1.93 (m, 16H), 2.32 (dd, 1H, J = 7.0, 14.6 Hz), 3.99 (t, 1H, J = 5.5 Hz), 7.19 (m, 1H), 7.36 (d, 1H, J = 8.0 Hz), 7.67 (m, 1H), 8.44 (d, 1H, J = 4.5 Hz); ^{13}C NMR δ 28.5, 28.7, 33.1, 36.8, 42.1, 44.1, 121.0, 123.8, 138.0, 147.8, 158.5, 173.2; MS (EI) *m*/*z* 317 (M$^+$), 299, 273, 182, 164, 136, 79, 41; HRMS calcd for $C_{18}H_{23}NO_2S$ 317.14496, found 317.14362.

4,4-Dimethyl-2-(2-pyridinylthio)pentanoic Acid (4d): IR ν_{max} 2401, 1730, 1588 cm^{-1}; ^{1}H NMR δ 0.96 (s, 9H), 1.57 (dd, 1H, J = 4.8, 14.6 Hz), 2.45 (dd, 1H, J = 6.8, 14.6 Hz), 3.90 (t, 1H, J = 5.8 Hz), 7.21 (m, 1H), 7.37 (d, 1H, J = 8.1 Hz), 7.68 (m, 1H), 8.44 (d, 1H, J = 4.6 Hz); ^{13}C NMR δ 29.3, 31.2, 43.4, 43.9, 121.1, 123.8, 138.0, 147.9, 158.3, 173.2; MS (EI) *m*/*z* 239 (M$^+$), 195, 182, 138, 111, 67, 41.

4-Phenyl-2-(2-pyridinylthio)butyric Acid (4e): IR ν_{max} 2401, 1729, 1589 cm^{-1}; ^{1}H NMR δ 2.06−2.11 (m, 1H), 2.40−2.50 (m, 1H), 2.80−2.93 (m, 2H), 3.84 (t, 1H, J = 7.4 Hz), 7.15−7.26 (m, 6H), 7.43 (d, 1H, J = 7.9 Hz), 7.68 (m, 1H), 8.40 (d, 1H, J = 4.7 Hz); ^{13}C NMR δ 31.7, 33.0, 47.0, 121.3, 124.2, 126.2, 128.5, 128.5, 138.2, 140.5, 147.9, 157.9, 172.7; MS (EI) *m*/*z* 273 (M$^+$), 255, 229, 182, 164, 138, 125, 91, 39; HRMS calcd for $C_{15}H_{15}NO_2S$ 273.08234, found 273.08347.

3-Cyclohexyl-2-(2-pyridinylthio)propionamide (5b): ^{1}H NMR δ 0.83−1.00 (m, 2H), 1.14−1.25 (m, 3H), 1.55−1.80 (m, 7H), 2.03 (m, 1H), 4.00 (t, 1H, J = 7.4 Hz), 7.21 (m, 1H), 7.40 (d, 1H, J = 8.0 Hz), 7.68 (m, 1H), 8.42 (d, 1H, J = 4.4 Hz); ^{13}C NMR δ 26.0, 26.1, 26.4, 32.7, 33.2, 34.9, 37.3, 45.3, 121.1, 124.1, 138.0, 147.8, 158.4, 172.9.

Methyl 4-(2-Cyclopentene)-2-(2-pyridinylthio)butanoate (8): IR ν_{max} 2859, 1732, 1578, 1455 cm^{-1}; ^{1}H NMR δ 1.30−

2.10 (m, 6H), 2.24−2.38 (m, 2H), 2.68 (m, 1H), 3.73 (s, 3H), 4.58 (t, 1H, $J = 7.3$ Hz,), 5.60−5.75 (m, 2H), 6.99 (m, 1H), 7.19 (m, 1H), 7.48 (m, 1H), 8.40 (m, 1H); ^{13}C NMR δ 29.6, 30.3, 32.0, 33.5, 45.2, 46.6, 52.5, 119.9, 122.3, 130.8, 134.5, 136.1, 149.5, 157.4, 173.3; MS (EI) *m*/*z* 277 (M^+), 244, 164, 112, 80.

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(2-pyridinylthio)-1-pentalenecarboxylate (10a): IR ν_{max} 2871, 1731, 1570, 1447 cm^{-1}; ^{1}H NMR δ 1.30−1.42 (m, 2H), 1.62−1.82 (m, 2H), 1.90−2.08 (m, 3H), 2.22 (m, 1H), 2.60−2.65 (m, 1H), 2.65−2.75 (m, 2H), 3.66 (s, 3H), 3.90 (m, 1H), 6.95 (m, 1H), 7.15 (m, 1H), 7.45 (m, 1H), 8.39 (m, 1H); ^{13}C NMR δ 31.3, 31.9, 33.1, 33.2, 42.9, 49.3, 50.8, 51.7, 54.6, 119.3, 122.5, 135.7, 149.4, 159.7, 176.0; MS (EI) *m*/*z* 277 (M^+), 244, 184, 111, 79.

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(2-pyridinylthio)-1-pentalenecarboxylate (10b): ^{1}H NMR δ 1.28 (m, 1H), 1.48−1.68 (m, 3H), 1.73−1.79 (m, 1H), 1.87−2.10 (m, 2H), 2.32−2.40 (m, 1H), 2.62−2.70 (m, 2H), 2.70−2.80 (m, 1H), 3.57 (s, 3H), 3.73 (m, 1H), 6.94 (m, 1H), 7.14 (m, 1H), 7.45 (m, 1H), 8.40 (m, 1H); ^{13}C NMR δ 27.4, 31.7, 33.2, 36.2, 42.8, 45.3, 47.6, 50.8, 51.4, 119.2, 122.0, 135.8, 149.5, 160.0, 174.2; MS (EI) *m*/*z* 277 (M^+), 244, 184, 111, 79.

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(methoxycarbonyl)-2-(2-pyridinylthio)-1-pentalenepropanoate (12a): IR ν_{max} 2865, 2359, 1729, 1586, 1457 cm^{-1}; ^{1}H NMR δ 1.10−1.16 (m, 2H), 1.40−1.95 (m, 7H), 2.05−2.12 (m, 2H), 2.29 (m, 1H), 2.55 (m, 1H), 2.70 (m, 1H), 3.68 (s, 3H), 3.75 (s, 3H), 4.48 (dd, 1H, $J = 10.9$, 3.7 Hz), 6.98 (m, 1H), 7.17 (m, 1H), 7.47 (m, 1H), 8.39 (m, 1H); ^{13}C NMR δ 26.9, 31.3, 33.5, 33.6, 38.7, 41.2, 43.6, 45.5, 47.9, 51.3, 51.8, 52.4, 119.8, 122.1, 136.1, 149.5, 157.4, 172.8, 174.3; MS (EI) *m*/*z* 363 (M^+), 332, 196, 111, 79.

Methyl (1α,3aα,6α,6aα)-Octahydro-6-(methoxycarbonyl)-2-(2-pyridinylthio)-1-pentalenepropanoate (12b): IR ν_{max} 2861, 2373, 1729, 1588, 1464 cm^{-1}; ^{1}H NMR δ 1.00−1.14 (m, 2H), 1.38−1.60 (m, 2H), 1.65−1.98 (m, 7H), 2.31 (m, 1H), 2.54 (m, 1H), 2.70 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 4.51 (dd, 1H, $J = 10.1$, 4.3 Hz), 6.98 (m, 1H), 7.19 (m, 1H), 7.47 (m, 1H), 8.38 (m, 1H); ^{13}C NMR δ 27.0, 31.3, 33.5, 33.5, 37.4, 40.9, 43.7, 45.8, 48.0, 51.3, 51.7, 52.5, 119.8, 122.3, 136.0, 149.3, 157.5, 173.6, 174.4; MS (EI) *m*/*z* 363 (M^+), 332, 196, 111, 79.

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