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Amide-Based Protecting/Radical Translocating (PRT) Groups. Generation of Radicals Adjacent to Carbonyls by 1,5-Hydrogen Transfer Reactions of *o*-Iodoanilides

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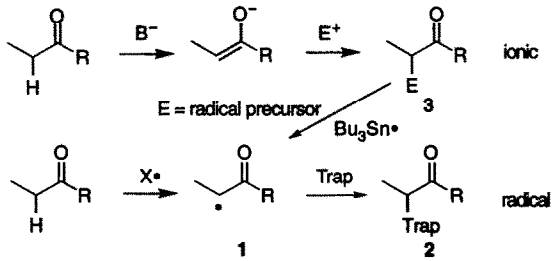
Summary: *The o-iodoanilide group is shown to be broadly useful for the generation and subsequent reactions of radicals adjacent to carboxyl groups. The results indicate that this group is one of the best "protecting/radical translocating" (PRT) groups introduced to date. Beyond its good performance in radical translocation reactions, it is easy to introduce, serves as a reasonable protecting group both before and after the translocation, and (with appropriate modifications) is easy to remove.*

Introduction: The carbonyl group has always been a central functionality in organic synthesis. Carbonyl groups are common features in target molecules, and they are also precursors of a wide variety of other functional groups. But the real strategic value of the carbonyl group lies in its ability to facilitate carbon-carbon bond formation by a large assortment of ionic (addition, alkylation) and pericyclic (cycloaddition) reactions. As radical reactions have gained favor in synthesis,[1] the carbonyl group has naturally played an important role.[2] Carbonyl groups see frequent use as activators of alkene acceptors in radical additions and cyclizations. More recently, direct radical additions to carbonyls have been exploited.[3]

One of the most valuable reactions of the carbonyl group is functionalization at the α-carbon (Figure 1). This transformation occurs by a sequence of deprotonation and trapping of the resulting enolate with an electrophile (E^+), and it is one of the best general methods for direct replacement of a C–H bond by a C–C bond. Figure 1 illustrates that a conceptually analogous radical functionalization is also possible. A hydrogen abstracting radical (X•) may abstract an α-hydrogen atom from a ketone to generate radical **1**, which in turn reacts with a radical trap (usually an alkene) to provide product **2**. Such a radical alkylation benefits from all the features that make radical reactions attractive in synthesis;[1] most importantly, the new bond to the trap can be formed without ever exposing the molecule to a strong base.

Figure 1. Anionic and Radical Functionalizations Adjacent to Carbonyl Groups



In both ionic and radical alkylations, there is a serious selectivity problem in generating the reactive intermediate for alkylation. In the ionic alkylation method, a selective deprotonation requires the presence of only one type of acidic proton with an appropriate pK_a for a given base. To

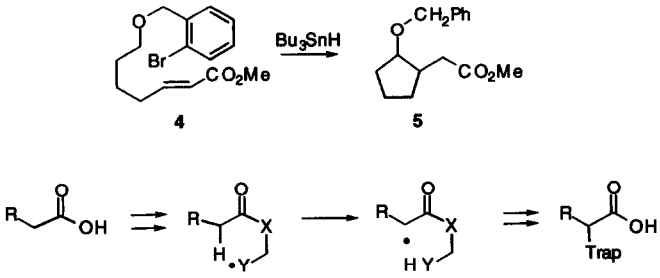
meet this requirement, other functional groups are masked such that their protons either decrease in acidity (for example, the conversion of a ketone to a ketal) or are removed entirely (for example, the conversion of an alcohol to a silyl ether). In the radical alkylation method, the problem of selective hydrogen atom removal is considerably more difficult to solve. Rates and selectivities in hydrogen abstraction reactions are controlled by a combination of enthalpic and polar effects.[4] Because C–H bonds are rather strong, very reactive radicals X• (such as ^{t}BuO•) must be used as hydrogen abstractors. Such radicals are not very selective. Further, most functional groups weaken adjacent C–H bonds, and it is almost impossible to envision highly functionalized molecule with only one type of weak C–H bond. In radical hydrogen abstractions, the protecting group strategy is often counterproductive. For example, protection of a ketone as a dioxolane ketal strengthens the C–H bonds that were adjacent to the ketone, but it also introduces four weak C–H bonds adjacent to the oxygens of the ketal.

Even though there has been significant recent progress[5] in developing selective hydrogen abstracting radicals X•, the direct application of the radical alkylation shown in Figure 1 is largely limited to simple substrates.[6] While the yield of the product **2** is sometimes acceptable based on the trap, it is rarely acceptable based on the carbonyl precursor because a large excess of this precursor is usually used to improve the efficiency of hydrogen transfer steps.

Indirect methods are typically used to generate radicals adjacent to carbonyl groups from C–H bonds. Prominent among these methods are oxidations by metals such as Mn(III).[7] Though largely limited to generating radicals from enolizable β-dicarbonyls, these oxidative methods are very powerful, and they are "indirect" only in a formal sense (the radical is not generated by direct hydrogen abstraction but by loss of a proton to form a metal enol, followed by oxidation). To conduct radical alkylations adjacent to mono-carbonyl compounds, enolate intermediates are often generated by deprotonation, and then trapped with heteroatom electrophiles (See **3** in Figure 1, E = Br, I, SePh). These α-E precursors **3** are then used for the radical reactions. This strategy of forming α-carbonyl radical precursors through enolates negates some of the most attractive features of the radical alkylation.

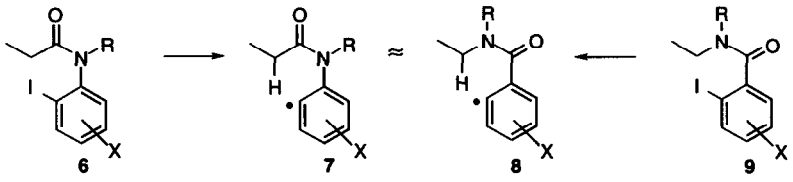
We have recently introduced the notion that protecting groups can be modified to selectively generate radicals from carbon-hydrogen bonds by 1,5-hydrogen transfer reactions.[8] A simple example is the reduction of **4** to give **5** illustrated in Figure 2. The *o*-bromobenzyl group meets the requirements for a combined "protecting/radical translocating" group (hereafter called a "PRT" group). It is easy to introduce, it functions as a typical alcohol protecting group before the radical reaction, it selectively generates a radical adjacent to the ether under standard radical conditions, it is a protecting group after the radical reaction, and it is easily removed. Related protecting groups that effect generation of radicals adjacent to carboxyl groups would be valuable additions to the synthetic arena because they would address the problem of selective generation of radicals adjacent to carbonyls from C–H bonds. This concept is illustrated in the lower part of Figure 2.

Figure 2. Radical Translocation from Protecting Groups



As a first example of a carboxyl-based PRT group, we selected the *o*-iodoanilide motif **6** shown in Figure 3. Though not often used, anilides should be reasonable protecting groups of carboxylic acids. A simple inspection of models suggested that anilide radical **7** would also meet the requirements for radical 1,5-hydrogen transfer. This transformation is related to the very fast 1,5-hydrogen transfer reactions of benzamide radicals **8**. These radicals transfer hydrogen from the "carbon-end" of the amide (with respect to the C–N bond) to the "nitrogen-end".[8b-d] Though anilide radicals **7** transfer hydrogen from the "nitrogen-end" to the "carbon-end", the overall shapes of the two transition states should be quite similar. The idea that the shapes of amides are similar regardless of which way the amide group is inserted has been well recognized in the peptide field.[9] Using the peptide terms, **7** can be described as a "retro-amide" analog of **8**.

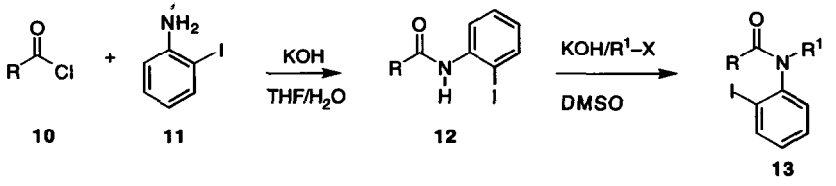
Figure 3. Similarities between Anilides (7) and Benzamides (8)



We report herein the full details of our study of the parent *N*-methyl-*N*-*o*-iodoanilide group[10] as the first carboxyl-based PRT group.[11] This paper focuses on intramolecular reactions of translocated radicals; related intermolecular reactions, set in the context of 1,2-asymmetric induction, have been reported separately.[12] We envision that the groups R and X on the basic motif **6** can be varied in a predictable fashion to alter various properties of the group. To illustrate this notion, we introduce the *o*-iodo-*p*-trifluoromethyl group as a modified PRT group which is much more easily removed than the parent. Recently, Esker and Newcomb have introduced a new class of carboxyl PRT group based on the *N*-acyl-*N*-alkylcarbamoyloxy functionality.[13]

Results and Discussion: Most of the *o*-iodoanilide precursors for the radical translocation studies were prepared by the simple sequence of reactions outlined in eq 1. Schotten-Baumann acylation of an appropriate acid chloride **10** with *o*-iodoaniline (**11**) provided the 2°-anilide **12**. Like other 2°-amides, these anilides exist predominately in the *Z* (O and Ar cis) geometry.[14] N-Alkylation of **12** with an appropriate alkylating agent R^1–X (usually CH_3I) then provided the corresponding 3°-anilide **13**, which now exists predominantly in the *E* (O and Ar trans) geometry. The acid chlorides were typically prepared by treating the corresponding acids with thionyl chloride. Simpler acids were commercially available, while more complex ones were prepared by straightforward routes that are described in the Experimental Section and discussed in the Ph.D. thesis of H. Liu.[15]

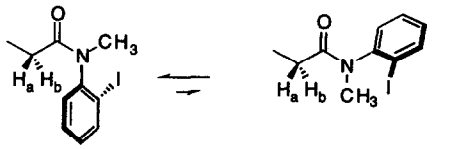
eq 1



As with their benzamide predecessors,[8b-d] the conformations of these anilides are crucial to the success of the radical translocation reactions. The conformational features of *N*-methyl-*N*-*o*-iodophenyl propanamide (**14b**) are representative of all the substrates in this study, and these features are summarized in Figure 4. *N*-Methyl-*N*-phenyl acetamide and related anilides exist

predominantly in the *E* conformation,[16] and we therefore expected that conformation **14bE** would be favored over **14bZ**. The 300 MHz NMR spectrum of **14b** recorded in $CDCl_3$ indicates that a single conformer is highly preferred. However, slightly downfield from the resonance of the major *N*-Me group (δ 3.16) is a minor *N*-Me resonance (δ 3.29), and the integrated ratio of these resonances is 97/3 at 25°C. Warming the solution to 50°C results in disappearance of the minor peak (coalescence), suggesting that this peak belongs to rotamer **14bZ** rather than to a small impurity. The amount of the minor *Z* rotamer should decrease as the polarity of the solvent decreases,[14] and indeed a spectrum of **14b** recorded in benzene-d_6 (the solvent for the radical translocations) at 25°C showed only one set of resonances; no minor peaks could be seen. The behavior of other *o*-iodoanilides was similar. Minor peaks could sometimes be detected in chloroform at 25°C, but never in benzene. These observations suggest that rotamer populations are about 97/3 in chloroform and >97/3 in benzene.

Figure 4. Conformations of 3°-*o*-Iodoanilides



14b E > 97%
derived radical
can translocate H

14b Z < 3%
derived radical
cannot translocate H

The predominance of the *E* rotamer is a crucial design feature of this PRT group. By analogy to the benzamides,[8b-d] it is likely that the anilide C–N bond cannot rotate during the lifetime of the radical. Thus, radicals generated from rotamer **14bE** have the opportunity to translocate a hydrogen atom adjacent to the carbonyl while those generated from rotamer **14bZ** do not. Since these amides exist as >97% *E* rotamer in benzene, >97% of the radicals that are generated have the opportunity to translocate hydrogen.

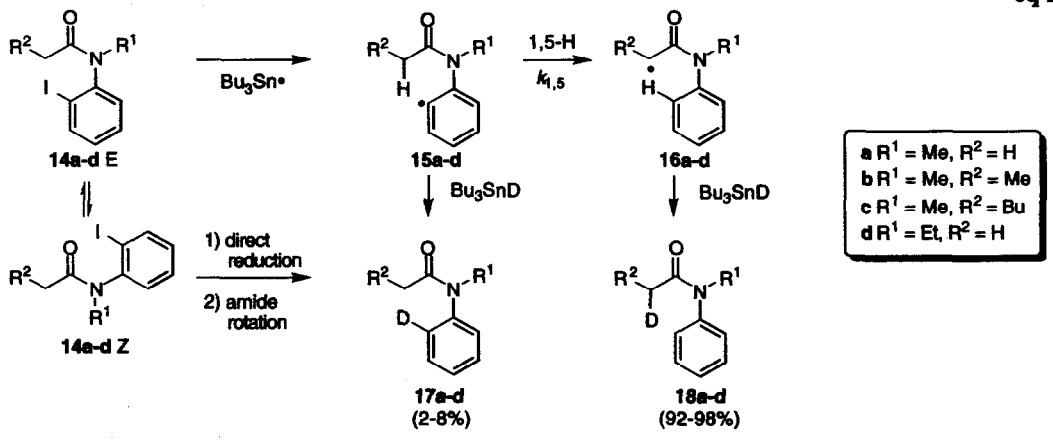
The ^1H NMR spectra of anilides like **14** consistently showed chemical shift non-equivalence of geminal methylene protons (see H_a and H_b in Figure 4). This non-equivalence originates because the plane of the aryl ring of *o*-substituted anilide is twisted with respect to the plane of the amide, and because the interconversion of the two twisted rotamers (an enantiomerization in the case of **14E**) is slow on the NMR time scale.[17] Calculations and X-ray structures suggest[17b] that the twist angle between the aryl ring and the amide planes is close to 90° for such *o*-iodoanilides. For convenience, all subsequent *o*-iodoanilides are shown in standard "flat" representations, but it is worth bearing in mind that these structures do not represent well the ground state conformations of these molecules. Rotations of both the amide C–N and N–Ar bonds are fast on the laboratory time scale, and all compounds behave as homogeneous samples on preparative and analytical chromatography.

To gauge the effectiveness of these substrates in 1,5-hydrogen transfer reactions, we conducted a series of reductions of model precursors with tributyltin deuteride. These experiments are summarized in eq 2. Precursors **14** were reduced with Bu_3SnD at either 0.02M or 0.2M, and ratios of labeled products **17/18** were measured by integration of the crude ^2H NMR spectrum. The products were then purified by flash chromatography, and isolated yields of **17/18** ranged from 83-93%. Mass spectral analyses showed that deuterium incorporation was high in all cases (>95% d_1).

Reduction of acetanilide **14a** with Bu_3SnD at 0.02M provided labeled products **17a** and **18a** in a ratio of 7/93 by the mechanism shown in eq 2. Reductions of propananilide **14b** and hexanilide **14c** at 0.02 M gave improved ratios of **17** to **18**: 2/98 for **14b**, and 3/97 for **14c**. These improvements

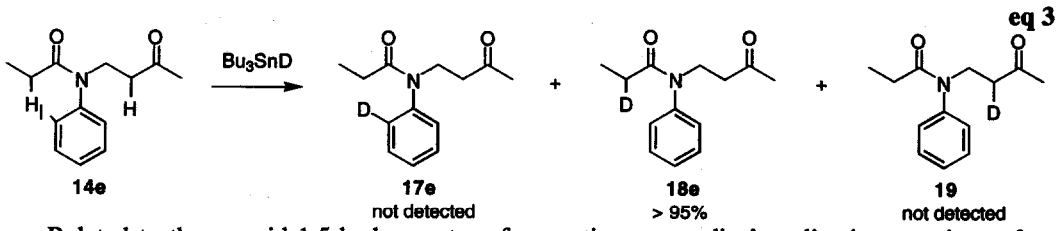
are expected because the strength of the target C–H bond is decreased in going from methyl to methylene. In the reduction of **14c**, the product **18c** is labeled exclusively in the α-position showing that 1,5-hydrogen transfer is much faster than 1,6- or higher hydrogen transfers. The traces of **17** that are formed (2-3%) approach the amount of **14Z** rotamer that may be present in these reactions, so it is not clear if these products come from direct reduction of *E* radical **15** (eq 2) or from generation of a radical (not shown) from **14Z** which cannot translocate hydrogen. Conducting a reduction at higher tin deuteride concentration provided clear evidence that radical **15** could be trapped prior to 1,5-hydrogen transfer. Reduction of **14b** at 0.2M starting Bu_3SnD concentration still gave predominately the translocated product: **17b/18b** = 7/93. Since the yield of product **17b** arising from the *Z* rotamer should be constant, the increase in the yield of **17b** (~5%) going from 0.02M to 0.2M represents the minimum amount of **17b** formed by direct reduction of **15**. *N*-Ethyl acetanilide **14d** presents two methyl groups with hydrogens positioned for 1,5-hydrogen atom transfer, but reduction of **14d** at 0.02 M is analogous to the *N*-methyl analog **14a** and provides only **17d/18d** in a ratio of 8/92.

eq 2



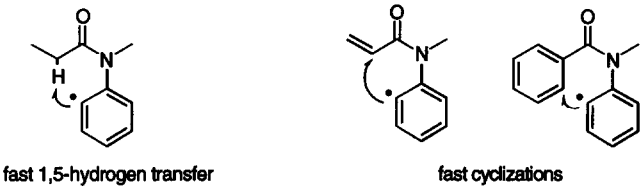
To provide a fair competition of C–H bonds in R^1 and R^2 with respect to bond strength, we prepared propananilide **14e** (eq 3). This substrate presents to the radical two pairs of 2° C–H bonds adjacent to carbonyl groups: one in the acyl substituent adjacent to the amide carbonyl and the other in the nitrogen substituent adjacent to the ketone carbonyl. If anything, bond dissociation energies might slightly favor the C–H bond adjacent to the ketone. In the actual experiment, this C–H bond is ignored. Reduction of **14e** at 0.02M gave a crude product that showed a single peak in the ^2H NMR spectra attributed to **18e**. Since ^2H NMR spectra are rather broad, we cannot exclude the presence of traces of **17e** and **19**; however, we estimate that amounts of these products do not exceed a few percent.

These labeling studies show that 1,5-hydrogen transfer of radicals **15** (eq 2) are very fast, and are highly selective for the hydrogens adjacent to the amide carbonyl. No evidence was obtained either for other hydrogen transfers further down the acyl chain or for 1,5-hydrogen transfer from the nitrogen substituent of the amide. From these data and from the estimated rate constant k_H for the reaction of phenyl radical with tributyltin hydride,[18] we can estimate that the rate constant for 1,5-hydrogen transfer from a secondary C–H bond is $> 5 \times 10^8\ M^{-1}\ s^{-1}$. With larger R^2 groups, the 1,5-hydrogen transfer becomes even faster, and we have examples where even the use of neat tributyltin deuteride fails to trap significant amounts of aryl radicals prior to H-transfer.[12]



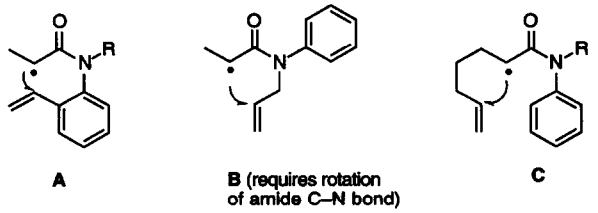
Related to these rapid 1,5-hydrogen transfer reactions are radical cyclization reactions of *o*-iodoacrylanilides and benzoylanilides (Figure 5).[10] These cyclizations are also unusually fast, thus supporting our recent suggestion[8d,e] that there is an analogy between radical cyclizations and 1,5-hydrogen transfer reactions in structurally related substrates. Why the aryl-amide linker group promotes such rapid radical reactions is not entirely clear, and this has been a matter of some debate. Jones and Storey have recently suggested a model based on the twisting of the N–Ar bond of the radical precursors.[17a] Such twisting is clearly a key feature of these molecules (see Figure 4). However, we have questioned several of tenets of the Jones/Storey model and proposed a more traditional model based on the favorable geometry imposed by the amide linker.[17b]

Figure 5. Cyclization/Hydrogen Transfer Analogs



A major goal of this study was to evaluate the usefulness of the new translocating group for conducting typical radical additions and cyclizations. Studies on radical additions have been reported separately,[12] and Figure 6 shows three different motifs for translocation/cyclization. The radical acceptor can be located on the same nitrogen substituent as the translocating group (A), on the other nitrogen substituent (B), or on the amide carbon substituent (C). Motif C is an application of the PRT group concept. In motifs A and B, the anilide becomes attached through a new C–C bond to another part of the molecule, and thus it does not function as a removable protecting group. However, these reactions could still be useful for synthesis of benzo-fused lactams.

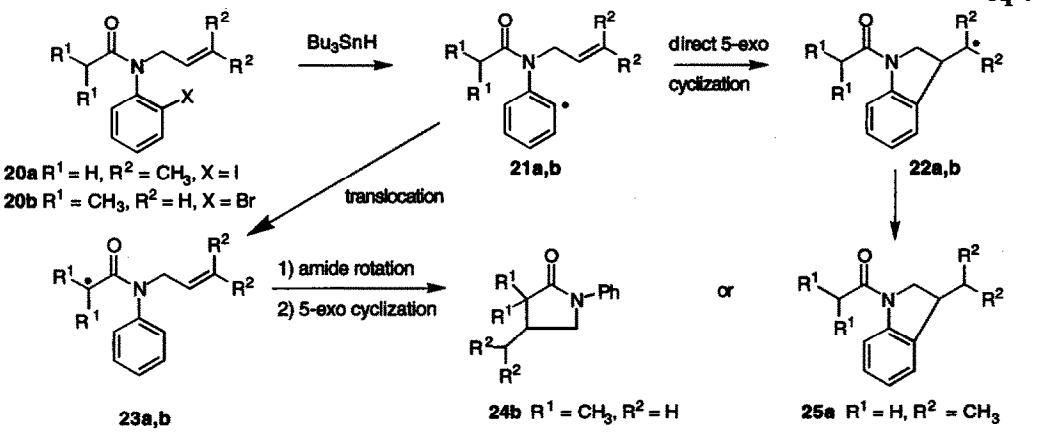
Figure 6. Motifs for Cyclization of Translocated Radicals



To date, we have not investigated a substrate corresponding to motif A. Eq 4 shows examples of substrates **20** corresponding to motif B. The initial aryl radicals **21** generated from these substrates may suffer 1,5-hydrogen transfer to give **23**, but competing direct cyclization to the double bond to give **22** is also possible. When readily available isopropenyl *o*-iodoacetanilide **20a**

was reduced with tributyltin hydride (0.02M), we isolated dihydroindole **25a** in 89% yield. There was no evidence for the expected translocation/cyclization product **24a**. Related cyclizations have been observed by Dittami and Ramanathan,[10b] and this is indeed a useful method for making dihydroindoles. We concluded from these results that motif B did not show much promise for translocation/cyclization due to the rapid direct cyclization; however, this conclusion must now be modified in light of recent observations by Jones and Storey.[17a] They observed that reduction of bromide **20b** with tributyltin hydride provided only the radical translocation/cyclization product **24b** in 92% yield. Apparently, the 1,5-hydrogen abstraction of the 3°-hydrogen in **21b** is sufficiently rapid so as to supersede direct cyclization to **22b**. After 1,5-hydrogen transfer, the new radical **23b** adjacent to the carbonyl must rotate its amide C–N bond prior to cyclization. Such rotations are facilitated by high temperatures.[19] The conversion of **20b** to **24b** suggests that motif B may be viable in some cases, provided that there is either an unusually slow direct cyclization or an unusually fast 1,5-hydrogen transfer.

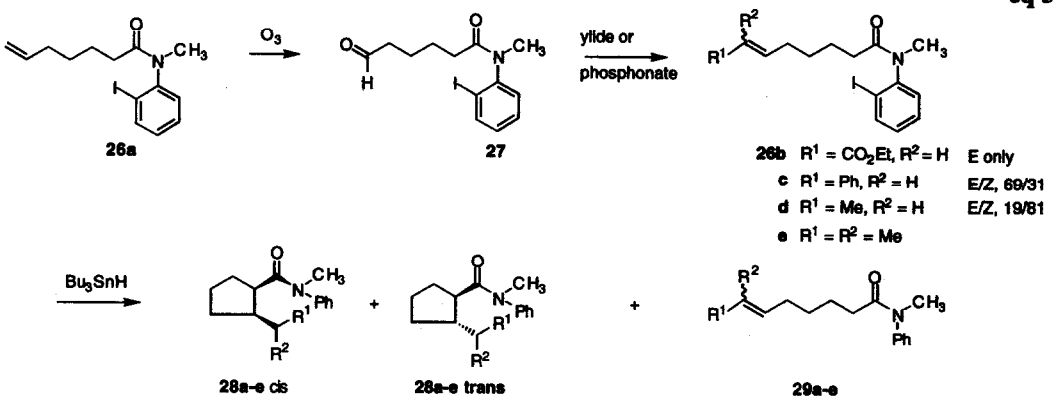
eq 4



To investigate the PRT group motif (C), we prepared and reduced a number of substituted *N*-methyl *N*-*o*-iodophenyl-5-heptenamides **26a-e**, as shown in eq 5. The substituted derivatives **26b-d** were prepared from the readily available parent **26a** by a sequence of ozonolysis, followed by olefination of the aldehyde **27** with the appropriate phosphonium ylide or phosphonate anion. Compound **26e** was prepared by a standard N-alkylation, N-acylation sequence (see Experimental). These iodides were reduced under a standard set of conditions by heating a benzene solution of the substrate (0.01M), tributyltin hydride (0.02M), and AIBN (0.002M) at 80°C for 8-12 h. The tin products were removed by using a DBU workup,[20] and isolated yields were determined after flash chromatographic purification. According to the above labeling studies, the efficiency of 1,5-hydrogen transfer in these substrates should be ≥95%.

Reduction of the parent substrate **26a** was surprisingly inefficient. Under the standard conditions, chains would not propagate efficiently and significant quantities of unreacted **26a** remained even after prolonged heating. Eventually, some of the starting iodide **26a** was consumed to give a very complex mixture. Resonances attributable to the expected products **28a** and **29a** could not be located in the crude ^{1}H NMR spectrum of this mixture. The apparent inability to propagate chains with this substrate puzzled us for some time. All of the steps in the chain (iodine abstraction, 1,5-hydrogen transfer, cyclization, and hydrogen abstraction from tin hydride) should be sufficiently rapid to propagate a good chain. Further evidence arises below that suggests a possible explanation for the poor reaction of **26a**.

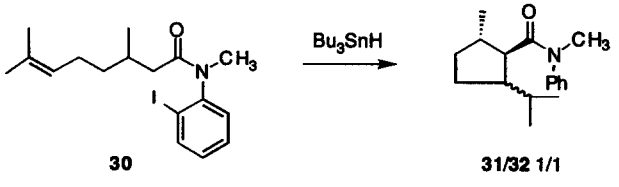
eq 5



The problem of chain propagation was solved simply by placing a substituent on the terminal carbon of the alkene. In a dramatic contrast to the result with **26a**, reduction of **26b** ($R^1 = CO_2Et$) was exceptionally clean and provided a separable mixture of **28b**-*cis* and **28b**-*trans* in 93% combined yield. The starting material was consumed smoothly over 8 h, and the directly reduced product **29b** was not formed in significant amounts. Likewise, reduction of the phenyl analog **26c** and the dimethyl analog **26e** provided **28c,e**-*cis*/**28c,e**-*trans* (1.2-1.3/1) in 83 and 81% yields. Reduction of the mono-methyl analog **26d** provided a 67% yield of a 1.3/1 mixture of **28d**-*cis* and **28d**-*trans* alongside directly reduced product **29d** in 18% yield (mostly *cis*). Since 1,5-hydrogen transfer is fast and efficient under these conditions, **29d** must result from reduction of the translocated radical prior to cyclization. If so, then the yield of **28d** could be increased by lowering the tin hydride concentration. The configurations of the major isomers were tentatively assigned as *cis* in all cases by using established trends in the ^1H NMR spectra.[21] In the case of **28c**-*cis*, we confirmed this assignment by independent synthesis.[15] As expected,[20] the *cis*/*trans* selectivities are low, but stereochemistry can probably be altered by epimerization.

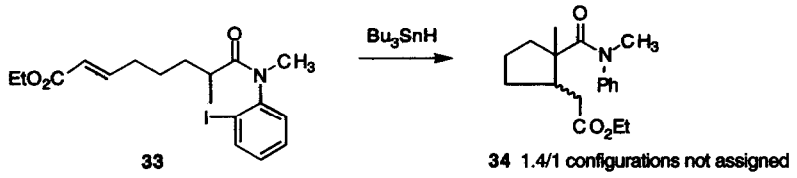
Eq 6 illustrates that a 3-substituent on the carbon chain adjacent to the radical is tolerated, and that asymmetric induction results. Reduction of **30** with tributyltin hydride provided two major products **31/32** in a 1/1 ratio in a combined yield of 84%. The less polar isomer was isolated in very pure form, while the more polar isomer was contaminated with traces of unidentified impurities (possibly the other two stereoisomers?). Beckwith's guidelines predict that the methyl and carboxanilide groups will be trans in both isomers,[22] and this prediction is now supported by a good number of related cyclizations.[23] Thus, we tentatively assign structures **31** and **32** as shown; the relative disposition of the isopropyl and carboxamide groups is not currently known.

eq 6



Eq 7 shows that the translocation/cyclization sequence is nicely applicable to 3°C–H bonds. Reduction of **33** under the standard conditions gave an 80% yield of **34** in a ratio of 1.4/1. In this example, configurations were not assigned because the proton α to the amide (used in the chemical shift trend analysis) is no longer present.

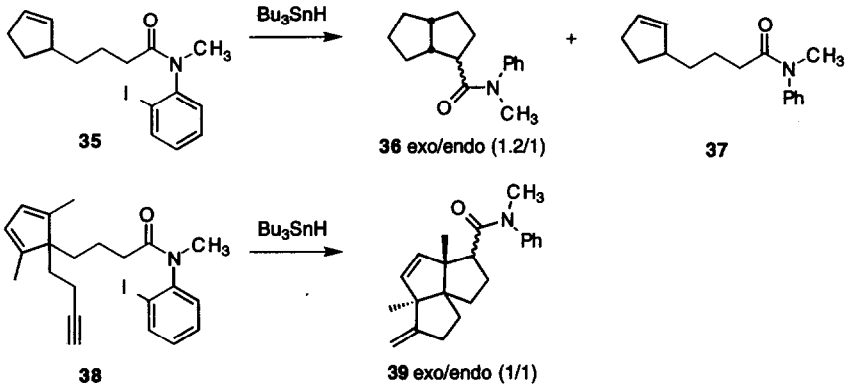
eq 7



33 34 1.4/1 configurations not assigned

Bicyclic and tricyclic rings can also be formed with ease, as shown in eq 8. Reduction of **35** with tributyltin hydride provided a 60% yield of a separable mixture of **36**-*exo* and **36**-*endo* (1.2/1) alongside 20% of the directly reduced product **37**. It is again likely that reduced product **37** results from successful translocation and failed cyclization, and that the yield of **36** could be increased by reducing the tin hydride concentration. In reduction of **38**, tandem cyclization follows translocation,[24] and **39** is isolated as an inseparable 1/1 mixture of diastereomers in 75% yield.

eq 8

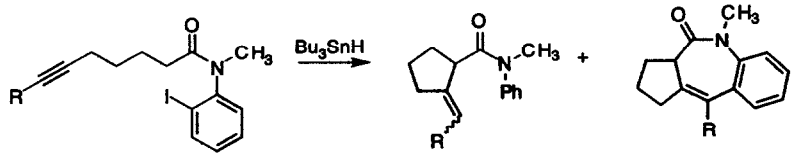


35 36 exo/endo (1.2/1) 37

38 39 exo/endo (1/1)

Triple bonds also proved useful as radical acceptors, and these substrates provided some insight into potential problems with the translocation/cyclization sequence. Eq 9 shows the results of reductions of two simple hexynyl anilides **40a,b**. The terminal alkyne **40a** proved to be an even more recalcitrant substrate than terminal alkene **26a**. Compound **40a** was not consumed even after prolonged heating and addition of more AIBN. Given these poor results, we turned quickly to phenyl-substituted alkyne **40b**. Reduction of **40b** did not go to completion under the standard conditions; however, **40b** was consumed after addition of a further 20% AIBN and heating for several more hours. From this reaction we isolated the expected product **41b** and a novel tricyclic product **42b** in a ratio of 43/57 in 52% combined yield. Alkene **41b** was a single, unassigned stereoisomer.[25] Tricycle **42b** exhibited no resonances for vinyl protons in the ^{1}H NMR spectrum, and integration revealed that only nine aromatic hydrogens were present. The ^{13}C NMR spectrum of **42b** was revealing, exhibiting twelve resonances in the alkene/aryl region (120-146 ppm), five of which belonged to quaternary carbons. The carbon of the lactam carbonyl resonated at 173 ppm.

eq 9

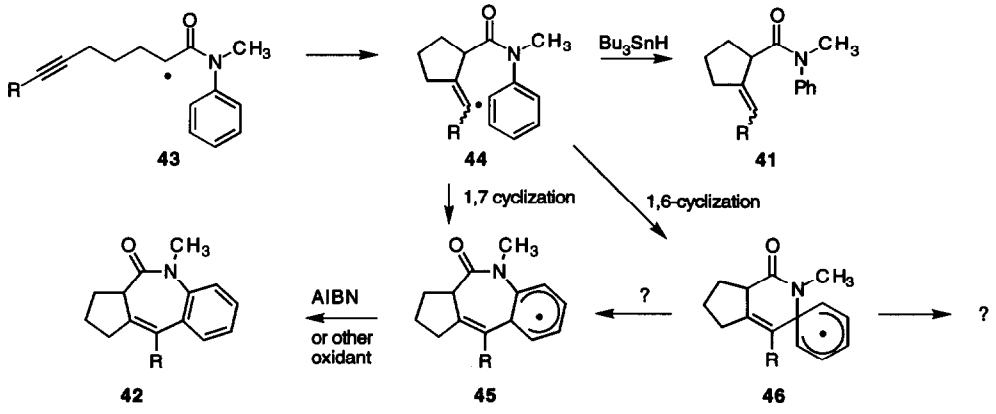


40a R = H
40b R = Ph

41a,b **42a,b**

To interpret these results, we suggest the pathways outlined in Figure 7. Under the reaction conditions, translocated radical **43** probably undergoes efficient cyclization to give **44**. Depending on substituent R, **44** can either be trapped by tributyltin hydride to give the desired product **41**, or it can add to the aromatic ring. Because of the geometry of the amide **44**, the vinyl radical is quite close to the aromatic ring, and it could undergo either 1,6-cyclization to give spirocyclohexadienyl radical **46**, or 1,7-cyclization to give the fused cyclohexadienyl radical **45**.[26] Oxidation of radical **45** to **42** is well precedented if not well understood,[27] and we now add AIBN to the list of possible oxidants for aromatization of radicals like **45**.[28] The fate of radical **46** is less clear. Rearrangement of **46** to **45** could occur by a number of mechanisms, and has precedent.[26] Radical **46** may also decompose by radical/radical or radical/solvent reactions, thus explaining the complex mixtures. Both radicals **45** and **46** are relatively unreactive, and they may not react with tin hydride under the reaction conditions. Thus, the rapid conversion of a radical like **44** to either **45** or **46** is a chain-breaking event.

Figure 7. Possible Fates of Cyclized Radicals



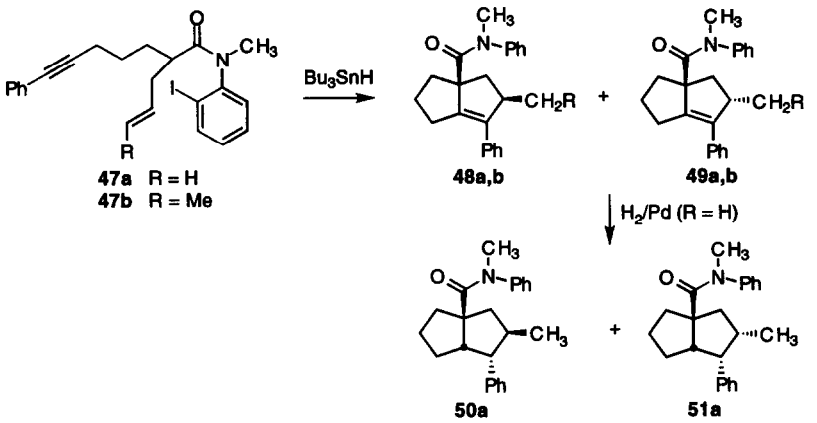
The mechanism in Figure 7 predicts that an increase in the tin hydride concentration above 0.02M should result in an increase in the ratio of **41** to **42**. This prediction was borne out by experiment. Reduction of **40b** at 0.1M tin hydride concentration provided a 54% isolated yield of **41b** and **42b** in a ratio of 64/36.

Though a full explanation of the results with these two alkynes is not possible, we have still gained some important clues from these experiments. It is likely that the poor chains observed with alkene **26a** and alkynes **40a,b** are coupled to the propensity of their cyclized radicals to undergo further cyclization to the aromatic ring. Fortunately, for the alkene substrates, the presence of even a single terminal substituent seems to slow the rate of the cyclization enough so that it does not interfere. Vinyl radicals are more reactive than their alkyl counterparts, and thus even the presence of a phenyl group in **40b** does not completely suppress the addition to the aromatic ring.

Conducting a tandem cyclization should be a viable strategy to suppress the addition of the first cyclized radical to the aromatic ring provided that the second cyclization of this radical is rapid. This idea was confirmed by preparing and reducing the three substrates shown in eqs 10 and 11. Reduction of **47a** with tributyltin hydride provided a relatively clean reaction mixture from which a single major fraction was obtained in 62% yield after flash chromatography. This fraction gave a single peak in the GC chromatogram, but inspection of its ^{1}H NMR spectrum suggested that a major and minor isomer were present in a ratio that could not be accurately discerned due to peak overlapping. The major isomer clearly had the expected general structure **48/49**. The problems of

isomer ratio and assignment of relative configuration were resolved by catalytic hydrogenation of the mixture. This provided two stereoisomers **50a** and **51a** in a ratio of 87/13. Assuming that direct cis hydrogenation of the double bonds[29] occurred to form a cis-fused diquinane, this result suggests that the precursor was also an 87/13 mixture of isomers **48a** and **49a**. Configurations were readily assigned from proton NMR spectra; in the isomer **50a** with the ring methyl and phenyl groups cis, the doublet of the methyl group is quite shielded (0.52 ppm), while the *trans* isomer **50a** exhibited a normal methyl doublet (0.87 ppm). Reduction of the ethyl analog **47b** provided two inseparable diastereomers **48b** and **49b** in 71% yield in a ratio of 89/11. This time, the ratio was readily determined by both GC and ^{1}H NMR, and configurations were assigned by analogy to **48a/49a**.

eq 10

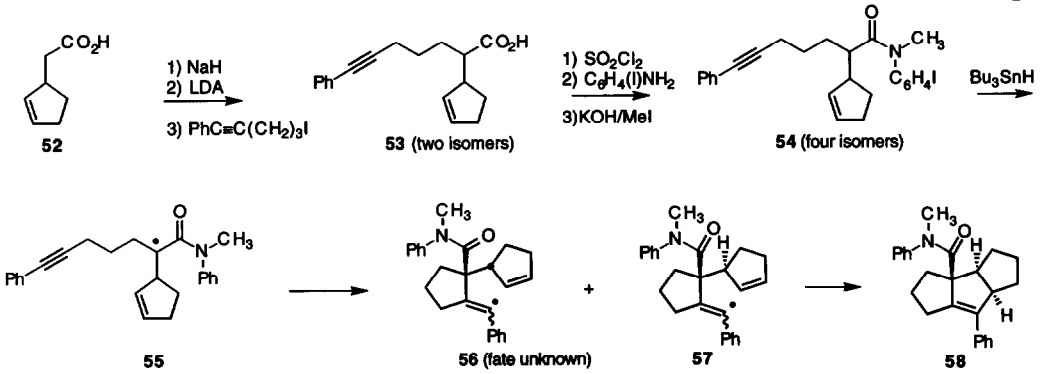


47a R = H
47b R = Me

48a,b **49a,b** **50a** **51a**

With the goal of forming a linear triquinane, we prepared *o*-iodoanilide **54** by the route summarized in eq 11. There was no diastereoface selectivity in the alkylation reaction (**52** → **53**), so **54** was formed as a 1/1 mixture of diastereomers on the laboratory time scale. The ^{1}H NMR spectrum of **54** was very complex. On the NMR time scale, the axial chirality of the N–Ar bond adds another element of stereochemistry, and there are actually four diastereomers observed. However, the radical translocation process erases two of the three elements of stereochemistry, and in principle, all four of the diastereomers of **54** should generate the same radical **55**. Reduction of **54** under the standard conditions provided a complex mixture containing one major product and a number of minor ones. We isolated the pure major product by flash chromatography in 35% yield. This product was clearly a tricyclic compound of the general structure **58**, and we tentatively assigned the relative

eq 11



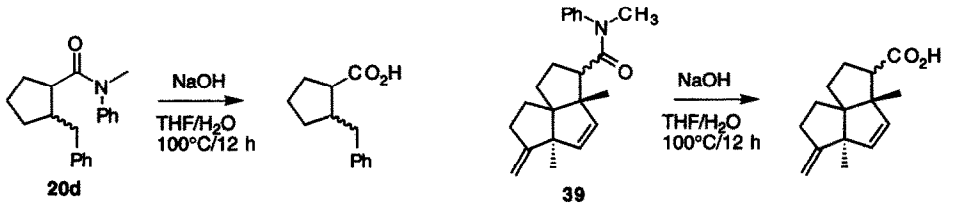
52 **53** (two isomers) **54** (four isomers)

55 **56** (fate unknown) **57** **58**

configurations based on the mechanistic rationale in eq 11. Translocated radical **55** is expected to cyclize with little or no stereoselectivity to give **56** and **57**. Radical **57** can complete the tandem cyclization to give a less strained anti/cis triquinane **58**, while radical **56** would cyclize to give a more strained syn/cis triquinane (not shown). The major product should arise from radical **57**.[30] While radical **56** may suffer some cyclization (we did not attempt to characterize the minor products), it may also react via other pathways such as addition to the aromatic ring. In this analysis, the low yield in this experiment is not due to problems in the radical translocation, but instead to (not unanticipated) stereochemical problems in the tandem cyclization. We consider that the results in eqs 10 and 11 validate the notion that tandem cyclizations can be used to prevent the back additions of cyclized vinyl radicals to the aromatic ring.

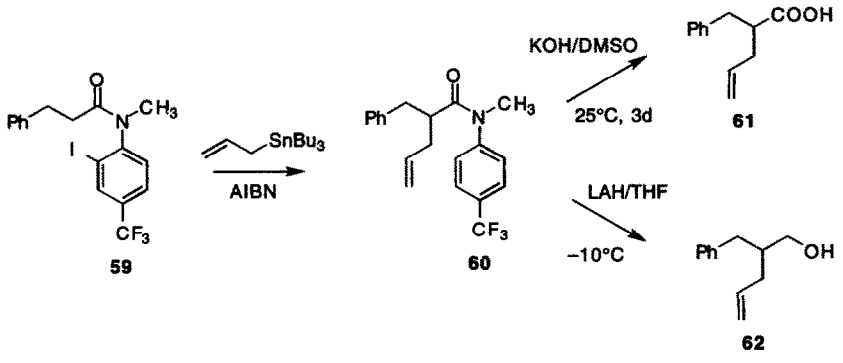
At this stage, the *o*-iodoanilide emerges as a reasonable candidate meeting most of the requirements for a carbonyl PRT group. It is easy to introduce, and it is a reasonable protecting group both before and after translocation. Most importantly, it is clearly an excellent translocating group. However, cleavage of this group may require more stringent conditions than desirable. For example, hydrolytic cleavages of the two anilides shown in eq 12 occurred in good yields, but the conditions were rather harsh: NaOH, THF/H_2O, 100°C, 12 h.

eq 12



While there are milder conditions for amide hydrolyses that may be applicable to these parent substrates, we envision that it will now be relatively easy to design and implement modified PRT groups with different options for cleavage. We demonstrated this point with a few simple reactions shown in eq 13. *p*-Trifluoromethyl-*o*-iodoanilide **59** was readily prepared, and was reacted with allyltributylstannane[31] to provide the translocation/allylation product **60** in 45% yield. As expected, the *p*-trifluoromethyl group facilitated hydrolysis, and **60** was cleaved to acid **61** by saponification with KOH in DMSO/H_2O for 3 days at 25 °C. Furthermore, on reduction with lithium aluminum hydride, **60** behaved like an ester not an amide, producing primary alcohol **62** (78%) instead of a 2°-amine.

eq 13



Conclusions: The results of this study strongly support the original design premise. Based on the rapid radical translocation reactions of *o*-iodobenzamides,[8b-d] we predicted that the "retro" analogs, *o*-iodoanilides, would also be excellent substrates for radical translocation reactions. They clearly are. Beyond that, *o*-iodoanilides show much better potential than *o*-iodobenzamides as PRT groups because the subsequent reactions of the translocated radicals are better understood and more well behaved. Indeed, *o*-iodoanilides are among the most efficient and useful PRT groups developed to date.

The *o*-iodoanilide group is well suited for forming C–C bonds from C–H bonds adjacent to carbonyls by radical methods. Cyclization reactions of the translocated radicals appear to be especially general, and successful substrates for cyclization by this PRT method can be readily designed by combining the information in this study with the standard body of knowledge on radical cyclizations. Bimolecular additions of these translocated radicals will also be useful;[12] however, these additions are restricted compared to enolate additions and alkylations. Nonetheless, the mildness of the radical PRT conditions could make this the method of choice in some cases, especially where the introduction of allyl groups is desired.

Finally, *o*-iodoanilide and *p*-trifluoromethyl-*o*-iodoanilide groups are only the first members of a whole class of carboxylate PRT groups that could be developed by altering the substituents on the anilide nitrogen. The most important feature that can be modulated by such variations is probably the method of the cleavage of the group from the final product. Especially desirable for fine synthesis would be groups that are cleaved under even milder conditions than the *p*-trifluoromethyl acetanilide, and also groups that might be reacted directly with nucleophiles or reducing agents to produce aldehydes or ketones.

Experimental

General: All reactions were run under a nitrogen atmosphere. Tetrahydrofuran (THF), diethyl ether, and benzene were distilled under nitrogen from sodium-benzophenone. Methylene chloride, dimethyl sulfoxide (DMSO), *N,N*-dimethylformamide (DMF), hexamethylphosphoramide (HMPA), and triethylamine were distilled from calcium hydride. Medium pressure liquid chromatography (MPLC) was performed with Kieigel 60 (230-400 mesh ASTM) silica gel or on a prepacked EM lobar LiChroprep Si/60 columns. Flash column chromatography was performed with silica gel (230-400 mesh) packed columns. High resolution mass spectra were measured on a Varian CH5-DF mass spectrometer at a resolution greater than 5500 by the peak matching method using PFK as the standard. Purities of all compounds were assessed by inspection of ^{1}H NMR and/or ^{13}C NMR spectra in conjunction with a capillary GC analysis.

Synthesis of Radical Precusors

***N*-(2-Iodophenyl)ethanamide. (General Acylation Procedure):** To a mixture of 2-iodoaniline (2.190 g, 10 mmol) and sodium hydroxide (1.04 g, 26 mmol) in THF/H_2O (4 mL, 1/1) at 0 °C was added dropwise acetyl chloride (0.906 g, 12 mmol). The reaction mixture was stirred for 2 h at 0 °C. Then the mixture was diluted with water (20 mL), and extracted with ether (3 x 30 mL). The combined organic layers were washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash chromatography (hexanes/EtOAc = 10/1) afforded the amide (2.158 g, 83%): ^{1}H NMR ($CDCl_3$) δ 8.20 (1 H, d, J = 8.1 Hz), 7.77 (1 H, d, J = 8.0 Hz), 7.41 (1 H, broad), 7.34 (1 H, m), 6.84 (1 H, m), 2.24 (3 H, s); IR (thin film) 3270, 3027, 1659, 1530, 1292, 750 cm^{-1}; MS *m/z* 261, 219, 134, 92, 65, 55; HRMS, *m/z* Calc for C_8H_8INO, 260.9651, found, 260.9651.

***N*-(2-Iodophenyl)-*N*-methylethanamide (14a). (General *N*-Alkylation Procedure):** To a suspension of finely powdered KOH (0.695 g, 12.4 mmol) in DMSO (1 mL) at 0 °C was added dropwise a solution of the above amide (2.158 g, 8.3 mmol) in DMSO (3 mL). After 2 h, a solution of iodomethane in DMSO (2 mL) was added over 30 min. After stirring for another 4 h, the reaction mixture was quenched with water (20 mL), and extracted with ether (3 x 40 mL). The organic layer was washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc = 6/1) afforded **14a** (2.150 g, 94%): ^{1}H NMR ($CDCl_3$) δ 7.92 (1 H, d, J = 8.0 Hz), 7.42 (1 H, m), 7.28 (1 H, d, J = 7.6 Hz), 7.07 (1 H, m), 3.17 (3 H, s), 1.79 (3 H, s); IR (thin film) 3053, 2928, 1670, 1470, 1377, 1300, 770 cm^{-1}; MS *m/z* 276

(M+H), 260, 245, 243, 148, 77, 43; HRMS, *m/z* Calc for C_7H_3IN (M – CH_3CO), 231.9623, found, 231.9623.

***N*-(2-Iodophenyl)propanamide.** Prepared following the general acylation procedure by using 2-iodoaniline (1.752 g, 8 mmol), propionyl chloride (1.110 g, 12 mmol), and sodium hydroxide (0.96 g, 24 mmol). Purification by chromatography (hexanes/EtOAc = 6/1) gave the amide (1.190 g, 54%): ^{1}H NMR ($CDCl_3$) δ 8.25 (1 H, d, *J* = 7.5 Hz), 7.77 (1 H, d, *J* = 7.9 Hz), 7.45 (1 H, broad), 7.32 (1 H, m), 6.84 (1 H, m), 2.47 (2 H, q, *J* = 7.4 Hz), 1.30 (3 H, t, *J* = 7.4 Hz); IR (thin film) 3272, 2936, 1657, 1528, 1424, 1285, 760 cm^{-1}; MS *m/z* 275, 219, 148, 92, 57, 39; HRMS, *m/z* Calc for $C_9H_{10}INO$, 274.9807, found, 274.9807.

***N*-(2-Iodophenyl)-*N*-methylpropanamide (14b).** Compound **14b** was prepared following the general N-alkylation procedure by using *N*-(2-iodophenyl)propanamide (1.150 g, 4.0 mmol), potassium hydroxide (0.336 g, 6.0 mmol), and iodomethane (0.852 g, 6.0 mmol). Purification by chromatography (hexanes/EtOAc = 3/1) afforded **14b** as a clear oil (1.101 g, 95%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, d, *J* = 8.0 Hz), 7.41 (1 H, m), 7.26 (1 H, m), 7.07 (1 H, m), 3.18 (3 H, s), 1.95 (2 H, q, *J* = 7.5 Hz), 1.07 (3 H, t, *J* = 7.5 Hz); IR (thin film) 2938, 1669, 1470, 1379, 1382, 768 cm^{-1}; MS, *m/z* 260, 245, 233, 162, 104, 77, 57; HRMS, *m/z* Calc for $C_{10}H_{12}NO$ (M – I), 162.0919, found, 162.0919.

***N*-(2-Iodophenyl)hexanamide.** Prepared following the standard acylation procedure by using 2-iodoaniline (0.876 g, 4.0 mmol), hexanoyl chloride (0.807 g, 6.0 mmol), and sodium hydroxide (0.48 g, 12 mmol). Purification by flash chromatography (hexanes/EtOAc = 8/1) gave the amide (0.930 g, 73%): ^{1}H NMR ($CDCl_3$) δ 8.24 (1 H, d, *J* = 7.6 Hz), 7.77 (1 H, d, *J* = 8.0 Hz), 7.44 (1 H, broad), 7.34 (1 H, m), 6.84 (1 H, m), 2.43 (2 H, t, *J* = 7.4 Hz), 1.78 (2 H, m), 1.41 (4 H, m), 0.92 (3 H, t, *J* = 6.7 Hz); IR (thin film) 3274, 2930, 2869, 1663, 1522, 1433, 1285 cm^{-1}; MS *m/z* 317, 261, 219, 190, 92, 71, 55, 43; HRMS, *m/z* Calc for $C_{12}H_{16}INO$, 317.0277, found, 317.0277.

***N*-(2-Iodophenyl)-*N*-methylhexanamide (14c).** Compound **14c** was prepared following the general N-alkylation procedure by using *N*-(2-iodophenyl)hexanamide (0.930 g, 2.9 mmol), potassium hydroxide (0.24 g, 4.2 mmol), and iodomethane (0.600 g, 4.2 mmol). Purification by flash chromatography (hexanes/EtOAc = 4.5/1) afforded **14c** (0.854 g, 89%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, dd, *J* = 1.3, 8.0 Hz), 7.41 (1 H, m), 7.23 (1 H, m), 7.08 (1 H, m), 3.17 (3 H, s), 1.93 (2 H, t, *J* = 7.4 Hz), 1.59 (2 H, m), 1.20 (4 H, m), 0.83 (3 H, t, *J* = 6.7 Hz); IR (thin film) 2953, 2856, 1659, 1469, 1380, 767 cm^{-1}; MS *m/z* 332 (M + H), 288, 275, 260, 233, 204, 148, 77; HRMS, *m/z* Calc for $C_{10}H_{11}INO$ (M – C_3H_7), 287.9885, found, 287.9885.

***N*-(2-Iodophenyl)-*N*-ethylethanamide (14d).** Compound **14d** was prepared following the general *N*-alkylation procedure by using *N*-(2-iodophenyl)acetamide (0.524 g, 2.0 mmol), potassium hydroxide (0.168 g, 3.0 mmol), and iodoethane (0.468 g, 3.0 mmol). Purification by flash column chromatography (hexanes/EtOAc = 4/1) afforded **14d** (0.367 g, 64%): ^{1}H NMR ($CDCl_3$) δ 7.95 (1 H, dd, *J* = 1.3, 8.0 Hz), 7.40 (1 H, m), 7.21 (1 H, dd, *J* = 1.4, 7.7 Hz), 7.08 (1 H, m), 4.20 (1 H, m), 3.18 (1 H, m), 1.77 (3 H, s), 1.34 (3 H, t, *J* = 7.2 Hz); IR (thin film) 2930, 2872, 1657, 1470, 1395, 1298 cm^{-1}; MS *m/z* 290 (M+H)$^+$, 274, 261, 232, 162, 134, 91, 77; HRMS, *m/z* Calc for $C_{10}H_{12}NO$ (M – I), 162.0919, found, 162.0919.

4-(2-Iodophenylamino)-2-butanone. A solution of 2-iodoaniline (1.100 g, 5.0 mmol) and methyl vinyl ketone (1.750 g, 25.0 mmol) in ether (2 mL) was stirred at 25 °C for 72 h. Ether and excess methyl vinyl ketone were removed under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc = 8/1) afforded the amine as a clear oil (0.980 g, 68%): ^{1}H NMR ($CDCl_3$) δ 7.65 (1 H, d, *J* = 7.7 Hz), 7.21 (1 H, m), 6.58 (1 H, d, *J* = 8.2 Hz), 6.45 (1 H, m), 4.42 (1 H, broad), 3.46 (2 H, t, *J* = 6.1 Hz), 2.78 (2 H, t, *J* = 6.3 Hz), 2.19 (3 H, s); IR (thin film) 3384, 2987, 2897, 1707, 1587, 1507, 742 cm^{-1}; MS *m/z* 289, 232, 105, 91, 77, 65; HRMS, *m/z* Calc for $C_{10}H_{12}INO$, 288.9964, found, 288.9964.

***N*-(2-Iodophenyl)-*N*-(3-oxobutyl)propanamide (14e).** Compound **14e** was prepared following the standard acylation procedure by using the above amine (0.900 g, 3.1 mmol) and propionyl chloride (0.434 g, 4.7 mmol). Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave **14e** as a clear oil (0.824 g, 77%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, d, *J* = 8.0 Hz), 7.41 (1 H, m), 7.21 (1 H, d, *J* = 7.8 Hz), 7.08 (1 H, m), 4.21 (1 H, m), 3.43 (1 H, m), 2.8 (2 H, m), 2.16 (3 H, s), 1.91 (2 H, q, *J* = 7.4 Hz), 1.04 (3 H, t, *J* = 7.4 Hz); IR (thin film) 2938, 1717, 1653, 1458, 1275 cm^{-1}; MS *m/z* 345, 302, 246, 218, 148, 118, 57, 43; HRMS, *m/z* Calc for $C_{11}H_{13}INO$ (M – $COCH_3$), 302.0042, found, 302.0042.

***N*-(2-Iodophenyl)-*N*-(3-methyl-2-butenyl)ethanamide (20a).** Compound **20a** was prepared following the general N-alkylation procedure by using *N*-(2-iodophenyl)ethanamide (0.516 g, 2.0 mmol), potassium hydroxide (0.168 g, 3.0 mmol), and allyl bromide (0.447 g, 3.0 mmol). Purification by flash column chromatography (hexanes/EtOAc = 4.5/1) afforded **20a** as a clear oil (0.585 g, 89%): ^{1}H NMR ($CDCl_3$) δ 7.92 (1 H, dd, *J* = 1.2, 8.2 Hz), 7.37 (1 H, m), 7.14 (1 H, dd, *J* = 1.4, 7.9 Hz), 7.05 (1 H, m), 5.24 (1 H, m), 4.72 (1 H, dd, *J* = 6.5, 14.5 Hz), 3.71 (1 H, dd, *J* = 8.3, 14.5 Hz), 1.78 (3 H, s), 1.64 (3 H, s), 1.38 (3 H, s).

***N*-(2-Iodophenyl)-6-heptenamide.** A solution of triphenylphosphine (2.75 g, 10.5 mmol), bromotrichloromethane (4.160 g, 21.0 mmol), 6-heptenoic acid (1.280 g, 10.0 mmol), and 2-iodoaniline (4.380 g, 20.0 mmol) in THF (30 mL) was refluxed for 2 h. The reaction mixture was cooled to 25 °C , and the amine salt was removed by filtration. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 6/1) gave the amide (2.290 g, 70%): ^{1}H NMR ($CDCl_3$) δ 8.24 (1 H, d, J = 7.9 Hz), 7.77 (1 H, d, J = 8.93 Hz), 7.43 (1 H, broad), 7.34 (1 H, m), 6.84 (1 H, m), 5.80 (1 H, m), 5.01 (2 H, m), 2.49 (2 H, t, J = 7.41), 2.13 (2 H, m), 1.76 (2 H, m), 1.53 (2 H, m); IR (thin film) 3269, 3073, 2932, 1661, 1524, 1433, 1287, 750 cm^{-1}; MS *m/z* 329, 261, 219, 92, 55, 39; HRMS, *m/z* Calc for $C_{13}H_{16}INO$, 329.0277, found, 329.0277.

***N*-(2-Iodophenyl)-*N*-methyl-6-heptenamide (26a).** Compound **26a** was prepared following the general N-alkylation procedure by using the above amide (2.290 g, 7.0 mmol), potassium hydroxide (0.55 g, 9.7 mmol), and iodomethane (1.420 g, 10 mmol). Purification by flash column chromatography (hexanes/EtOAc = 6/1) afforded **26a** as a clear oil (1.87 g, 79%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, d, J = 7.9 Hz), 7.42 (1 H, m), 7.24 (1 H, m), 7.07 (1 H, m), 5.45 (1 H, m), 4.93 (2 H, m), 3.17 (3 H, s), 1.96 (4 H, m), 1.61 (2 H, m), 1.33 (2 H, m); IR (thin film) 3073, 2926, 1661, 1524, 1433, 1287, 750 cm^{-1}; MS *m/z* 302, 288, 275, 260, 233, 216, 148, 105, 77, 55; HRMS, *m/z* Calc for $C_{11}H_{13}INO$ (M – C_3H_5), 302.0042, found, 302.0042.

***N*-(2-Iodophenyl)-*N*-methyl-7-ethoxycarbonyl-6-heptenamide (26b).** Ozonolysis: A solution of amide **26a** (1.376 g, 4.0 mmol) in CH_2Cl_2/MeOH (60 mL, 5/1) was ozonized in the presence of sodium bicarbonate (34 mg, 0.4 mmol) at –78 °C. The ozonolysis was terminated when the solution became blue. The solution was bubbled with air until it became colorless, then dimethyl sulfide (1 mL) was added. The reaction mixture was allowed to warm to 25 °C. The solvent was removed in vacuo to afford aldehyde **27** as a clear oil. Wittig reaction: To a suspension of sodium hydride (0.120 g, 5.0 mmol) in THF (20 mL) was added triethyl phosphonoacetate (1.121 g, 5.0 mmol). The reaction mixture was stirred until gas evolution ceased. A solution of crude aldehyde **27** in THF (3 mL) was added dropwise at –78 °C. The reaction mixture was allowed to warm to 25 °C, and stirred for 5 h. The reaction mixture was quenched with water (20 mL), and extracted with ether (3 x 40 mL). The combined organic layers were washed with water (2x) and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 3/1) gave **26b** as a clear oil (1.040 g, 63%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, dd, J = 1.0, 7.8 Hz), 7.42 (1 H, m), 7.24 (1 H, m), 7.08 (1 H, m), 6.89 (1 H, dd, J = 7.0, 15.6 Hz), 5.75 (1 H, d, J = 15.6 Hz), 4.15 (2 H, q, J = 7.1 Hz), 3.17 (3 H, s), 2.13 (2 H, m), 1.94 (2 H, t, J = 7.3 Hz), 1.61 (2 H, m), 1.39 (2 H, m), 1.27 (3 H, t, J = 7.1 Hz); IR (thin film) 3056, 2934, 1716, 1663, 1472, 1383, 1269, 769 cm^{-1}; MS *m/z* 415, 370, 342, 288, 274, 260, 233, 148, 105, 81; HRMS, *m/z* Calc for $C_{17}H_{22}INO_3$, 415.0644, found, 415.0644.

***N*-(*o*-Iodophenyl)-*N*-methyl-7-phenyl-6-heptenamide (26c).** Compound **26c** was prepared following the procedure for **26b** by using amide **26a** (and benzyltriphenylphosphionium ylide). Purification by flash chromatography (hexanes/EtOAc = 4/1) afforded **26c** as a clear oil (56%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, dd, J = 1.0, 8.1 Hz), 7.37 (1 H, m), 7.24 (1 H, m), 7.06 (1 H, m), 6.34 (1 H, m), 6.14 (td, J = 6.7, 15.8 Hz) and 5.59 (1 H, td, J = 7.3, 11.7 Hz), 3.17 and 3.16 (3 H, s), 2.25 and 2.27 (2 H, m), 1.94 (2 H, m), 1.63 (2 H, m), 1.41 (2 H, m); IR (thin film) 3058, 2934, 1665, 1471, 1385, 758 cm^{-1}; MS *m/z* 419, 344, 308, 292, 275, 260, 233, 218, 162, 148, 117, 105, 91, 77, 67.

***N*-(2-Iodophenyl)-*N*-methyl-6-octenamide (26d).** Compound **26d** was prepared following the procedure for **26b** by using amide **26a** (and ethyltriphenylphosphonium ylide). Purification by flash column chromatography (hexanes/EtOAc = 6/1) afforded **26d** as a clear oil (70%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, dd, J = 1.3, 7.9 Hz), 7.42 (1 H, td, J = 1.3, 7.7 Hz), 7.24 (1 H, dd, J = 1.5, 7.7 Hz), 7.07 (1 H, td, J = 1.5, 7.6 Hz), 5.35 (2 H, m), 3.17 (3 H, s), 1.93 (4 H, m), 1.60 (5 H, m), 1.25 (2 H, m); IR (thin film) 3056, 2926, 1659, 1470, 1383, 769 cm^{-1}, MS *m/z* 358, 288, 275, 260, 231, 148, 105, 77, 55; HRMS, *m/z* Calc for $C_{15}H_{21}INO$, 358.0326, found, 358.0326.

5-Methyl-4-hexenoic Acid. To a suspension of sodium hydride (1.727 g, 72 mmol) in THF (80 mL) at 0 °C were added diisopropylamine (6.07 g, 60 mmol) and acetic acid (3.603 g, 60 mmol). The reaction mixture was brought to reflux for 15 min. After the reaction mixture was cooled to 0 °C, HMPA (10 mL) and *n*-butyllithium (41.3 mL, 60 mmol) were added. The reaction was retained at 0 °C for 15 min, and stirred at 35 °C for 30 min. Then the reaction mixture was cooled to 0 °C, and prenyl bromide (5.962 g, 40 mmol) was added dropwise. After 3 h stirring at 25 °C, the solvent was removed under reduced pressure, and the reaction was quenched with water (40 mL). The water phase was washed with methylene chloride (3x). Then the water phase was acidified with 6N HCl (20 mL, 120 mmol), and extracted with ether (4 x 60 mL). The combined organic layers were washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave the acid as a clear oil (3.740 g, 74%): ^{1}H NMR ($CDCl_3$) δ 5.10 (1 H, m), 2.34 (4 H, m), 1.69 (3 H, s), 1.63 (3 H, m); IR (thin film) 2500-3600 (broad), 1711, 1414, 1286, 827 cm^{-1}; MS *m/z* 128, 82, 69, 55, 41; HRMS, *m/z* Calc for $C_7H_{12}O_2$, 128.0837, found, 128.0837.

5-Methyl-4-hexenol. To a solution of the above acid (3.740 g, 30 mmol) in ether (60 mL) at 0 °C was added lithium aluminum hydride (2.200 g, 60 mmol). The reaction mixture was stirred for 10 h. The excess lithium aluminum hydride was destroyed by addition of water (20 mL). The aqueous layer was extracted with ether (3 x 80 mL). The combined organic layers were filtered through celite, and dried over $MgSO_4$. Concentration gave the alcohol as a colorless oil (3.112 g, 91%): ^{1}H NMR ($CDCl_3$) δ 5.15 (1 H, m), 3.64 (2 H, t, J = 6.4 Hz), 2.07 (2 H, m), 1.68 (3 H, s), 1.61 (3 H, s), 1.60 (2 H, m); IR (thin film) 3330, 2928, 2864, 1449, 1337, 739 cm^{-1}, MS *m/z* 114, 96, 81, 69, 55, 41; HRMS, *m/z* Calc for $C_7H_{14}O$, 114.1045, found, 114.1045.

6-Iodo-2-methyl-2-hexene. To a solution of the above alcohol (3.112 g, 27 mmol) in methylene chloride (54 mL) at 0 °C was added triethylamine (5.45 g, 54 mmol) and methanesulfonyl chloride (3.091 g, 27 mmol). The mixture was stirred for 1 h, and was poured into water (20 mL). The aqueous layer was extracted with methylene chloride (3 x 60 mL). The combined organic layers were washed with water (2x) and brine (1x), and dried over $MgSO_4$. Concentration gave the methanesulfonate. To a solution of the methanesulfonate (27 mmol) in acetone (100 mL) was added sodium iodide (11.34 g, 81 mmol). The mixture was refluxed for 12 h. The acetone was removed under reduced pressure, and water (40 mL) was added. The aqueous layer was extracted with ether (3 x 60 mL). The combined organic layers were washed with sodium bicarbonate (1x), sodium thiosulfate (1x), water (2x) and brine (1x), and dried over $MgSO_4$. Concentration yielded the iodide (5.140 g, 85%): ^{1}H NMR ($CDCl_3$) δ 5.05 (1 H, m), 3.18 (2 H, t, J = 6.9 Hz), 2.11 (2 H, m), 1.87 (2 H, m), 1.69 (3 H, s), 1.64 (3 H, s); IR (thin film) 2928, 1446, 1377, 831 cm^{-1}; MS *m/z* 224, 97, 81, 69, 55, 41; HRMS, *m/z* Calc for $C_7H_{13}I$, 224.0062, found, 224.0062.

7-Methyl-6-octenoic Acid. This compound was prepared following the procedure for 5-methyl-4-hexenoic acid by using the above iodide (2.240 g, 10.0 mmol) and acetic acid (0.900 g, 15 mmol). Purification gave the acid as a clear oil (1.133 g, 73%): ^{1}H NMR ($CDCl_3$) δ 5.10 (1 H, m), 2.35 (2 H, t, J = 7.4 Hz), 2.01 (2 H, m), 1.68 (3 H, s), 1.64 (2 H, m), 1.60 (3 H, s), 1.38 (2 H, m); IR (thin film) 2500-3600 (broad), 1707, 1412, 1240, 938, 831 cm^{-1}; MS *m/z* 156, 138, 96, 84, 69, 48, 41; HRMS, *m/z* Calc for $C_9H_{16}O_2$, 156.1150, found, 156.1150.

***N*-(2-Iodophenyl)-7-methyl-6-octenamide.** A solution of the above acid (0.312 g, 2.0 mmol) in thionyl chloride (2.5 mL) was refluxed for 3 h. Excess thionyl chloride was removed under reduced pressure to afford the corresponding acyl chloride as a yellow oil. The amide was prepared following the standard acylation procedure by using 2-iodoaniline (0.482 g, 2.2 mmol) and the acyl chloride. Purification by flash column chromatography (hexanes/EtOAc = 15/1) afforded the amide (0.478 g, 67%): ^{1} H NMR ($CDCl_3$) δ 8.24 (1 H, d, J = 7.4 Hz), 7.77 (1 H, dd, J = 1.0, 7.9 Hz), 7.43 (1 H, broad), 7.34 (1 H, m), 6.84 (1 H, m), 5.12 (1 H, m), 2.43 (2 H, t, J = 7.4 Hz), 2.07 (2 H, m), 1.79 (2 H, m), 1.80–1.60 (6 H, m), 1.44 (2 H, m); IR (thin film) 3271, 3022, 2932, 1659, 1525, 1431, 754 cm^{-1}; MS *m/z* 357, 261, 219, 134, 95, 69; HRMS, *m/z* Calc for C_{15} $H_{20}INO$, 357.0590, found, 357.0590.

***N*-(2-Iodophenyl)-*N*-methyl-7-methyl-6-octenamide (26e).** Compound **26e** was prepared following the general *N*-alkylation procedure by using the above amide (0.450 g, 1.2 mmol), potassium hydroxide (0.101 g, 1.8 mmol), and iodomethane (0.256 g, 1.8 mmol). Purification by flash column chromatography (hexanes/EtOAc = 6/1) gave **26e** as a clear oil (0.409 g, 92%): ^{1}H NMR ($CDCl_3$) δ 7.92 (1 H, dd, J = 1.1, 7.8 Hz), 7.40 (1 H, m), 7.24 (1 H, m), 7.06 (1 H, m), 5.02 (1 H, m), 3.17 (3 H, s), 1.88 (4 H, m), 1.60 (8 H, m), 1.20 (2 H, m); IR (thin film) 3056, 2924, 2855, 1655, 1471, 1381, 767 cm^{-1}; MS *m/z* 371, 288, 233, 148, 95; HRMS, *m/z* Calc for $C_{16}H_{22}INO$, 371.0746, found, 371.0744.

***N*-(*o*-Iodophenyl)-*N*-methyl-3,7-dimethyl-6-octenamide (30).** Compound **30** was prepared following the general N-alkylation procedure by using appreciate the amide (3.400 g, 9.0 mmol), potassium hydroxide (0.706 g, 12.6 mmol), and iodomethane (1.789 g, 12.6 mmol). Purification by flash column chromatography (hexanes/EtOAc = 8/1) gave **30** (3.049 g, 88%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, m), 7.41 (1 H, m), 7.22 (1 H, m), 7.07 (1 H, m), 5.05 (1 H, m), 3.17 (3 H, s), 1.92 (4 H, m), 1.75 (1 H, m), 1.64 (3 H, s), 1.55 (3 H, s), 1.24 (1 H,m), 1.08 (1 H, m), 0.87 (3 H, d, J = 6.5 Hz); IR (thin film) 3056, 2959, 1655, 1470, 1370, 767; MS *m/z* 385, 302, 275, 258, 233, 176, 148, 133, 109, 105, 91, 81, 77, 69.

2-Methyl-2-carboxy-6-heptenoic Acid. A solution of the corresponding diester (4.270 g, 20.0 mmol, prepared from dimethyl malonate by sequential alkylation) and sodium hydroxide (4.00 g, 100 mmol) in $MeOH/H_2O$ (70 mL, 1/1) was refluxed for 5 h. Methanol was removed under reduced pressure. The remaining water phase was washed with methylene chloride (3x). Then the aqueous phase was acidified with 6N HCl (25 mL, 150 mmol), and extracted with ether (3 x 80 mL). The combined organic layers were washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave the diacid (3.590 g, 97%): ^{1}H NMR ($CDCl_3$) δ 5.75 (1 H, m), 4.98 (2 H, m), 2.07 (2 H, m), 1.99 (2 H, m), 1.49 (3 H, s), 1.43 (2 H, m); IR (thin film) 2500-3600 (broad), 1709, 1410, 912 cm^{-1}; MS *m/z* 187, 118, 100, 87, 69, 54, 41; HRMS, *m/z* Calc for $C_9H_{15}O_4$, 187.0970, found, 187.0970.

2-Methyl-6-heptenoic Acid. The above diacid (3.590 g, 19.3 mmol) was heated at 155 °C for 8 h. A 2N NaOH aqueous solution (15 mL, 30 mmol) was added. The aqueous solution was washed with methylene chloride (3x), and acidified with a 5N HCl aqueous solution (8 mL, 40 mmol). The aqueous phase was extracted with ether (3 x 50 mL). The combined organic layers were washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave the acid (2.485 g, 91%): ^{1}H NMR ($CDCl_3$) δ 5.79 (1 H, m), 4.98 (2 H, m), 2.48 (1 H, m), 2.05 (2 H, m), 1.69 (2 H, m), 1.41 (2 H, m), 1.18 (3 H, d, J = 6.7 Hz); IR 2500-3600 (broad), 1711, 1466, 1240, 912 cm^{-1}; MS *m/z* 142, 124, 101, 96, 74, 69, 55, 41; HRMS, *m/z* Calc for $C_8H_{14}O_2$, 192.0994, found, 192.0994.

***N*-(2-Iodophenyl)-2-methyl-6-heptenamide.** The compound was prepared following the general acylation procedure by using the above acid (2.485 g, 17.5 mmol). Purification by flash column chromatography (hexanes/EtOAc = 15/1) gave the amide (4.628 g, 77%): ^{1}H NMR ($CDCl_3$) δ 8.24 (1 H, m), 7.77 (1 H, dd, J = 1.1, 7.9 Hz), 7.49 (1 H, broad), 7.34 (1 H, m), 6.84 (1 H, m), 5.81 (1 H, m), 4.96 (2 H, m), 2.44 (1 H, m), 2.11 (2 H, m), 1.82 (1 H, m), 1.54 (3 H, m), 1.28 (3 H, d, J = 6.8 Hz); IR (thin film) 3345, 3067, 2971, 1676, 1541, 1431, 746 cm^{-1}; MS *m/z* 343, 275, 219, 147, 119, 97, 55, 39; HRMS, *m/z* Calc for $C_{14}H_{18}INO$, 343.0433, found, 343.0433.

***N*-(2-Iodophenyl)-*N*-methyl-2-methyl-6-heptenamide.** This compound was prepared following the general *N*- alkylation procedure by using the above amide (4.450 g, 13 mmol), potassium hydroxide (1.109 g, 18 mmol), and iodomethane (2.584 g, 18 mmol). Purification by flash column chromatography (hexanes/EtOAc = 6/1) gave the amide (4.170 g, 90%): ^{1}H NMR ($CDCl_3$) δ 7.94 (1 H, m), 7.41 (1 H, m), 7.24 (1 H, m), 7.06 (1 H, m), 5.75 (1 H, m), 4.91 (2 H, m), 3.18 and 3.17 (3 H, s), 2.16–1.82 (3 H, m), 1.82–1.61 (1 H, m), 1.41–1.21 (3 H, m), 1.12 and 1.10 (3 H, d, J = 6.7 Hz); IR (thin film) 3073, 2932, 2858, 1663, 1470, 1385, 767 cm^{-1}; MS *m/z* 357, 316, 230, 162, 97, 77, 55; HRMS, *m/z* Calc for $C_{15}H_{20}NO$ (M – I), 230.1545, found, 230.1545.

***N*-(2-Iodophenyl)-*N*-methyl-2-methyl-7-ethoxycarbonyl-6-heptenamide (33).** Compound **33** was prepared following the procedure for **26b** by using the above iodide (0.714 g, 2.0 mmol). Purification by flash column chromatography (hexanes/EtOAc = 3/1) afforded **33** (0.602 g, 72%): ^{1}H NMR ($CDCl_3$) δ 7.94 (1 H, m), 7.43 (1 H, m), 7.24 (1 H, m), 7.08 (1 H, m), 6.88 (1 H, m), 5.76 (1 H, m), 4.17 (2 H, m), 3.17 and 3.16 (3 H, s), 2.10 (3 H, m), 1.84–1.50 (1 H, m), 1.5–1.4 (1 H, m), 1.27 (5 H, m), 1.12 and 1.10 (3 H, d, J = 6.6, 6.8 Hz); IR (thin film) 3056, 2934, 1717, 1659, 1469, 1385, 766 cm^{-1}; MS *m/z* 384, 356, 302, 233, 162, 123, 95, 77; HRMS, *m/z* Calc for $C_{16}H_{19}INO_2$, 384.0460, found, 384.0460.

4-(2-Cyclopentenyl)butanoic Acid. This acid was prepared following the procedure for 5-methyl-4-hexenoic acid by using 2-(2-cyclopentenyl)-1-iodoethane (2.220 g, 10.0 mmol) and acetic acid (0.900 g, 15 mmol). The acid was obtained as a clear oil (1.070 g, 69%): ^{1}H NMR ($CDCl_3$) δ 5.73 (1 H, m), 5.67 (1 H, m), 2.63 (1 H, m), 2.36 (2 H, t, J = 7.4 Hz), 2.12 (2 H, m), 2.08 (1 H, m), 1.63 (2 H, m), 1.41 (3 H, m); IR (thin film) 2500-3600 (broad), 1713, 1458, 1287, 937 cm^{-1}; MS *m/z* 154, 136, 94, 79, 67, 45.

***N*-(2-Iodophenyl)-4-(2-cyclopentenyl)butanamide.** This was prepared following the procedure for *N*-(2-iodophenyl)-6-heptenanide by using the above acid (1.000 g, 6.5 mmol) and 2-iodoaniline (1.55 g, 7.2 mmol). Purification by flash column chromatography (hexanes/EtOAc = 10/1) gave the amide (1.510 g, 65%): ^{1}H NMR ($CDCl_3$) δ 8.24 (1 H, d, J = 7.9 Hz), 7.77 (1 H, dd, J = 1.3, 8.1 Hz), 7.44 (1 H, broad), 7.34 (1 H, m), 6.84 (1 H, m), 5.72 (2 H, m), 2.70 (1 H, m), 2.44 (2 H, t, J = 7.6 Hz), 2.32 (2 H, m), 2.08 (1 H, m), 1.81 (2 H, m), 1.6–1.3 (3 H, m); IR (thin film) 3267, 2934, 2897, 1653, 1584, 1456, 763 cm^{-1}; MS *m/z* 355, 288, 274, 261, 219, 148, 134, 119, 93, 77, 67; HRMS, *m/z* Calc for $C_{15}H_{18}INO$, 355.0433, found, 355.0433.

***N*-(2-Iodophenyl)-*N*-methyl-4-(2-cyclopentenyl)butanamide (35).** Compound **35** was prepared following the general *N*-alkylation procedure by using the above amide (1.330 g, 3.7 mmol), potassium hydroxide (0.314 g, 5.6 mmol), and iodomethane (0.800 g, 5.6 mmol). Purification by flash column chromatography (hexanes/EtOAc = 6/1) afforded **35** (1.350 g, 100%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, dd, J = 1.2, 7.9 Hz), 7.42 (1 H, m), 7.24 (1 H, m), 7.07 (1 H, m), 5.69 (1 H, m), 5.62 (1 H, m), 3.17 (3 H, s), 2.54 (1 H, m), 2.23 (2 H, m), 2.00 (1 H, m), 1.94 (2 H, t, J = 7.5 Hz), 1.61 (1 H, m), 1.4–1.2 (4 H, m); IR (thin film) 2936, 2845, 1661, 1578, 1469, 1327, 768 cm^{-1}; MS *m/z* 369, 302, 288, 275, 242, 232, 162, 148, 119, 93, 77, 55; HRMS, *m/z* Calc for $C_{16}H_{20}INO$, 369.0590, found, 369.0690.

***N*-(2-Iodophenyl)-7-phenyl-6-heptynamide.** This was prepared following the procedure for *N*-(2-iodophenyl)-6-heptenmide by using corresponding acid (1.770 g, 8.8 mmol) and 2-iodoaniline (2.119 g, 9.7 mmol). Purification by flash column chromatography (hexanes/EtOAc = 6/1) gave the amide (2.514 g, 71%): ^{1}H NMR ($CDCl_3$) δ 8.23 (1 H, d, J = 7.7 Hz), 7.77 (1 H, dd, J = 1.0, 8.0 Hz), 7.45 (1 H, broad), 7.38 (3 H, m), 7.24 (3 H, m), 6.84 (1 H, m), 2.50 (4 H, m), 1.97 (2 H, m), 1.72 (2 H, m); IR (thin film) 3264, 3025, 2938, 2860, 1655, 1433, 1289, 754 cm^{-1}; MS *m/z* 403, 385, 285, 219, 156, 143, 128, 91, 77, 65; HRMS, *m/z* Calc for $C_{21}H_{20}INO$, 403.0433, found, 403.0433.

***N*-(2-Iodophenyl)-*N*-methyl-7-phenyl-6-heptynamide (40b).** Compound **40b** was prepared following the general *N*-alkylation procedure by using the above amide (1.720 g, 4.3 mmol), potassium hydroxide (0.337 g, 6.0 mmol), and iodomethane 90.852 g, 6.0 mmol). Purification by flash column chromatography (hexanes/EtOAc = 3/1) afforded **40b** as a clear oil (1.684 g, 94%): ^{1}H NMR ($CDCl_3$) δ 7.92 (1 H, dd, J = 1.4, 8.0 Hz), 7.35 (3 H, m), 7.23 (4 H, m), 7.06 (1 H, m), 3.18 (3 H, s), 2.34 (2 H, t, J = 7.1 Hz), 2.00 (2 H, t, J = 7.3 Hz), 1.76 (2 H, m), 1.58 (2 H, m); IR (thin film) 2928, 1659, 1649, 1468, 1433, 1018, 756, 691 cm^{-1}; MS *m/z* 417, 290, 260, 233, 148, 128, 105, 91, 77; HRMS, *m/z* Calc for $C_{20}H_{20}INO$, 417.0590, found, 417.0590.

Methyl 2-Methoxycarbonyl-2-(2-propenyl)-7-phenyl-6-heptynoate. This was prepared by sequential alkylation of dimethylmalonate with 5-iodo-1-phenylpentane and allyl bromide. The diester was obtained as a clear oil (3.140 g, 100%): ^{1}H NMR ($CDCl_3$) δ 7.18 (2 H, m), 7.23 (3 H, m), 5.66 (1 H, m), 5.09 (2 H, m), 3.72 (6 H, s), 2.68 (2 H, m), 2.41 (2 H, t, J = 7.1 Hz), 2.07 (2 H, m), 1.52 (2 H, m); IR (thin film) 3076, 2952, 2843, 1734, 1437, 758 cm^{-1}; MS *m/z* 314, 283, 241, 195, 155, 128, 115, 91, 71,56; HRMS, *m/z* Calc for $C_{19}H_{22}O_4$, 314.1518, found, 314.1518.

2-Carboxy-2-propenyl-7-phenyl-6-heptynoic Acid. This was prepared by NaOH saponification of the above diester (3.140 g, 10.0 mmol). Purification gave the diacid (2.610 g, 91%): ^{1}H NMR ($CDCl_3$) δ 7.17 (2 H, m), 7.26 (3 H, m), 5.70 (1 H, m), 5.14 (2 H, m), 2.43 (2 H, t, J = 6.9 Hz), 2.12 (2 H, m), 2.11 (2 H, m), 1.62 (2 H, m); IR (thin film) 2500-3600 (broad), 1703, 1489, 928 cm^{-1}; MS *m/z* 242, 227, 197, 167, 143, 128, 91, 77, 59; HRMS, *m/z* Calc for $C_{16}H_{18}O_2$ (M – CO_2), 242.1307, found, 242.1307.

2-Propenyl-7-phenyl-6-heptynoic Acid. This was prepared by heating the above diacid at 150 °C for 8 h. Extraction and concentration afforded the acid (1.940 g, 88%): ^{1}H NMR ($CDCl_3$) δ 7.38 (2 H, m), 7.24 (3 H, m), 5.79 (1 H, m), 5.17 (2 H, m), 2.58-2.25 (5 H, m), 1.84–1.84 (4 H, m); IR (thin film) 2500-3600 (broad), 1703, 1442, 1248, 916 cm^{-1}; MS *m/z* 242, 224, 197, 155, 130, 115, 91, 77; HRMS, *m/z* Calc for $C_{16}H_{18}O_2$, 242.1307, found, 242.1307.

***N*-(2-Iodophenyl)-2-propenyl-7-phenyl-6-heptynamide.** This was prepared following the procedure for *N*-(2-iodophenyl)-6-heptenamide by using the above acid (1.452 g, 6.0 mmol) and 2-iodoaniline (1.580 g, 7.2 mmol). Purification by flash column chromatography gave the amide (1.781 g, 67%): ^{1}H NMR ($CDCl_3$) δ 8.22 (1 H, d, J = 8.1 Hz), 7.77 (1 H, d, J = 7.8 Hz), 7.44 (1 H, broad), 7.40-7.23 (6 H, m), 6.85 (1 H, m), 5.87 (1 H, m), 5.11 (2 H, m), 2.60-2.30 (5 H, m), 1.98–1.70 (4 H, m); IR (thin film) 3256, 3075, 2936, 2861, 1659, 1583, 1431, 914, 754 cm^{-1}; MS *m/z* 443, 402, 352, 143, 128, 115, 91; HRMS, *m/z* Calc for $C_{22}H_{22}INO$, 443.0746, found, 443.0746.

***N*-(2-Iodophenyl)-*N*-methyl-2-propenyl-7-phenyl-6-heptynamide (47a).** Compound **47a** was prepared following the general *N*-alkylation procedure by using the above amide (1.340 g, 3 mmol), potassium hydroxide (0.250 g, 4.5 mmol), and iodomethane (0.840 g, 6 mmol). Purification by flash column chromatography (hexanes/EtOAc = 6/1) afforded **47a** as a clear oil (1.270 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, m), 7.35 (3 H, m), 7.24 (4 H, m), 7.06 (1 H, m), 5.64 (1 H, m), 4.98 (2 H, m), 3.18 (3 H, s), 2.60-2.24 (3 H, m), 2.07 (2 H, m), 1.42–1.90 (4 H, m); IR (thin film) 3058, 2942, 2860, 1653, 1576, 1472, 725 cm^{-1}; MS *m/z* 457, 416, 330, 288, 260, 233, 197, 155, 115, 91, 77; HRMS, *m/z* Calc $C_{23}H_{24}INO$, 457.0903, found, 457.0903.

Methyl 2-Methoxycarbonyl-2-(2-butenyl)-7-phenyl-6-heptynoate: This series of compounds was prepared analogously to the above series. ^{1}H NMR ($CDCl_3$) δ 7.37 (2 H, m), 7.27 (3 H, m), 5.54 (1 H, m), 5.27 (1 H, m), 3.71 (6 H, s), 2.69 (d, J = 7.7 Hz) and 2.60 (2 H, d, J = 7.2 Hz), 2.40 (2 H, t, J = 7.0 Hz), 2.05 (2 H, m), 1.70–1.50 (4 H, m); IR (thin film) 2953, 1734, 1437, 1269, 758 cm^{-1}; MS *m/z* 328, 268, 241, 209, 145, 128, 115, 65; HRMS, *m/z* Calc for $C_{20}H_{24}O_4$, 328.1675, found, 328.1675.

2-Carboxyl-2-(2-butenyl)-7-phenyl-6-heptynoic Acid: ^{1}H NMR ($CDCl_3$) δ 7.38 (2 H, m), 7.26 (3 H, m), 5.62 (1 H, m), 5.30 (1 H, m), 2.77 and 2.66 (2 H, m), 2.43 (2 H, t, J = 6.9 Hz), 2.12 (2 H, m), 1.60 (4 H, m); IR (thin film) 2500-3600 (broad), 1707, 1491, 1273, 756 cm^{-1}; MS *m/z* 300, 256, 181, 155, 128, 115, 91, 55; HRMS, *m/z* Calc for $C_{18}H_{20}O_4$, 300.1362, found, 300.1362.

2-(2-Butenyl)-7-phenyl-6-heptynoic Acid: ^{1}H NMR ($CDCl_3$) δ 7.37 (2 H, m), 7.25 (3 H, m), 5.60-5.30 (2 H, m), 2.50-2.18 (5 H, m), 1.80–1.60 (7 H, m); IR (thin film) 2500-3600, 1701, 1491, 1441 cm^{-1}; MS *m/z* 256, 181, 169, 155, 143, 129, 115, 91, 55; HRMS, *m/z* Calc for $C_{17}H_{20}O_2$, 256.1463, found, 256.1463.

***N*-(2-Iodophenyl)-2-(2-Butenyl)-7-phenyl-6-heptynamide:** ^{1}H NMR ($CDCl_3$) δ 8.21 (1 H, m), 7.76 (1 H, m), 7.14-7.43 (7 H, m), 6.82 (1 H, m), 5.49 (2 H, m), 2.51-2.24 (5 H, m), 1.91–1.46 (7 H, m); IR (thin film) 3262, 2932, 2855, 1655, 1512, 1431, 752 cm^{-1}; MS *m/z* 457, 402, 339, 274, 219, 128, 115, 91, 55; HRMS, *m/z* Calc for $C_{23}H_{24}INO$, 457.0903, found, 457.0903.

***N*-(2-Iodophenyl)-*N*-methyl-2-(2-Butenyl)-7-phenyl-6-heptynamide (47b):** ^{1}H NMR ($CDCl_3$) δ 7.93 (1 H, m), 7.43-7.20 (7 H, m), 7.08 (1 H, m), 5.42-5.18 (2 H, m), 3.18 and 3.19 (3 H, s), 2.49-2.20 (3

H, m), 2.08 (2 H, m), 1.71–1.50 (7 H, m); IR (thin film) 2938, 2857, 1661, 1472, 1437, 692 cm^{-1}; MS *m/z* 471, 416, 344, 288, 233, 155, 128, 115, 91, 77, 55; HRMS, *m/z* Calcd for $C_{24}H_{26}INO$, 471.1059, found, 471.1059.

2-(2-Cyclopentenyl)-7-phenyl-6-heptynoic Acid (53). This was prepared following the procedure for 5-methyl-4-hexenoic by using cyclopentenyl acetic acid (0.631 g, 5.0 mmol). Acid **53** was obtained as a clear oil (0.810 g, 61%): ^1H NMR ($CDCl_3$) δ 7.37 (2 H, m), 7.26 (3 H, m), 5.70 (2 H, m), 3.02 (1 H, m), 2.48-2.20 (6 H, m), 2.08 (1 H, m), 1.81–1.42 (4 H, m); IR (thin film) 2500-3600 (broad), 3054, 2946, 1701, 1489, 754 cm^{-1}; MS *m/z* 268, 238, 221, 195, 179, 155, 128, 115, 105, 91, 67; HRMS, *m/z* Calc for $C_{18}H_{20}O_2$, 268.1463, found, 268.1463.

***N*-(2-Iodophenyl)-2-(2-cyclopentenyl)-7-phenyl-6-heptynamide.** This was prepared following the procedure for *N*-(2-iodophenyl)heptenamide by using acid **53** (0.810 g, 3.0 mmol) and 2-iodoaniline (1.643 g, 7.3 mmol). Purification by flash column chromatography (hexanes/EtOAc = 10/1) gave the amide (0.905 g, 64%): ^1H NMR ($CDCl_3$) δ 8.22 (1 H, d, *J* = 8.2 Hz), 7.76 (1 H, d, *J* = 7.9 Hz), 7.42 (1 H, broad), 7.40-7.26 (6 H, m), 6.83 (1 H, m), 5.85-5.70 (2 H, m), 3.03 (1 H, m), 2.45 (2 H, t, *J* = 5.5 Hz), 2.42-2.05 (4 H, m), 1.94–1.50 (5 H, m); IR (thin film) 3258, 3052, 2930, 2851, 1655, 1509, 1489, 1431, 754 cm^{-1}; MS *m/z* 469, 402, 378, 326, 274, 219, 157, 115, 91, 67; HRMS, *m/z* Calc for $C_{24}H_{24}INO$, 469.0903, found, 469.0903.

***N*-(2-iodophenyl)-*N*-methyl-2-(2-cyclopentenyl)-7-phenyl-6-heptynamide (54).** Compound **54** was prepared following the general *N*-alkylation procedure by using the above amide (0.900 g, 1.9 mmol), potassium hydroxide (0.165 g, 2.9 mmol), and iodomethane (0.675 g, 4.8 mmol). Purification by flash column chromatography (hexanes/EtOAc = 5/1) gave **54** as a clear oil (0.845 g, 92%): ^1H NMR ($CDCl_3$) δ 7.92 (1H ,m), 7.42-7.20 (7 H, m), 7.05 (1 H, m), 5.85-5.50 (2 H, m), 3.21 and 3.20 (3 H, s), 3.03 (1 H, m), 2.41-2.20 (4 H, m), 2.20–1.45 (7 H, m); IR (thin film) 3052, 2934, 2847, 1655, 1470, 1383, 756 cm^{-1}; MS *m/z* 483, 392, 340, 288, 260, 233, 195, 115, 91, 67; HRMS, *m/z* Calc for $C_{25}H_{26}INO$, 483.0925, found, 483.0925.

4-Amino-3-iodo-1-trifluoromethylbenzene. To a solution of 4-amino-1-trifluoromethylbenzene (3.000 g, 18 mmol) in AcOH (40 mL) and H_2O (10 mL) was added a solution of ICl (3.030 g, 18 mmole) in AcOH (10 mL) over 30 min. The reaction mixture was heated to 90 °C, and then cooled to 25 °C. The reaction was quenched with $Na_2S_2O_3$ and water, and extracted with ethyl ether. Purification by flash chromatography (hexanes/EtOAc = 10/1) gave the amine (3.250 g, 61%) as a brown oil: ^1H NMR ($CDCl_3$) δ 7.87 (1 H, s), 7.35 (1 H, d, *J* = 8.5 Hz), 6.74 (1 H, d, *J* = 8.3 Hz), 4.42 (2 H, br s).

***N*-(2-Iodo-4-trifluoromethylphenyl)-3-phenylpropanamide.** To a solution of 3-phenylpropanoic acid (0.200 g, 1.33 mmole) in CH_2Cl_2 (20 mL) at –78 °C was slowly added $POCl_3$ (0.125 ml, 1.6 mmol). After stirring for 1 h at 25 °C, the reaction mixture was cooled to –78 °C, and the above amine was added. The mixture was warmed to 25 °C in 2 h, and was diluted with ethyl ether. The ether solution was washed with 10% aqueous HCl and brine, and dried over $MgSO_4$. Purificarion by flash chromatography (hexanes/EtOAc = 3/1) afforded the amide (0.317 g, 83%) as a white solid mp 156-158 °C; ^1H NMR ($CDCl_3$) δ 8.43 (1 H, d, *J* = 8.6 Hz), 7.99 (1 H, s), 7.59 (1 H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.61, 141.15, 140.11, 135.77, 128.84, 128.43, 127.59, 127.14, 120.90, 121.22, 88.47, 39.74, 31.35, 0.08.

***N*-(2-Iodo-4-trifluomethylphenyl)-*N*-methyl-3-phenylpropanamide (59).** This was prepared following the general *N*-alkylation precedure: ^1H NMR ($CDCl_3$) δ 8.14 (1 H, s), 7.58 (1 H, d, *J* = 8.3 Hz), 7.26-7.00 (6 H, m), 3.60 (3 H, s), 3.02-2.83 (2 H, m), 2.30-2.14 (2 H, m).

Radical Reductions

***N*-(2-Deuteriophenyl)-*N*-methylpropanamide (17b) and *N*-Methyl-*N*-phenyl-2-deuteriopropanamide (18b). (Standard Labeling Experiment):** A solution of **14b** (58.0 mg, 0.2 mmol), tributyltin deuteride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol) in benzene (20 mL) was heated at 80 °C for 8 h. Benzene was removed under reduced pressure. The residue was diluted with wet ether (20 mL), and DBU (0.4 mmol) was added. The mixture was stirred for 10 min, and passed through a small column packed with silica gel. The filtrate was concentrated, and purified by MPLC (hexanes/EtOAc = 6/1). The mixture of **17b** and **18b** was obtained as a clear oil (29.2 mg, 90%). The spectra of labeled products we compared with those of authentic all-protio samples: ^1H NMR ($CDCl_3$) δ 7.39 (2 H, m), 7.32 (1 H, m), 7.17 (2 H, d, *J* = 7.7 Hz), 3.26 (3 H, s), 2.08 (1 H, broad), 1.03 (3 H, d, *J* = 7.4 Hz); ^2H NMR ($CHCl_3$) δ 7.30, 2.08 (2/98); IR (thin film) 2936, 1657, 1595, 1497, 1377, 702 cm^{-1}; MS *m/z* 164, 107, 77, 69, 58, 51, 41; HRMS, *m/z* Calc for $C_{10}H_{12}DNO$, 164.1059, found, 164.1059.

***N*-(2-Deuteriophenyl)-*N*-methylhexamamide (17c) and *N*-Methyl-*N*-phenyl-2-deuteriohexanamide (18c).** These were prepared following the standard labeling procedure by using iodide **14c** (66.0 mg, 0.2 mmol), tributyltin deuteride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol).

Purification by MPLC (hexanes/EtOAc = 8/1) afforded **17c** and **18c** as a clear oil (37.5 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 7.28-7.40 (3 H, m), 7.16 (2 H, d, J = 7.8 Hz), 3.25 (3 H, s), 2.03 (1 H, broad), 1.56 (2 H, m), 1.21 (4 H, m), 0.81 (3 H, t, J = 6.4 Hz); ^{2}H NMR ($CHCl_3$) δ 7.15, 2.03 (2/98); IR (thin film) 2930, 2867, 1663, 1595, 1497, 1377, 702 cm^{-1}; MS *m/z* 206, 150, 107, 93, 84, 77, 49; HRMS, *m/z* Calc for $C_{13}H_{18}DNO$, 206.1529, found, 206.1529.

***N*-(2-Deuteriophenyl)-N-ethylethanamide (17d) and *N*-Ethyl-*N*-phenyl-2-deuterioethanamide (18d).** Compounds **17d** and **18d** were prepared following the standard labeling procedure by using iodide **14d** (58 mg, 0.2 mmol), tributyltin deuteride (133 mg, 0.4 mmol), and AIBN (4 mg, 0.02 mmol). Purification by MPLC afforded **17d** and **18d** (28 mg, 85%): ^{1}H NMR ($CDCl_3$) δ 7.41 (3 H, m), 7.21 (2 H, m), 3.6-4.0 (2 H, m), 1.92 (2 H, s), 0.99 (3 H, t, J = 7.2 Hz); ^{2}H NMR ($CHCl_3$) δ 7.28, 1.92 (8/92); IR (thin film) 2961, 1628, 1593, 1458, 700 cm^{-1}; MS *m/z* 164, 106, 77, 44; HRMS, *m/z* Calc for $C_{10}H_{12}DNO$, 164.1059, found, 164.1059.

***N*-Phenyl-*N*-(3-oxobutyl)-2-deuteropropanamide (18e).** Compound **18e** was prepared following the standard labeling procedure by using iodide **14e** (69.0 mg, 0.2 mmol), tributyltin deuteride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 3.5/1) afforded **18e** (37.0 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 7.39 (3 H, m), 7.16 (2 H, d, J = 7.4 Hz), 3.95 (2 H, t, J = 7.3 Hz), 2.72 (2 H, t, J = 7.3 Hz), 2.14 (3 H, s), 2.00 (1 H, m), 1.00 (3 H, d, J = 7.4 Hz); ^{2}H NMR ($CHCl_3$) δ 2.00; IR (thin film) 2936, 1707, 1653, 1495, 1397, 1259 cm^{-1}; MS *m/z* 220, 177, 163, 150, 120, 106, 77, 58, 43; HRMS, *m/z* Calcd for $C_{13}H_{16}DNO_2$, 220.1322, found, 220.1322.

***N*-Acetyl-2-(2-methylethyl)dihydroindole (25a). (Standard Reduction Procedure):** A solution of iodide **20a** (52.0 mg, 0.16 mmol), tributyltin hydride (106.0 mg, 0.32 mmol), and AIBN (4.0 mg, 0.02 mmol) was heated at 80 °C for 8 hr. Benzene was removed under reduced pressure. The residue was diluted with wet ethyl ether (20 mL), and DBU (0.32 mmol) was added. The ether solution was passed through a small column packed with silical gel and the filtrate was concentrated. Purification by MPLC (Hexane/EtOAc = 7/1) afforded **25a** as a white solid (28.8 mg, 89%): mp 54°-56°C; ^{1}H NMR ($CDCl_3$) δ 8.19 (1 H, d, J = 8.0 Hz), 7.30-7.12 (2 H, m), 7.00 (1 H, m), 4.00 (1 H, m), 3.78 (1 H, dd, J = 4.9, 10.6 Hz), 3.34 (1 H, m), 2.22 (3 H, s), 2.02 (1 H, m), 0.97 (3 H, d, J = 6.8 Hz), 0.79 (3 H, d, J = 6.8 Hz).

cis* and *trans* Ethyl (2-(*N*-Methyl-*N*-phenylcarbamoyl)cyclopentyl)ethanoate (28b-*cis/trans*).** These compounds were prepared following the standard reduction procedure by using iodide **26b** (83.0 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 5/1) gave **28b-*cis (37.0 mg, 64%) and **28b-*trans*** (17.0 mg, 29%): **28b-*cis*:** ^{1}H NMR ($CDCl_3$) δ 7.42 (2 H, m), 7.33 (1 H, m), 7.23 (2 H, d, J = 7.4 Hz), 4.12 (2 H, q, J = 7.1 Hz), 3.23 (3 H, s), 2.76 (1 H, m), 2.55 (1 H, dd, J = 6.3, 15.3 Hz), 2.30 (2 H, m), 1.97 (1 H, m), 1.62–1.90 (3 H, m), 1.35–1.60 (2 H, m), 1.26 (3 H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.30 (q), 23.88 (t), 29.63 (t), 32.42 (t), 36.22 (t), 37.43 (q), 39.09 (d), 42.24 (d), 60.15 (t), 127.44 (d), 127.65 (d), 129.72 (d), 144.40 (s), 173.48 (s), 174.41 (s); IR (thin film) 3061, 2959, 1728, 1651, 1495, 1389, 773 cm^{-1}; MS *m/z* 289, 244, 216, 183, 155, 127, 107, 81, 67, 55; HRMS, *m/z* Calc for $C_{17}H_{23}NO_3$, 289.1678, found, 289.1678; **28b-*trans*:** ^{1}H NMR ($CDCl_3$) δ 7.94 (3 H, m), 7.19 (2 H, m), 4.08 (2 H, q, J = 7.1 Hz), 3.26 (3 H, s), 2.69 (1 H, m), 2.28 (2 H, m), 2.06 (1 H, m), 1.94 (1 H, m), 1.41–1.82 (5 H, m), 1.24 (3 H, t, 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.30 (q), 24.41 (t), 31.45 (t), 32.27 (t), 37.63 (q), 38.98 (t), 40.78 (d), 48.05 (d), 60.26 (t), 127.71 (d), 127.79 (d), 129.76 (d), 144.25 (s), 172.62 (s), 175.40 (s); IR (thin film) 3061, 2961, 1732, 1655, 1497, 1388, 1182, 776 cm^{-1}; MS *m/z* 289, 264, 244, 216, 183, 155, 134, 107, 81, 67, 55; HRMS, *m/z* Calc for $C_{17}H_{23}NO_3$, 289.1678, found, 289.1678.

cis* and *trans*-*N*-Methyl-*N*-phenyl2-Benzylcyclopentanecarboxamide (28c-*cis/trans*).** These were prepared following the standard reduction procedure by using iodide **28c** (84.0 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 8.5/1) gave **28c-*cis (27.5 mg, 47%) and **28c-*trans*** (21.0 mg, 36%): **28c-*cis*:** ^{1}H NMR ($CDCl_3$) δ 7.32 (5 H, m), 7.18 (3 H, m), 6.88 (2 H, d, J = 7.2 Hz), 3.21 (3 H, s), 2.83 (1 H, dd, J = 7.0, 13.8 Hz), 2.69 (2 H, m), 2.08 (2 H, m), 1.82 (1 H, m), 1.80–1.40 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 24.42 (t), 30.25 (t), 32.30 (t), 37.10 (t), 37.30 (t), 44.12 (d), 44.64 (d), 125.76 (d), 127.43 (d), 127.49 (d), 127.27 (d), 128.98 (d), 129.56 (d), 142.01 (s), 144.50 (s), 174.89 (s); IR (thin film) 3025, 2950,1 1653, 1495, 1391, 746 cm^{-1}; MS *m/z* 293, 162, 107, 91, 77; HRMS, *m/z* Calc for $C_{20}H_{23}NO$, 293.1780, found, 293.1780; **28c-*trans*:** ^{1}H NMR ($CDCl_3$) δ 7.35 (3 H, m), 7.19 (3 H, m), 7.19 (2 H, d, J = 7.2 Hz), 7.05 (2 H, d, J = 7.32 Hz), 3.20 (3 H, s), 2.63 (2 H, m), 2.31 (2 H, m), 1.72 (5 H, m), 1.50 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 24.62 (t), 31.83 (t), 32.38 (t), 37.57 (q), 40.76 (t), 45.74 (d), 48.10 (d), 125.81 (d), 127.59 (d) 128.17 (d), 129.01 (d), 129.63 (d), 141.18 (s), 144.28 (s), 176.24 (s); IR (thin film) 3025, 2950, 1653, 1495, 1334, 774 cm^{-1}; MS *m/z* 293, 202, 187, 159, 107, 91, 81, 67, 55; HRMS, *m/z* Calc for $C_{20}H_{23}NO$, 293.1780, found, 293.1780.

***cis* and *trans*-*N*-Methyl-*N*-phenyl-2-ethylcyclopentanecarboxamide (28d-*cis/trans*) and *N*-Methyl-*N*-phenyl-6-octenamide (29d).** These were prepared following the standard reduction procedure

by using iodide **26d** (72.0 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 8.5/1) gave **28d-*cis*** (17.0 mg, 38%), **28-*trans*** (13.7 mg, 25%), and **29d** (8.5 mg, 18%): **28d-*cis*:** ^{1}H NMR ($CDCl_3$) δ 7.41 (2 H, m), 7.33 (1 H, m), 7.15 (2 H, m), 3.25 (3 H, s), 2.72 (1 H, m), 2.01 (1 H, m), 1.86 (1 H, m), 1.71–1.20 (7 H, m), 0.85 (3 H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.25 (q), 24.59 (t), 29.90 (t), 31.48 (t), 37.49 (q), 45.09 (d), 45.26 (d), 24.41 (t), 127.52 (d), 129.69 (d), 144.71 (s), 174.02 (s); IR (thin film) 3036, 2957, 1655, 1495, 1389, 774 cm^{-1}; MS *m/z* 231, 188, 162, 134, 107, 97, 84, 77, 55, 49; HRMS, *m/z* Calc for $C_{15}H_{21}NO$, 231.1623, found, 231.1623; **28d-*tans***: ^{1}H NMR ($CDCl_3$) δ 7.42 (3 H, m), 7.15 (2 H, d, J = 7.4 Hz), 3.27 (3 H, s), 2.19 (2 H, m), 1.94 (1 H, m), 1.71 (3 H, m), 1.50 (1 H, m), 1.30 (1 H, m), 1.02 (2 H, m), 0.80 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 12.73 (q), 24.62 (t), 27.40 (t), 31.68 (t), 31.91 (t), 37.64 (q), 46.66 (d), 48.46 (d), 127.64 (d), 129.72 (d), 144.52 (s), 176.66 (s); IR (thin film) 3050, 2957, 1655, 1595, 1495, 1389, 773; MS *m/z* 231, 202, 162, 125, 107, 97, 77, 55; HRMS, *m/z* Calc for $C_{15}H_{21}NO$, 231.1623, found, 231.1623; **29d:** ^{1}H NMR ($CDCl_3$) δ 7.39 (3 H, m), 7.17 (2 H, d, J = 7.7 Hz), 5.35 (2 H, m), 3.26 (3 H, s), 2.10 (2 H, m), 1.92 (2 H, m), 1.62 (5 H, m), 1.28 (2 H, m); IR (thin film) 3013, 2928, 1661, 1595, 1497, 1385, 773; MS *m/z* 231, 183, 162, 149, 134, 107, 84, 77, 55, 49; HRMS, *m/z* Calc for $C_{15}H_{21}NO$, 231.1623, found, 231.1623.

cis* and *trans* -*N*-Methyl-*N*-phenyl-2-Isopropylcyclopentanecarboxamide (28e-*cis/trans*).** These were prepared following the standard reduction procedure by using iodide **26e** (75.0 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 11/1) gave **28e-*cis (21.5 mg, 44%) and **28e-*trans*** (18.0 mg, 37%): **28e-*cis***: ^{1}H NMR ($CDCl_3$) δ 7.40 (2 H, m), 7.31 (1 H, m), 7.17 (2 H, d, J = 7.3 Hz), 3.23 (3 H, s), 2.73 (1 H, m), 1.9–1.6 (6 H, m), 1.52 (1 H, m), 1.33 (1 H, m), 0.86 (3 H, d, J = 6.6 Hz), 0.78 (3 H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 22.36 (q), 23.00 (q), 24.40 (t), 29.17 (d), 30.64 (t), 31.84 (t), 37.27 (q), 43.25 (d), 53.60 (d), 127.33 (d), 127.39 (d), 129.64 (d), 144.83 (s), 176.08 (s); IR (thin film) 3038, 2953, 2864, 1653, 1495, 1385, 1115 cm^{-1}; MS *m/z* 245, 224, 202, 162, 107, 77, 69, 55; HRMS, *m/z* Calc for $C_{16}H_{23}NO$, 245.1780, found, 245.1780; **28e-*trans***: ^{1}H NMR ($CDCl_3$) δ 7.42 (2 H, m), 7.33 (1 H, m), 7.17 (2 H, m), 3.26 (3 H, s), 2.24 (2 H, m), 1.70 (5 H, m), 1.42 (1 H, m), 1.09 (1 H, m), 0.80 (3 H, d, J = 6.7 Hz), 0.71 (3 H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 20.05 (q), 21.63 (q), 25.17 (t), 29.76 (t), 31.70 (d), 32.67 (t), 37.65 (q), 46.00 (d), 51.09 (d), 127.49 (d), 127.63 (d), 129.69 (d), 144.47 (s), 177.12 (s); IR (thin film) 3040, 2955, 1655, 1595, 1495, 1387, 1119 cm^{-1}; MS *m/z* 245, 230, 202, 162, 134, 107, 77, 69, 55; HRMS, *m/z* Calc for $C_{16}H_{23}NO$, 245.1780, found, 245.1780.

***N*-Methyl-*N*-phenyl-5-isopropyl-2-methylcyclopentanecarboxamide (31 and 32).** These compounds were prepared following the standard reduction procedure by using iodide **30** (77.0 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 10/1) gave **31** and **32**: less polar isomer (21.5 mg, 42%): ^{1}H NMR ($CDCl_3$) δ 7.41 (2 H, m), 7.32 (1 H, m), 7.18 (2 H, m), 3.24 (3 H, s), 2.31 (2 H, m), 2.04 (1 H, m), 1.79 (3 H, s), 1.52 (1 H, m), 1.09 (1 H, m), 0.86 (3 H, d, J = 6.6 Hz), 0.80 (3 H, d, J = 6.4 Hz), 0.79 (3 H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.39 (q), 21.80 (q), 23.14 (q), 29.27 (d), 30.08 (t), 33.45 (t), 37.41 (q), 39.49 (d), 50.98 (d), 51.68 (d), 127.52 (d), 127.61 (d), 129.56 (d), 144.60 (s), 175.56 (s); IR (thin film) 2949, 2863, 1651, 1593, 1495, 956, 700 cm^{-1}, MS *m/z* 259, 176, 153, 134, 125, 107, 81, 77, 69; more polar isomer (22 mg, 42%): ^{1}H NMR ($CDCl_3$) δ 7.39 (2 H, m), 7.31 (1 H, m), 7.17 (2 H, m), 3.28 (3 H, s), 2.23 (2 H, m), 2.03 (1 H, m), 1.81 (1 H, m), 1.64 (1 H, m), 1.49 (1 H, m), 1.24 (1 H, m), 1.05 (1 H, m), 0.81 (6 H, m), 0.56 (3 H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.30 (q), 19.51 (q), 22.12 (q), 25.96 (t), 30.41 (d), 33.64 (t), 37.98 (q), 40.92 (d), 51.86 (d), 53.09 (d), 127.69 (d), 128.30 (d), 129.53 (d), 144.12 (s), 176.57 (s); IR (thin film) 3056, 2953, 1653, 1495, 1385, 773 cm^{-1}; MS *m/z* 259, 176, 153, 125, 107, 83, 69, 55; HRMS, *m/z* Calc for $C_{17}H_{25}NO$, 259.1936, found, 259.1936.

***cis* and *trans* Ethyl (2-Methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)cyclopentane)acetate (34-*cis/trans*).** These compounds were prepared following the standard reduction procedure by using iodide **33** (86 mg, 0.2 mmol), tributyltin hydride (133 mg, 0.4 mmol), and AIBN (4 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 5/1) afforded a cis/trans mixture (48.6 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 7.25 (3 H, m), 7.19 (2 H, m), 4.12 (2 H, m), 3.26 and 3.24 (3 H, s), 3.0-2.4 (1 H, m), 2.26–1.70 (4 H, m), 1.70–1.41 (3 H, m), 1.12–1.05 (4 H, m), 1.02 and 0.82 (3 H, s); IR (thin film) 2970, 2880, 1732, 1638, 1595, 1495, 1356, 704 cm^{-1}; MS *m/z* 303, 258, 230, 216, 197, 169, 123, 107, 95, 81; HRMS, *m/z* Calc for $C_{18}H_{25}NO_3$, 303.1834, found, 303.1834.

***cis* and *trans* *N*-Methyl-*N*-phenyl-*cis*-bicyclo[3.3.0]octane-2-carboxamide (36-exo/endo) and *N*-Methyl-*N*-phenyl-4-(2'-cyclopentenyl)butanamide (37).** These compounds were prepared following the standard reduction procedure by using iodide **35** (74.0 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 11/1) afforded **36**-exo/endo (16.0 mg, 33%), (13.0 mg, 27%), and **27** (10.5 mg, 22%): less polar isomer: ^{1}H NMR ($CDCl_3$) δ 7.38 (3 H, m), 7.20 (2 H, m), 3.24 (3 H, s), 2.56 (1 H, m), 2.19 (1 H, m), 1.92 (2 H, m), 1.86–1.50 (4 H,

m), 1.5–1.0 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 27.37 (t), 27.72 (t), 29.53 (t), 31.32 (t), 34.88 (t), 37.66 (q), 43.28 (d), 45.39 (d), 47.35 (d), 127.67 (d), 129.61 (d), 144.15 (s), 173.92 (s); IR (thin film) 3041, 2945, 2863, 1655, 1595, 1485, 773 cm^{-1}; MS *m/z* 243, 162, 149, 134, 107, 77, 55; HRMS, *m/z* Calc for $C_{16}H_{21}NO$, 243.1623, found, 243.1623; more polar isomer: ^{1}H NMR ($CDCl_3$) δ 7.35 (3 H, m), 7.14 (2 H, m), 3.26 (3 H, m), 2.71 (1 H, m), 2.52 (1 H, m), 2.23 (1 H, m), 1.96 (1 H, m), 1.64 (1 H, m), 1.60–1.32 (3 H, m), 1.3-0.8 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 25.63 (t), 29.76 (t), 32.60 (t), 33.24 (t), 34.27 (t), 37.71 (q), 43.77 (d), 48.68 (d), 49.82 (d), 127.70 (d), 129.71 (d), 144.42 (s), 176.44 (s); IR (thin film) 2942, 2861, 1655, 1595, 1495, 1389, 773 cm^{-1}; MS *m/z* 243, 198, 160, 149, 134, 107, 77, 55; HRMS, *m/z* Calc for $C_{16}H_{21}NO$, 243.1623, found, 243.1623; **37:** ^{1}H NMR ($CDCl_3$) δ 7.36 (3 H, m), 7.15 (2 H, m), 5.64 (1 H, m), 5.58 (1 H, m), 3.26 (3 H, s), 2.53 (1 H, m), 2.27 (2 H, m), 2.06 (2 H, t, *J* = 7.5 Hz), 1.97 (1 H, m), 1.71 (1 H, m), 1.54 (2 H, m), 1.20 (2 H, m); IR (thin film) 3050, 2926, 2849, 1659, 1595, 1497, 1385, 774 cm^{-1}; MS *m/z* 243, 176, 162, 149, 134, 107, 97, 77, 55; HRMS, *m/z* Calc for $C_{16}H_{21}NO$, 243.1623, found, 243.1623.

***N*-Methyl-*N*-phenyl-2-benzylidenecyclopentanecarboxamide (41b) and (42b).** These compounds were prepared following the standard reduction procedure by using iodide **40b** (83.4 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 6.5/1) afforded **41b** (13.0 mg, 22%) and **42b** (17.5 mg, 30%): **41b**: ^{1}H NMR ($CDCl_3$) δ 7.28 (6 H, m), 7.12 (1 H, d, *J* = 7.3 Hz), 6.98 (2 H, d, *J* = 7.2 Hz), 6.48 (1 H, broad), 3.42 (1 H, m), 3.17 (3 H, s), 2.75 (1 H, m), 2.44 (1 H, m), 1.91 (4 H, m); IR (thin film) 3065, 2928, 1651, 1593, 1497, 1392 cm^{-1}; MS *m/z* 291, 200, 184, 157, 134, 115, 107, 91, 77, 57; HRMS, *m/z* Calc for $C_{20}H_{21}NO$, 291.1617, found, 291.1617; **42b**: ^{1}H NMR ($CDCl_3$) δ 7.29 (5 H, m), 7.20 (2 H, m), 6.98 (2 H, m), 3.45 (3 H, s), 2.84 (1 H, m), 2.68(2 H, m), 2.40 (1 H, m), 1.92 (2 H, m), 1.78 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 26.30 (t), 28.06 (t), 32.99 (t), 36.85 (q), 47.87 (d), 122.61 (d), 123.90 (d), 126.98 (d), 127.26 (d), 128.17 (d), 129.76 (d), 129.96 (d), 130.94 (s), 136.52 (s), 140.98 (s), 141.51 (s), 146.65 (s), 172.53 (s); IR (thin film) 2953, 1667, 1489, 1442, 1364, 765 cm^{-1}; MS *m/z* 289, 260, 233, 220, 184, 165, 144, 108, 91, 77, 69; HRMS, *m/z* Calc for $C_{20}H_{19}NO$, 289.1492, found, 289.1492.

***cis* and *trans* 2-Phenyl-3-methyl-5-(*N*-methyl-*N*-phenylcarbamoyl)-bicyclo[3.3.0]oct–1-ene (48a/49a).** These compounds were prepared following the standard reduction procedure by using iodide **47a** (91.4 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 8/1) afforded **48a** and **49a** as a mixture (41.0 mg, 62%): ^{1}H NMR ($CDCl_3$) δ 7.40-7.18 (10 H, m), 3.33 (3 H, s), 2.64 (1 H, dd, *J* = 6.5, 12.8 Hz), 2.38 (2 H, m), 2.19 (1 H, m), 1.94 (3 H, m), 1.52 (2 H, m), 0.99 (3 H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.85 (q), 24.35 (t), 26.38 (t), 38.23 (t), 40.25 (q), 45.71 (t), 46.14 (d), 65.42 (s), 126.14 (d), 127.05 (d), 127.21 (d), 127.86 (d), 128.01 (d), 129.19 (d), 136.99 (s), 137.64 (s), 144.35 (s), 148.44 (s), 176.02 (s); IR (thin film) 3041, 2957, 1651, 1593, 1495, 1367, 756 cm^{-1}; MS *m/z* 331, 287, 197, 169, 155, 134, 115, 105, 91, 77; HRMS, *m/z* Calc for $C_{23}H_{25}NO$, 331.1936, found, 331.1936.

***cis/trans* 2-Phenyl-3-ethyl-5-(*N*-methyl-*N*-phenylcarbamoyl)bicyclo[3.3.0]oct–1-ene (48b/49b).** These compounds were prepared following the standard reduction procedure by using iodide **47b** (94.0 mg, 0.2 mmol), tributyltin hydride (133.0 mg, 0.4 mmol), and AIBN (4.0 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 8/1) afforded **48b** and **49b** as a mixture (49.0 mg, 71%): ^{1}H NMR ($CDCl_3$) δ 7.35 (2 H, m), 7.24 (5 H, m), 7.12 (3 H, m), 3.36 and 3.34 (3 H, s), 2.61 (1 H, m), 2.40 (2 H, m), 2.38-2.08 (2 H, m), 1.90 (2 H, m), 1.60–1.40 (4 H, m), 0.75 (3 H, t, *J* = 7.4 Hz); IR (thin film) 2959, 2872, 1640, 1595, 1495, 1364, 756 cm^{-1}; MS *m/z* 345, 225, 211, 197, 141, 105, 91, 77, 55; HRMS, *m/z* Calc for $C_{24}H_{27}NO$, 345.2093, found, 345.2093.

Tricycle (58). Compound **58** was prepared following the standard reduction procedure by using iodide **54** (97 mg, 0.2 mmol), tributyltin hydride (133 mg, 0.4 mmol), and AIBN (4 mg, 0.02 mmol). Purification by MPLC (hexanes/EtOAc = 8.5/1) gave **58** as a clear oil (25 mg, 35%): ^{1}H NMR ($CDCl_3$) δ 7.23 (8 H, m), 7.09 (2 H, m), 3.77 (1 H, broad), 3.32 (3 H, s), 2.82 (1 H, m), 2.44 (1 H, m), 2.34 (1 H, m), 2.10–1.80 (5 H, m), 1.80–1.40 (6 H, m); ^{13}C NMR ($CDCl_3$) δ 25.81 (t), 26.87 (t), 29.21 (t), 31.35 (t), 32.55 (t), 40.21 (q), 46.75 (d), 56.45 (d), 70.01 (s), 125.98 (d), 126.98 (d), 127.17 (d), 127.69 (d), 127.84 (d), 129.09 (d), 134.08 (s), 136.95 (s), 144.34 (s), 146.75 (s), 176.88 (s); IR (thin film) 2950, 2867, 1637, 1593, 1495, 1358, 756 cm^{-1}; MS *m/z* 357, 269, 223, 167, 141, 119, 91, 77, 55; HRMS, *m/z* Calc for $C_{25}H_{23}NO$, 357.2093, found, 357.2093.

***N*-Methyl-*N*-(4-trifluormethylphenyl)2-benzyl-4-pentenamide (60).** A solution of amide **59** (450.0 mg, 1.04 mmol), allyltributyltin (0.644 ml, 2.08 mmol) and AIBN (17.0 mg, 0.104 mmol) in benzene (3 mL) was refluxed for 24 h. The reaction mixture was diluted with ethyl ether, and treated with DBU/I_2 to remove the tin compound. The crude product was purified by flash chromatography (hexanes/EtOAc = 3/1) to give **60** (160.0 mg, 45%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.44 (2 H, d, *J* = 8.3), 7.32 (3 H, s), 7.02 (2 H, br s), 6.48 (2 H, br s), 5.78-5.55 (1 H, m), 5.61-5.03 (2 H, m), 3.12 (3 H, s), 2.94 (1 H, t, *J* = 9.5 Hz),

2.64-2.41 (3 H, m), 2.22-2.10 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.07, 146.71, 139.76, 135.48, 129.30, 129.18, 128.46, 128.47, 126.51, 126.43, 121.96, 117.33, 45.32, 39.56, 37.98, 37.20, 0.07.

Hydrolysis of Anilides

2-Benzyl-4-pentenoic acid (61). A solution of amide **60** (94.0 mg, 0.271 mmol) and KOH (174.0 mg, 8.13 mmol) in DMSO (6 mL) and H_2O (3 mL) was stirred for 3 days at 25 °C. The reaction mixture was acidified with 10% HCl at 0 °C, and extracted with ethyl ether. Purification by flash chromatography gave the acid **61** (42.0 mg, 83%): ^1H NMR ($CDCl_3$) δ 7.46-7.15 (5 H, m), 5.83-3.61 (1 H, m), 5.17-5.02 (2 H, m), 3.08-2.92 (1 H, m), 2.86-2.70 (2 H, m), 2.49-2.26 (2 H, m).

2-Benzyl-4-pentenol (62). To a solution of $LiAlH_4$ (30 mg, 0.762 mmol) in THF (5 mL) at –10 °C was added a solution of amide **60** (22 mg, 0.0635 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h, quenched with water (1 mL) and 10% NaOH (1 mL), and stirred for 3 h at 25 °C. The mixture was filtered to remove the salt, and then diluted with ethyl ether. The ether layer was washed with water and brine, and dried over $MgSO_4$. Purification by flash chromatography (hexanes/EtOAc = 3/1) gave **62** (8.6 mg, 78%): ^1H NMR ($CDCl_3$) δ 7.35-7.12 (5 H, m) 5.14-5.01 (2 H, m), 3.52 (2 H, d, J = 4.2 H), 2.71-2.54 (2 H, m), 2.12 (2 H, t, J = 6.3 Hz), 2.03-1.96 (1 H, m), 1.57 (1 H, br s).

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