Palladium-Catalyzed Cross-Coupling of 2,5-Cyclohexadienyl-Substituted Aryl or Vinylic Iodides and Carbon or Heteroatom Nucleophiles

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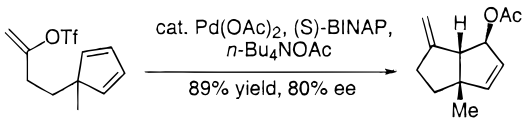
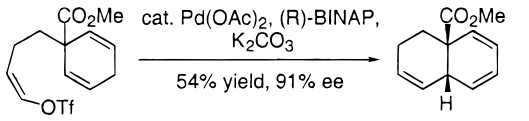
2,5-Cyclohexadienyl-substituted aryl or vinylic iodides have been reacted with carbon nucleophiles (diethyl malonate and 2-methyl-1,3-cyclohexanedione), nitrogen nucleophiles (morpholine, potassium phthalimide, *N*-benzyl tosylamide, di-*tert*-butyl iminodicarboxylate, lithium azide, and anilines), a sulfur nucleophile (sodium benzenesulfinate), and oxygen nucleophiles (lithium acetate and phenols) to afford products of cyclization and subsequent cross-coupling in good to excellent yields. In most cases, this process is highly diastereoselective. The reaction is believed to proceed via (1) oxidative addition of the aryl or vinylic iodide to Pd(0), (2) organopalladium addition to one of the carbon−carbon double bonds, (3) palladium migration along the carbon chain on the same face of the ring to form a π-allylpalladium intermediate, and (4) nucleophilic displacement of the palladium.

Introduction

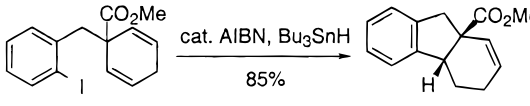
The intramolecular Heck reaction has been extensively used in the construction of polycyclic compounds and in the synthesis of natural products.[1] Shibasaki et al.[2] have reported asymmetric Heck reactions of conjugated dienyl-substituted vinylic triflates (eq 1) and 2,5-cyclohexadienyl-substituted vinylic triflates and iodides (eq 2). The radical ring-closure reactions of 2,5-cyclohexadienyl-substituted aryl iodides or vinylic bromides have been reported by Beckwith et al. (eq 3).[3] This methodology has proven to be a powerful tool for the rapid construction of polycyclic compounds.



(1)

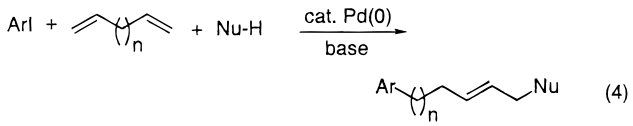


(2)



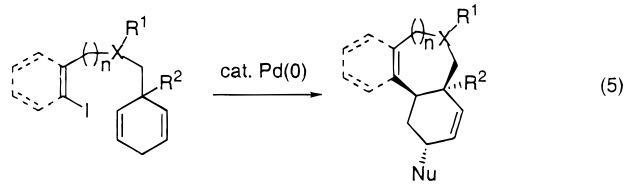
(3)

We have previously discovered that aryl halides, nonconjugated dienes, and carbon nucleophiles,[4] amines,[5] or heteroatom nucleophiles[6] can be coupled in high yields using $Pd(dba)_2$ as a catalyst (eq 4). We envisioned that if

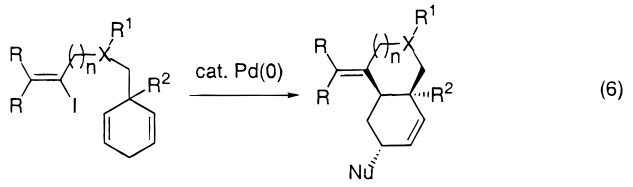


(4)

aryl or vinylic iodides and dienyl moieties were present in the same molecule, the reactions of the resulting dienyl-substituted aryl or vinylic iodides with external nucleophiles in the presence of a Pd(0) catalyst might afford very useful, highly functionalized polycyclic compounds (eqs 5 and 6).[7]



(5)



(6)

Results and Discussion

The starting materials were efficiently prepared by standard methodology. For example, aryl iodides **1**−**7** were prepared by the reactions shown in Scheme 1.

(1) (a) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447. (b) Negishi, E. I.; Coperet, C.; Ma, S.; Liou, S.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (c) Heumann, A.; Reglier, M. *Tetrahedron* **1996**, *52*, 9289. (d) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1996; Vol. 5, pp 153−260. (e) Tsuji, J. *Palladium Reagents and Catalysts − Innovations in Organic Synthesis*; Wiley: New York, 1995. (f) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(2) (a) Shibasaki, M. In *Advances in Organic-Metal Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1996; Vol. 5, pp 119−151. (b) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4219. (c) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.

(3) Beckwith, A. L.; O'Shea, D. M.; Roberts, D. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1445.

(4) Larock, R. C.; Lu, Y. D.; Bain, A. C. *J. Org. Chem.* **1991**, *56*, 4589.

(5) Larock, R. C.; Wang, Y., Lu, Y. D.; Russell, C. E. *J. Org. Chem.* **1995**, *59*, 8107.

(6) Larock, R. C.; Wang, Y.; Lu, Y. D., work in progress.

(7) For a preliminary communication of this work, see: Han, X.; Larock, R. C. *Synlett*, in press.

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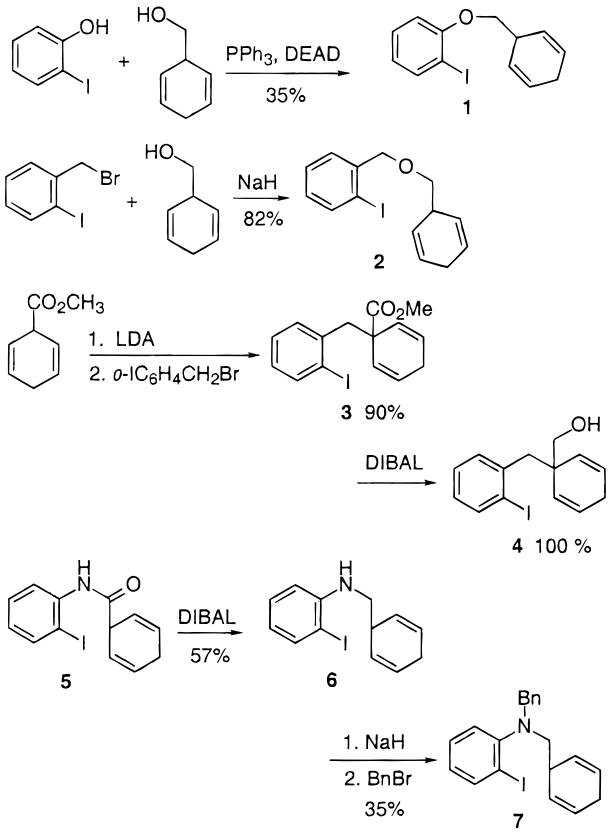
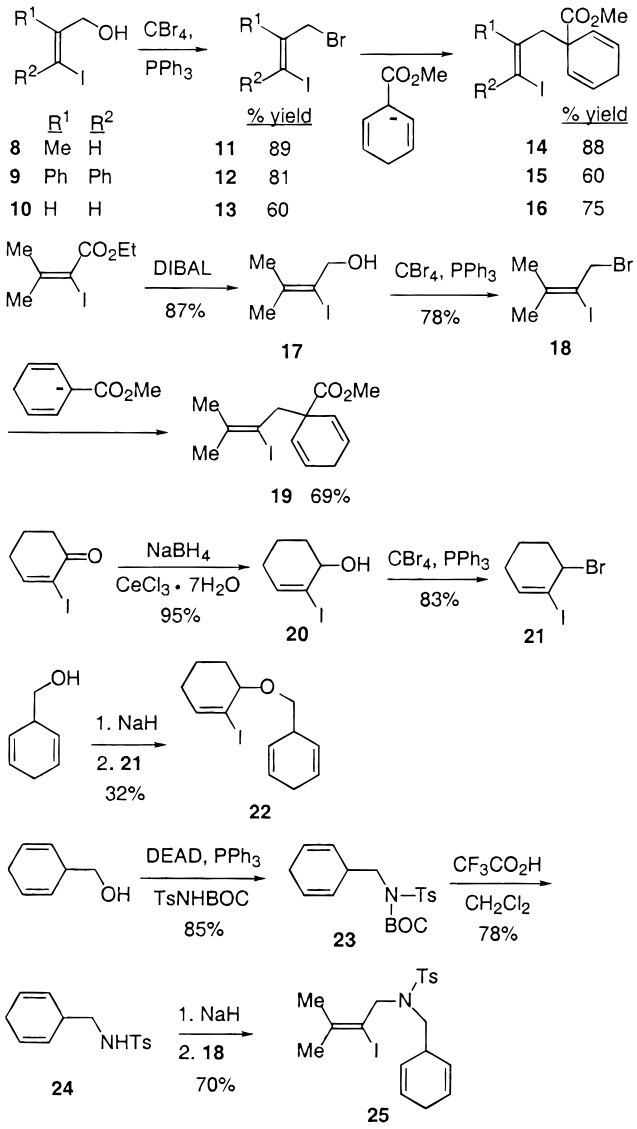
Published on Web 02/25/1999

Scheme 1



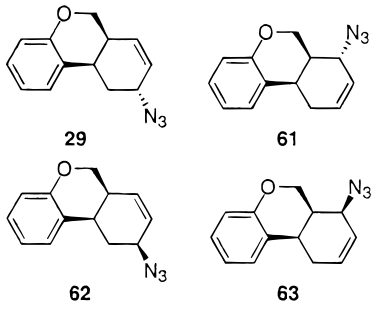
Scheme 2



Vinylic iodides **14**−**16**, **19**, **22**, and **25** were synthesized by the reactions shown in Scheme 2.

The reaction of a variety of carbon, nitrogen, oxygen, and sulfur nucleophiles[8,9] with aryl iodide **1** was carried out under conditions similar to our previous intermolecular versions of this chemistry.[4−6] Minimal efforts were made to optimize each reaction. The results are summarized in Table 1, entries 1−14. Carbon nucleophiles were observed to give good yields after some modification of our earlier reported reaction conditions (entries 1 and 2).

Nitrogen nucleophiles have also proven quite successful. The yield of the reaction of iodide **1** with morpholine could be increased from 31% to 91% by switching to DMSO as the solvent in the presence of 2 equiv of Na_2CO_3 (entries 3 and 4). The yield of the reaction of **1** with azide could also be improved from 36% using 1.5 equiv of NaN_3 to 51% using 2 equiv of LiN_3 (entries 5 and 6). The formation of a mixture of regioisomers (**29** vs **61** and **62** vs **63**) in this reaction might be due to the azide anion



undergoing backside attack on the π-allylpalladium intermediate at both ends of the allylic system and/or [3,3]-sigmatropic rearrangement of the allyl azide.[10,11] The formation of a mixture of stereoisomers (**29** vs **62**

(8) For recent reviews of nucleophilic attack on π-allylpalladium species, see: (a) Moreno-Manas, M.; Pleixats, R. *Adv. Heterocycl. Chem.* **1996**, *66*, 73. (b) Trost, B. M. *Pure Appl. Chem.* **1996**, *68*, 779. (c) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975. (d) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 585.

(9) For the nucleophiles used in this study, see refs 4 and 5. See also: stabilized carbanion (a) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649. Amines (b) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826. (c) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388. Azides (d) Murahashi, S. I.; Tanigawa, Y.; Imada, Y.; Taniquchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227. Di-*tert*-butyl iminodicarboxylate (e) Connel, R. D.; Rein, T.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845. Potassium phthalimide (f) Inoue, Y.; Taquchi, M.; Toyofuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3021. Lithium acetate (g) Bäckvall, J. E. *Pure Appl. Chem.* **1996**, *68*, 535. Phenols (h) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615. (i) Deardorff, D. R. *J. Org. Chem.* **1988**, *53*, 189. (j) Deardorff, D. R.; Linde, R. G.; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759. Sodium benzenesulfinate (k) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662 and references therein.

(10) Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36*, 8737.

(11) (a) Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1997**, *62*, 4665. (b) Murahashi, S. T.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.

Table 1. Palladium-Catalyzed Cross-Coupling of 2,5-Cyclohexadienyl-Substituted Aryl and Vinylic Iodides with Various Nucleophiles[a]

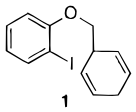
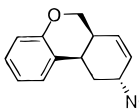
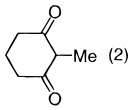
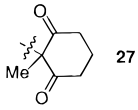
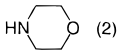
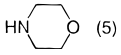
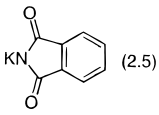
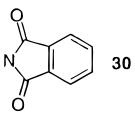
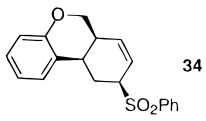
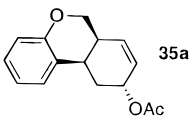
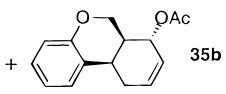
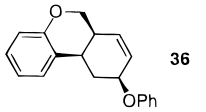
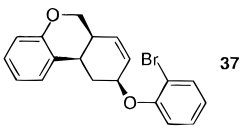
entry	iodide	nucleophile (equiv)	Cl^- (equiv), base (equiv), time (h)	product(s)[b] Nu =	% isolated yield (isomer ratio)[c]
	 **1**			 Nu	
1		$CH_2(CO_2Et)_2$ (2)	TBAC[d] (1.1), K_2CO_3 (2.5), 4	$CH(CO_2Et)_2$ **26**	72
2		 (2)	TBAC(1.1), $NaHCO_3$ (2.5), 20	 **27**	55
3		 (2)	TBAC (2), 20	 **28**	31 (58)[e]
4		 (5)	TBAC (2), Na_2CO_3 (2), 36	**28**	91
5		NaN_3 (1.5)	LiCl (1), 20	N_3 **29** + isomers	36 (80:10:5:5)
6		LiN_3 (2)	LiCl (1), 15	**29** + isomers	51[f] (80:10:5:5)
7		 (2.5)	LiCl (2), 18	 **30**	31
8		$TsNHCH_2Ph$ (2)	TBAC (2), Na_2CO_3 (2), 42	$N(Ts)CH_2Ph$ **31**	60
9		$HN(CO_2{}^tBu)_2$ (5)	TBAC (2), Na_2CO_3 (2), 16	$N(CO_2Bu^t)_2$ **32**	52[g]
10		$PhNH_2$ (5)	TBAC (2), Na_2CO_3 (2), 16	NHPh **33**	90
11		$PhSO_2Na$ (3)	TBAC (1) LiCl (1.5), 24	 **34**	62
12		$LiOAc{\bullet}2H_2O$ (3)	TBAC (1), LiCl (1.5), 15	 **35a** +  **35b**	80[h] (10:1)
13		PhOH (3)	TBAC (1.1), $NaHCO_3$ (2.5), 15	 **36**	62
14		*o*-BrC_6H_4OH (3)	TBAC (1.1), $NaHCO_3$ (2.5), 16	 **37**	59

Table 1 (Continued)

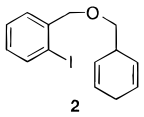
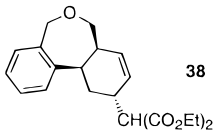
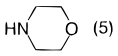
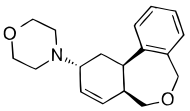
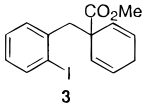
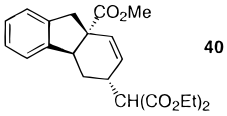
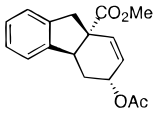
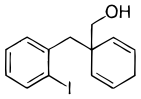
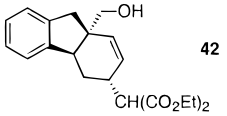
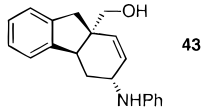
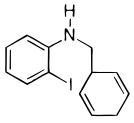
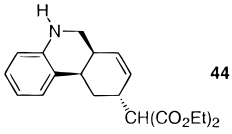
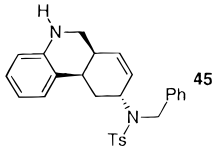
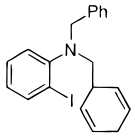
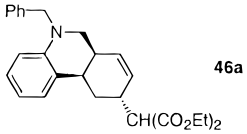
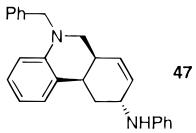
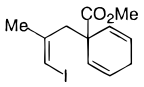
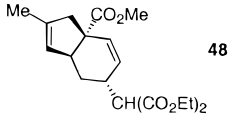
entry	iodide	nucleophile (equiv)	Cl^- (equiv), base (equiv), time (h)	product(s)[b] Nu =	% isolated yield (isomer ratio)[c]
15	 **2**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 28	 **38** + isomers	60 (66:13:14:7)
16		 (5)	TBAC (2), Na_2CO_3 (2), 24	 **39**	52
17	 **3**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 27	 **40**	80
18		$LiOAc•2H_2O$ (3)	TBAC (1), LiCl (1.5), 26	 **41**	67
19	 **4**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 24	 **42**	69
20		$PhNH_2$ (5)	TBAC (2), Na_2CO_3 (2), 24	 **43**	100
21	 **6**	$CH_2(CO_2Et)_2$ (3)	TBAC (1.1), K_2CO_3 (2.5), 24	 **44**	19 (26)[e]
22		$TsNHCH_2Ph$ (2)	TBAC (2), Na_2CO_3 (2), 24	 **45**	39
23	 **7**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 24	 **46a** + **46b**	64 (75:25)
24		$PhNH_2$ (5)	TBAC (2), Na_2CO_3 (2), 24	 **47**	59
25	 **14**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 22	 **48**	65

Table 1 (Continued)

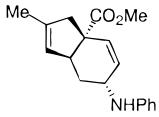
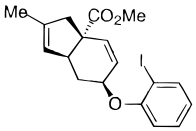
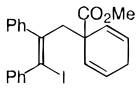
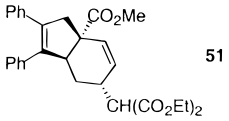
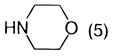
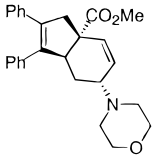
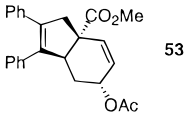
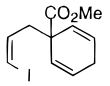
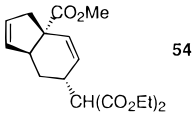
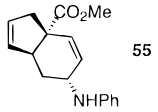
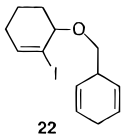
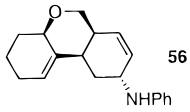
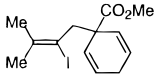
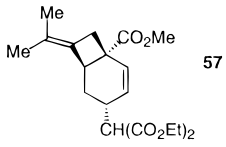
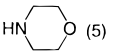
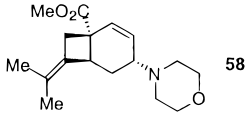
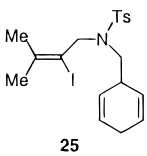
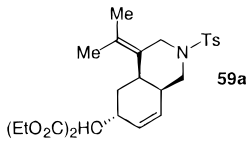
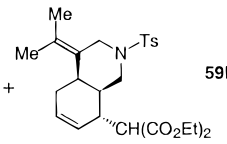
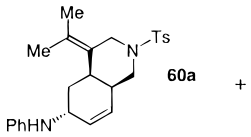
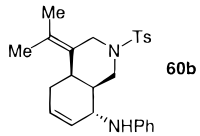
entry	iodide	nucleophile (equiv)	Cl^- (equiv), base (equiv), time (h)	product(s)[b] Nu =	% isolated yield (isomer ratio)[c]
26		$PhNH_2$ (5)	TBAC (2), Na_2CO_3 (2), 18	 **49**	79
27		*o*-IC_6H_4OH (3)	TBAC (1.1), $NaHCO_3$ (2.5), 23	 **50**	51
28	 **15**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 23	 **51**	80
29		 (5)	TBAC (2), Na_2CO_3 (2), 23	 **52**	78
30		$LiOAc•2H_2O$ (3)	TBAC (1), LiCl (1.5), 26	 **53**	50
31	 **16**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 22	 **54**	70
32		$PhNH_2$ (5)	TBAC (2), Na_2CO_3 (2), 22	 **55**	62
33	 **22**	$PhNH_2$ (5)	TBAC (2), Na_2CO_3 (2), 17	 **56**	62
34	 **19**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1), K_2CO_3 (2.5), 16	 **57**	70
35		 (5)	TBAC (2), Na_2CO_3 (2), 16	 **58**	54
36	 **25**	$CH_2(CO_2Et)_2$ (2)	TBAC (1.1) K_2CO_3 (2.5), 22	 **59a** +  **59b**	61 (60:40)

Table 1 (Continued)

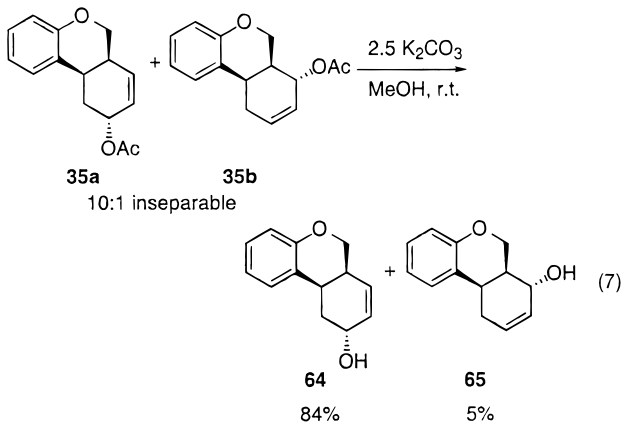
entry	iodide	nucleophile (equiv)	Cl^- (equiv), base (equiv), time (h)	product(s)[b] Nu =	% isolated yield (isomer ratio)[c]
37		$PhNH_2$ (5)	TBAC (2), Na_2CO_3 (2), 22	 **60a** +  **60b**	71 (62:38)

[a] All of the reactions were run in the presence of 10 mol % of $Pd(dba)_2$, 2 mL of DMSO (except entry 2, 5 mL of DMSO; entry 3, 5 mL of DMF; entries 8 and 22, 2 mL of DMF) at 100 °C (except entries 1, 17, 19, and 21, 80 °C). [b] For the assignment of the structures of these compounds, see the text and Supporting Information. In entries 5, 6, and 15, only the major isomer is shown. [c] Isomer ratios were determined by ^1H NMR or GC−MS. [d] TBAC = tetra-*n*-butylammonium chloride. [e] The yields are based on the recovery of starting materials. [f] The product has the same or a very similar ^1H NMR spectrum to that of entry 5. [g] After flash chromatography, an inseparable mixture of the product and 1,5-diphenyl-1,4-pentadien-3-one (dba) was obtained. The pure product was obtained after chromatography on a basic alumina column. [h] The reaction afforded an inseparable mixture of two isomers in the ratio of 10:1. Both isomers were obtained in pure form after hydrolysis of the acetate to the corresponding alcohols.

and **61** vs **63**) may result from the palladium-mediated isomerization of the intermediate π-allylpalladium species or a combination of frontside and backside displacement of palladium by azide.[11] Although allylic azides can be readily reduced to allylic amines, which are versatile intermediates in organic synthesis, the poor selectivity of this reaction prompted us to search for other protected primary amine derivatives to employ as nucleophiles. When potassium phthalimide (entry 7), *N*-benzyl tosylamide (entry 8), or di-*tert*-butyl iminodicarboxylate (entry 9) were used as nucleophiles, the desired products **30**−**32** were formed each as a single diastereoisomer in 31%, 60%, or 52% yields, respectively. Compounds **31** and **32**[9e] should be readily converted to the corresponding allylic amines under mild conditions. Aniline was chosen as a nucleophile, because allylic anilines can be employed in the 3-aza-Cope rearrangement,[12] and the initial product could potentially prove useful in further intramolecular Heck-type processes. Thus, the reaction of aryl iodide **1** and aniline afforded compound **33** as a single diastereoisomer in 90% yield (entry 10).

Allylic sulfones are versatile intermediates in organic synthesis, because sulfones can convert the adjacent carbon into either a nucleophilic or an electrophilic center.[9k] Allylic sulfones can be prepared by π-allylpalladium displacement processes.[9k] Thus, allylic sulfone **34** was produced in 62% yield as a single diastereoisomer when sodium benzenesulfinate was used as the nucleophile (entry 11).

Allylic alcohols and acetates are also versatile intermediates in organic synthesis. The reaction of aryl iodide **1** with 3 equiv of lithium acetate afforded an inseparable 10:1 mixture of two regioisomers in 80% yield in the presence of 1 equiv of TBAC and 1.5 equiv of LiCl in 2 mL of DMSO at 100 °C for 15 h (entry 12). When the above reaction was run for 5 or 32 h under otherwise the same conditions, compound **35** was produced in 74% or 76% isolated yields as an inseparable mixture of the same two regioisomers in the same 10:1 ratio. This suggests that the distribution of products is controlled by thermodynamics and this whole process is finished in less than 5 h. Saponification (K_2CO_3/MeOH) of the inseparable mixture (**35a** and **35b**) afforded two readily separable alcohols **64** (84% yield) and **65** (5% yield) (eq 7).



35a **35b** 10:1 inseparable

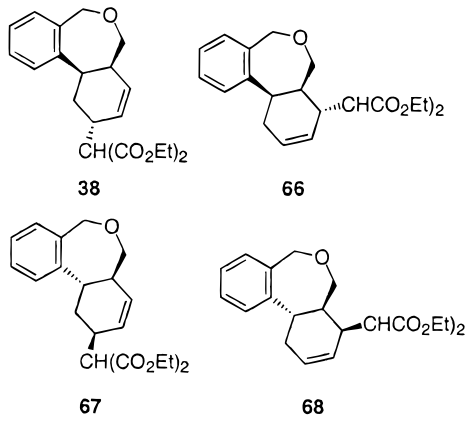
64 84% **65** 5% (7)

Because of the usefulness of allylic phenyl ethers in the Claisen rearrangement[12] and, more importantly, the potential tandem Heck reaction of the products obtained when 2-halophenols are used as the nucleophiles, phenol and 2-bromophenol were reacted with aryl iodide **1** to afford the desired products **36** and **37** as single diastereoisomers in 62% and 59% yields, respectively.

All of the nucleophiles so far discussed, except lithium azide and acetate, which are well known for their poor selectivities in π-allylpalladium chemistry,[13] react with aryl iodide **1** to form the desired products as single diastereoisomers. However, when aryl iodide **2** was reacted with diethylmalonate, an inseparable mixture of four isomers (**38**, **66**, **67**, and **68**) in the ratio of 66:13:14:7 was obtained in 60% yield (entry 15). Compounds **38** and **66** (with cis ring fusion between rings B and C) were no doubt formed by cis addition of the arylpalladium intermediate to one of the carbon−carbon double bonds

(12) (a) Blechert, S. *Synthesis* **1989**, 71. (b) Moody, C. J. *Adv. Heterocycl. Chem.* **1987**, *42*, 203. (c) Przheval'skii, N. M.; Grandberg, II. *Russ. Chem. Rev.* **1987**, *56*, 477.

(13) (a) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451. (b) Trost, B. M. Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

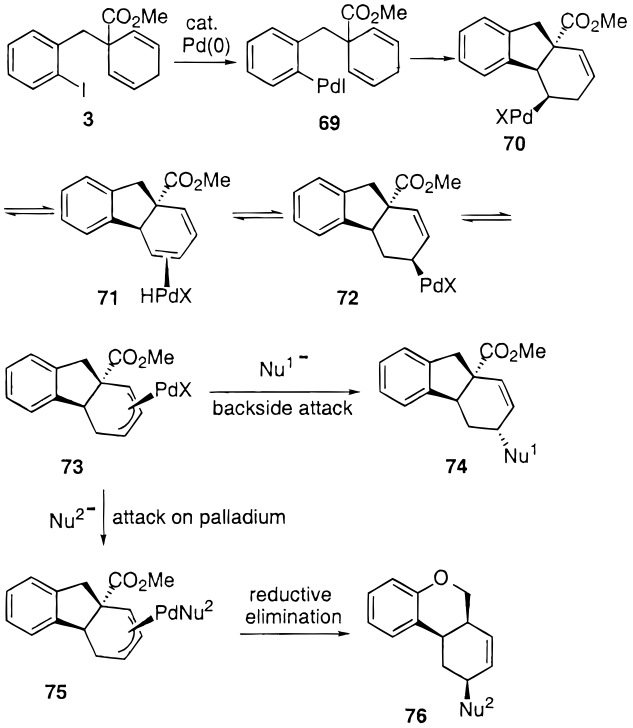


from the top face of the ring, followed by migration and subsequent backside nucleophilic attack on both ends of the π-allylpalladium intermediate. Similarly, compounds **67** and **68** (with trans ring fusion between rings B and C) were probably formed by cis addition of the arylpalladium to one of the carbon−carbon double bonds from the bottom face of the ring. The poor regioselectivity of the subsequent nucleophilic substitution of palladium can be attributed to the greater flexibility present in the 6,7,6-tricyclic ring of the π-allylpalladium intermediate. However, when morpholine was used as the nucleophile, the desired product was formed as a single diastereoisomer (entry 16). From the results of entries 15/16 and 23/24 we can see that amine nucleophiles (morpholine in entry 16 and aniline in entry 24) are more diastereoselective than diethylmalonate. It appears that these nitrogen nucleophiles are more sensitive to the steric hindrance present in the π-allylpalladium intermediate, but the reason for this is not clear.

Ester and alcohol functionalities can be tolerated in the starting aryl iodides employed in this reaction. For example, aryl iodides **3** and **4** were successfully reacted with carbon and heteroatom nucleophiles to give the desired products as single diastereoisomers in good to excellent yields (entries 17−20). The reaction of ester **3** with $LiOAc{\cdot}2H_2O$ afforded compound **41** as a single diastereoisomer in 67% yield (compare entries 12 and 18). The improved selectivity is presumably due to the increased steric hindrance toward backside nucleophilic attack present at the other end of the π-allylpalladium intermediate (see Scheme 3, intermediate **73**).

Because nitrogen-containing moieties are often present in naturally occurring compounds, it was desirable to establish if this process would work for substrates with a free NH group. Reactions of amide-containing aryl iodide **5** with diethyl malonate or morpholine gave none of the desired products, probably as a result of the presence of a relatively acidic amide hydrogen. The reaction of the secondary amine-containing aryl iodide **6** with diethyl malonate (entry 21) and *N*-benzyl tosylamide (entry 22) gave the desired products as single diastereoisomers in low yields, whereas aniline gave only a trace amount of the desired product. However, after protection of the problematic amine hydrogen in aryl iodide **6** by a benzyl group, the desired product was formed in 64% yield as a 75:25 inseparable mixture of two regioisomers (entry 23) when diethyl malonate was reacted with aryl iodide **7** and in 59% yield as a single diastereoisomer (entry 24) when aryl iodide **7** was reacted with aniline. The poor regioselectivity of the reaction in entry 23 might

Scheme 3



HNu^1 = diethyl malonate, 2-methyl-1,3-cyclohexanedione, morpholine, potassium phthalimide, *N*-benzyl tosylamide, di-*tert*-butyl iminodicarboxylate, lithium azide, anilines, and lithium acetate.

HNu^2 = phenols and sodium benzenesulfinate

be attributed to the conformational mobility present in the π-allylpalladium intermediate brought about by the benzyl side chain.

Although vinylic halides have not previously been employed in intermolecular versions of our migration chemistry because of the concern that the initial homoallylic palladium intermediate might migrate palladium back toward the carbon−carbon double bond originating in the vinylic moiety,[14] it appeared that the cyclic dienes employed here might circumvent this difficulty and afford unsaturated polycyclic products of considerable utility in natural product synthesis. To test this hypothesis, vinylic iodides **14**−**16**, **19**, **22**, and **25** were allowed to react with various nucleophiles. Indeed, vinylic iodides can be employed in this process, and the results are summarized in Table 1, entries 25−37.

The following observations can be made regarding these results. Vinylic iodide **14** afforded the desired products in good yields as single diastereoisomers (entries 25−27). Vinylic iodide **15**, with a phenyl group adjacent to the iodide, also afforded the desired products in good yields as single diastereoisomers (entries 28−30). When vinylic iodide **15** was reacted with lithium acetate, compound **53** was formed in 50% yield as a single diastereoisomer (compare this with entries 12 and 18). Most interestingly, vinylic iodide **16** with a hydrogen beta to the iodide also afforded the desired products in good yields as single diastereoisomers (entries 31 and 32). Vinylic iodide **22** afforded the anticipated product **56** in

(14) (a) Larock, R. C.; Mitchell, M. A. *J. Am. Chem. Soc.* **1976**, *98*, 6718. (b) Larock, R. C.; Mitchell, M. A. *J. Am. Chem. Soc.* **1978**, *100*, 180. (c) Larock, R. C.; Takagi, K.; Hershberger, S. S.; Mitchell, M. A. *Tetrahedron Lett.* **1981**, *22*, 5231.

62% yield as a single diastereoisomer when aniline was used as the nucleophile (entry 33).

Compounds **57** and **58** were produced in 70% and 54% yields as single diastereoisomers when vinylic iodide **19** was reacted with diethyl malonate or morpholine, respectively (entries 34 and 35). It is indeed interesting that the four-membered ring can be formed here, because we have shown previously that cyclobutylcarbinyl palladium compounds readily ring open and rearrange to π-allylpalladium intermediates.[15] Compounds **59** and **60** are formed in 61% or 71% yields as inseparable mixtures of two isomers in the ratios 60:40 and 62:38, respectively, when vinylic iodide **25** was reacted with diethyl malonate or aniline (entries 36 and 37). The poor selectivity in these reactions could possibly be due to conformational effects present in the π-allylpalladium intermediate introduced by the presence of a tosyl group.

The structures of our cyclization products have been elucidated by careful examination of their COSY, HMQC, and NOESY spectra. These data are summarized and discussed in the Supporting Information. The NOESY spectral studies indicate that carbon nucleophiles (diethyl malonate and 2-methyl-1,3-cyclohexanedione), anilines, and lithium acetate give backside attack on the π-allylpalladium intermediate, whereas sodium benzenesulfinate and phenols afford products of frontside attack. The stereochemistry of the rest of the compounds were assigned on the basis of the assumption that soft nucleophiles give backside nucleophilic substitution, and hard nucleophiles attack at palladium in the π-allylpalladium intermediates and undergo reductive elimination. The above assignment of hardness or softness to a specific nucleophile is in agreement with literature data.[6,9]

This overall coupling process likely proceeds according to the pathway illustrated in Scheme 3 (exemplified using iodide **3**). Generation and addition of an aryl- or vinylpalladium intermediate to the internal carbon−carbon double bond, followed by migration of palladium along the carbon chain on the same face of the ring, results in the formation of a π-allylpalladium species (**73**). Intermediate **73** undergoes backside intermolecular nucleophilic attack to afford products when soft nucleophiles, such as diethyl malonate, 2-methyl-1,3-cyclohexanedione, morpholine, potassium phthalimide, *N*-benzyl tosylamide, di-*tert*-butyl iminodicarboxylate, lithium azide, anilines, and lithium acetate, are used. However, hard nucleophiles, such as phenols and sodium benzenesulfinate, first attack on the palladium to form intermediate **75**, which subsequently undergoes reductive elimination to afford products of the type **76**. The observed regioselectivities of this process are in agreement with literature observations that the regioselectivity of nucleophilic attack on the π-allylpalladium intermediates depends greatly on very small steric differences that exist at the two termini of the allylic system and that nucleophiles other than organometallics attack at the less hindered terminus.[6,16] For some nucleophiles, such as lithium acetate and diethylmalonate, larger steric differences at the two termini of the allylic system are needed to afford the desired products as single diastereoisomers.

From the above results, we can conclude that not only aryl iodides but also vinylic iodides (even those which contain a hydrogen beta to palladium) afford the desired products in good yields, usually as single diastereoisomers. In addition, nucleophiles as diverse as morpholine, potassium phthalimide, *N*-benzyl tosylamide, di-*tert*-butyliminodicarboxylate, anilines, and phenols give the desired products as single diastereoisomers in most cases. Nucleophiles, such as diethyl malonate, usually give the desired products as single diastereoisomers, unless certain substrates were used (entries 15, 23, and 36). Nucleophiles, such as lithium azide and acetate, usually give the desired products as inseparable mixtures of at least two isomers (entries 5, 6, and 12). However, some substrates in which one end of the π-allylpalladium intermediate is much more sterically hindered than the other end afford the desired products as single diastereoisomers (entries 18 and 30).

This work presents a novel method for the highly diastereoselective synthesis of polycyclic compounds containing allylic functional groups and nicely complements the recent intramolecular asymmetric Heck chemistry of Shibasaki, in which beta hydride elimination, rather than palladium migration, is observed. The facile preparation of starting materials, good to excellent chemical yields, and high diastereoselectivity of this process suggest that this chemistry should find wide application in the total synthesis of naturally occurring compounds.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 and 75.5 or 100 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F) and was visualized with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O].

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous TBAC was purchased from Lancaster. Palladium chloride was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. $Pd(dba)_2$ was synthesized by a literature procedure.[17] The preparation of all starting materials is provided in the Supporting Information.

General Procedure for the Palladium-Catalyzed Reactions. $Pd(dba)_2$ (14.4 mg, 0.025 mmol), TBAC (or LiCl), base, nucleophile, organic iodide (0.25 mmol), and solvent (DMSO or DMF) were added accordingly to an Ar-flushed 2 dram vial. The vial was flushed with Ar for 2 min and heated in an oil bath at the indicated temperature for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with brine solution, dried over anhydrous Na_2SO_4, and decanted. The solvent was evaporated in vacuo, and the product was isolated by flash chromatography (EtOAc/hexanes) on a silica gel column. The following compounds were prepared by the above procedure, and the results are summarized in Table 1.

Compound 26 (entry 1). The reaction mixture was chromatographed using 1:12 EtOAc/hexanes to yield a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.83 (dt, J = 14.0, 4.0 Hz, 1H), 2.06 (m, 1H), 2.69 (m, 1H), 2.88 (m, 1H), 3.10 (m, 1H), 3.45 (d, J = 10.0 Hz, 1H), 3.87 (dd, J = 10.8, 8.4, 1H), 4.12 (dd, J = 11.2, 3.6 Hz, 1H), 4.22 (q, J = 6.8 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 5.74 (dq, J = 10.0, 1.6 Hz, 1H), 5.85 (dq, J = 10.0, 2.0 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.91 (td, J = 7.6, 1.2 Hz, 1H), 7.10

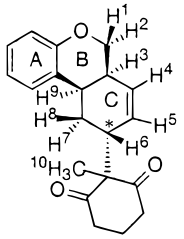
(15) (a) Larock, R. C.; Song, H. *Bull. Korean Chem. Soc.* **1996**, *17*, 877. (b) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529. (c) Larock, R. C.; Song, H.; Kim, S.; Jacobson, R. A. *J. Chem. Soc., Chem. Commun.* **1987**, 834. (d) Larock, R. C.; Varaprath, S. *J. Org. Chem.* **1984**, *49*, 3432.

(16) Keinan, E.; Sahai, M. *J. Chem. Soc., Chem. Commun.* **1984**, 648.

(17) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

(td, J = 8.0, 1.2 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 30.0, 31.0, 33.0, 33.7, 56.5, 61.4, 61.5, 66.5, 116.8, 120.8, 124.8, 127.4, 128.0, 129.0, 130.8, 154.7, 168.1, 168.2; IR ($CHCl_3$) 1748, 1727 cm^{-1}; HRMS for $C_{20}H_{24}O_5$ calcd 344.1624, found 344.1628.

Compound 27 (entry 2).



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The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a white solid: mp 152−153 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 3H, H^{10}), 1.59−1.73 (m, 1H), 1.77 (td, J = 10.0, 3.6 Hz, 1H, H^7), 1.93 (dt, J = 14.1, 5.7 Hz, 1H, H^8), 1.98−2.07 (m, 1H), 2.48 (dt, J = 15.3, 3.9 Hz, 1H, H^6), 2.58−2.69 (m, 5H, 4H + H^3), 3.31 (dd, J = 9.3, 5.1 Hz, 1H, H^9), 4.06 (dd, J = 10.8, 2.2 Hz, 1H, H^2), 4.15 (dd, J = 10.8, 3.4 Hz, 1H, H^1), 5.38 (dd, J = 3.6, 1.2 Hz, 1H, H^5), 5.80 (dt, J = 10.2, 2.1 Hz, 1H, H^4), 6.80 (dd, J = 8.1, 1.2 Hz, 1H), 6.93 (td, J = 7.5, 1.2 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.2, 18.1, 27.7, 31.3, 33.9, 37.3, 37.5, 37.8, 68.3, 70.0, 117.1, 121.1, 123.5, 127.1, 127.5, 127.7, 130.5, 155.2, 208.78, 208.86; IR ($CHCl_3$) 1726, 1692 cm^{-1}; HRMS for $C_{20}H_{22}O_3$ calcd 310.1569, found 310.1578. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.03; H, 7.39.

Compound 28 (entries 3 and 4). The reaction mixture was chromatographed using straight EtOAc to yield a white solid: mp 115−116.5 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.94−2.13 (m, 2H), 2.55−2.73 (m, 5H), 2.87−2.91 (m, 1H), 3.30 (quintet, J = 4.5 Hz, 1H), 3.73 (t, J = 4.5 Hz, 4H), 3.95 (dd, J = 10.8, 7.2 Hz, 1H), 4.10 (dd, J = 10.8, 3.0 Hz, 1H), 5.80−5.90 (m, 2H), 6.80 (dd, J = 8.1, 1.2 Hz, 1H), 6.90 (td, J = 7.5, 1.2 Hz, 1H), 7.10 (tdd, J = 7.2, 1.5, 0.6 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.8, 30.8, 34.1, 50.1, 56.9, 66.8, 67.4, 116.8, 120.8, 125.0, 127.3, 128.6, 129.5, 130.7, 154.7; IR ($CHCl_3$) 1115 cm^{-1}; HRMS for $C_{17}H_{21}NO_2$ calcd 271.1572, found 271.1568. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.21; H, 8.02; N, 5.07.

Compound 29 (entries 5 and 6). The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a white solid consisting of an inseparable mixture of four isomers (80:10:5:5): mp 62−64 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.64−1.76 (m, 0.05H), 1.97−2.14 (m, 1.80H), 2.2−2.6 (m, 0.25H), 2.74−2.81 (m, 0.95H), 2.95−3.05 (m, 0.10H), 3.16−3.24 (m, 0.90H), 3.67−3.82 (m, 0.95H), 3.88−3.93 (m, 0.75H), 4.02−4.22 (m, 1.25H), 5.84−6.04 (m, 2.0H), 6.78−6.96 (m, 2.0H), 7.09−7.21 (m, 2.0H); ^{13}C NMR ($CDCl_3$) δ major isomer 29.2, 33.5, 33.9, 54.2, 65.2, 116.9, 120.9, 124.5, 126.9, 127.7, 129.2, 131.2, 154.5; IR ($CHCl_3$) 2096 cm^{-1}; HRMS for $C_{13}H_{13}N_3O$ calcd 227.1059, found 227.1060. Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.78; H, 6.05; N, 18.26.

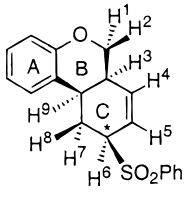
Compound 30 (entry 7). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a white solid: mp 150−152 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 2.36 (dt, J = 13.5, 6.3 Hz, 1H), 2.52 (ddd, J = 13.5, 8.4, 0.75 Hz, 1H), 2.91−2.96 (m, 1H), 3.54 (dd, J = 10.2, 6.3 Hz, 1H), 4.14 (s, 1H), 4.16 (s, 1H), 4.67−4.73 (m, 1H), 5.71 (dt, J = 9.9, 2.4 Hz, 1H), 5.97 (dt, J = 9.9, 2.7 Hz, 1H), 6.82 (dd, J = 8.4, 1.2 Hz, 1H), 6.96 (td, J = 7.5, 1.2 Hz, 1H), 7.13 (td, J = 7.2, 0.9 Hz, 1H), 7.27 (d, J = 6.9 Hz, 1H), 7.71 (dd, J = 5.4, 3.0 Hz, 2H), 7.83 (dd, J = 5.7, 3.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.3, 31.5, 33.7, 44.0, 67.7, 116.9, 121.2, 123.1, 123.3, 127.6, 128.1, 128.4, 130.0, 131.9, 134.0, 154.9, 168.1; IR ($CHCl_3$) 1711 cm^{-1}; HRMS for $C_{21}H_{17}NO_3$ calcd 331.1208; found: 331.1202. Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.09; H, 5.43; N, 4.12.

Compound 31 (entry 8). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a light yellow, very viscous liquid: ^{1}H NMR ($CDCl_3$) δ 1.88 (ddd, J = 14.0, 7.6, 3.6 Hz, 1H), 2.13 (dt, J = 14.0, 6.4 Hz, 1H), 2.42 (s, 3H), 2.49−2.54 (m, 1H), 2.85−2.90 (m, 1H), 3.92 (dd, J = 10.8, 5.6 Hz, 1H), 3.98 (dd, J = 11.0, 3.0 Hz, 1H), 4.20 (d, J = 16.4 Hz, 1H), 4.28−4.32 (m, 1H), 4.68 (d, J = 16.4 Hz, 1H), 5.22 (dt, J = 10.0, 2.6 Hz, 1H), 5.78 (dt, J = 10.0, 2.6 Hz, 1H), 6.74 (td, J = 8.0, 0.8 Hz, 2H), 6.84 (td, J = 7.6, 0.8 Hz, 1H), 7.06 (td, J = 7.6, 1.2 Hz, 1H), 7.25−7.30 (m, 3H), 7.35 (t, J = 7.6 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 30.9, 32.9, 33.3, 48.2, 51.7, 67.1, 116.6, 121.1, 123.2, 127.0, 127.3, 127.5, 127.6, 128.1, 128.5, 129.0, 129.7, 131.9, 137.8, 138.9, 143.2, 154.4; IR ($CHCl_3$) 1360, 1150 cm^{-1}; HRMS for $C_{27}H_{27}NO_3S$ calcd 445.1712, found 445.1712.

Compound 32 (entry 9). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a yellow liquid (a mixture of the desired product and 1,5-diphenyl-1,4-pentadien-3-one). The above mixture was chromatographed further using basic Alumina (Brockman activity III) with 1:15 EtOAc/hexanes as an eluent to afford an off-white solid: mp 85−86 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 18H), 2.41 (dd, J = 8.4, 4.5 Hz, 2H), 2.75−2.77 (m, 1H), 3.43 (dd, J = 9.3, 4.5 Hz, 1H), 4.08 (dd, J = 8.1, 1.8 Hz, 1H), 4.17 (dd, J = 8.1, 2.7 Hz, 1H), 4.45−4.47 (m, 1H), 5.69 (ddt, J = 19.2, 10.5, 1.8 Hz, 2H), 6.78 (dd, J = 8.1, 0.9 Hz, 1H), 6.92 (td, J = 7.5, 1.2 Hz, 1H), 7.10 (td, J = 7.5, 0.9 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 30.8, 32.1, 33.8, 50.4, 68.5, 82.3, 116.7, 121.1, 123.3, 127.4, 127.68, 127.70, 131.4, 152.5, 154.9; IR ($CHCl_3$) 1776, 1736 cm^{-1}; HRMS for $C_{23}H_{31}NO_5$ calcd 401.2202, found 401.2192. Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.78; H, 8.03; N, 3.36.

Compound 33 (entry 10). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a yellow liquid (74 mg, the desired product was inseparable from 1,5-diphenyl-1,4-pentadien-3-one). The mixture was added to $LiAlH_4$ (37 mg, 0.9 mmol) in ether (4 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and then at room temperature for 4 h. After a standard workup, the reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield 62.3 mg of a white solid (90% yield): mp 96−98 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.98 (td, J = 13.8, 4.2 Hz, 1H), 2.11 (dt, J = 13.5, 3.6 Hz, 1H), 2.70−2.75 (m, 1H), 3.14 (dt, J = 11.1, 4.8 Hz, 1H), 3.73 (br s, 1H), 3.84 (dd, J = 10.8, 9.3 Hz, 1H), 3.95 (dd, J = 8.1, 3.9 Hz, 1H), 4.14 (ddd, J = 10.8, 3.6, 0.6 Hz, 1H), 5.82 (ddd, J = 9.9, 4.2, 1.2 Hz, 1H), 5.99 (ddd, J = 9.9, 4.5, 1.2 Hz, 1H), 6.62 (dd, J = 8.4, 0.9 Hz, 2H), 6.72 (tt, J = 7.4, 0.9 Hz, 1H), 6.85 (ddd, J = 14.4, 7.5, 1.2 Hz, 2H), 7.07−7.12 (m, 2H), 7.19 (ddt, J = 8.1, 6.9, 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.4, 33.6, 33.7, 46.4, 65.6, 113.0, 116.7, 117.5, 120.8, 125.3, 127.4, 128.5, 129.3, 129.4, 130.7, 146.8, 154.6; IR ($CHCl_3$) 3408, 1051 cm^{-1}; HRMS for $C_{19}H_{19}NO$ calcd 277.1467, found 277.1461. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.14; H, 7.13; N, 4.96.

Compound 34 (entry 11).



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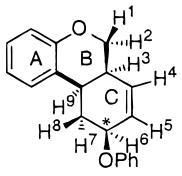
The reaction mixture was chromatographed using 1:4 EtOAc/hexanes to yield white needle crystals: mp 155−156 °C (EtOAc/hexames); ^{1}H NMR ($CDCl_3$) δ 2.18 (ddd, J = 14.7, 10.2, 6.0 Hz, 1H, H^8), 2.36 (dt, J = 14.7, 4.2 Hz, 1H, H^7), 2.64−2.70 (m, 1H, H^3), 3.21 (dt, J = 10.2, 5.1 Hz, 1H, H^9), 3.65−3.70 (m, 1H, H^6), 3.80 (dd, J = 11.1, 8.4 Hz, 1H, H^2), 4.11 (dd, J = 11.1, 3.3 Hz, 1H, H^1), 5.88 (ddd, J = 10.2, 3.6, 2.1 Hz, 1H, H^5), 6.08

(ddd, J = 10.2, 3.9, 2.0 Hz, 1H, H^4), 6.78 (d, J = 7.8 Hz, 1H), 6.90 (td, J = 7.4, 1.2 Hz, 1H), 7.10 (t, J = 7.2 Hz, 2H), 7.57−7.71 (m, 3H), 7.94 (dd, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.8, 29.1, 33.2, 60.0, 66.0, 116.9, 121.0, 121.4, 123.6, 127.8, 128.7, 129.0, 129.2, 133.8, 133.9, 137.5, 154.3; IR ($CHCl_3$) 1035, 1146 cm^{-1}; HRMS for $C_{19}H_{18}O_3S$ calcd 326.0977, found 326.0975. Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56. Found: C, 69.63; H, 5.51.

Compounds 35a and 35b (entry 12). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a light yellow liquid consisting of a 10:1 mixture of **35a**/**35b** and 1,5-diphenyl-1,4-pentadien-3-one (dba): ^{1}H NMR ($CDCl_3$) δ 1.93−2.14 (m, 2H), 2.10 (s, 3H), 2.42−2.55 (m, 0.2H), 2.72−2.80 (m, 1H), 3.14 (dt, J = 9.9, 4.8 Hz, 0.1H), 3.20 (dt, J = 12.0, 4.5 Hz, 1H), 3.76 (t, J = 10.8 Hz, 1H), 3.93 (t, J = 11.1 Hz, 0.1H), 4.14 (ddd, J = 10.8, 3.6, 0.9 Hz, 1H), 4.21 (ddd, J = 10.5, 3.9, 1.5 Hz, 0.1H), 5.07 (dd, J = 4.0, 2.0 Hz, 0.1H), 5.21 (dd, J = 7.8, 4.2 Hz, 1H), 5.80−5.83 (m, 0.1H), 5.93 (dd, J = 10.2, 4.2 Hz, 1H), 6.02 (dddd, J = 10.2, 4.5, 1.5, 0.9 Hz, 1H), 6.83 (dd, J = 8.1, 1.0 Hz, 1H), 6.91 (td, J = 7.2, 1.2 Hz, 1H), 7.11 (td, J = 7.8, 1.8 Hz, 1H), 7.18 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 21.3, 28.9, 29.2, 30.0, 33.4, 33.6, 35.5, 63.7, 64.8, 66.0, 66.6, 116.7, 116.8, 120.1, 120.8, 123.4, 124.9, 127.56, 127.64, 127.9, 128.3, 128.5, 128.8, 129.4, 130.8, 131.1, 154.4, 170.5 (missing the carbonyl peak of the minor isomer).

Compounds 64 and 65 (eq 8). The mixture of the corresponding acetate and 1,5-diphenyl-1,4-pentadien-3-one (49 mg) was added to a mixture of MeOH (2.5 mL) and K_2CO_3 (84.6 mg, 0.6 mmol) at rt. The resulting mixture was stirred at rt for 2.5 h, and then MeOH was removed in vacuo. Water (30 mL) was added to the residue, and the mixture was extracted with ether three times (30 mL, 10 mL, 10 mL). The combined ether layers were dried over Na_2SO_4 and chromatographed using 1:3 EtOAc/hexanes to afford the major isomer as a colorless liquid and the minor isomer as a colorless liquid. Alcohol **64** (major isomer): ^{1}H NMR ($CDCl_3$) δ 1.83 (br s, 1H), 1.93−2.11 (m, 2H), 2.71−2.77 (m, 1H), 3.24 (dt, J = 11.4, 5.1 Hz, 1H), 3.79 (dd, J = 11.1, 9.9 Hz, 1H), 4.12 (ddd, J = 11.1, 3.6, 0.9 Hz, 1H), 4.18 (dd, J = 7.8, 3.9 Hz, 1H), 5.84 (dd, J = 9.9, 4.5 Hz, 1H), 6.03 (dddd, J = 9.9, 4.5, 1.8, 0.9 Hz, 1H), 6.83 (dd, J = 8.1, 1.2 Hz, 1H), 6.91 (td, J = 7.2, 1.2 Hz, 1H), 7.11 (td, J = 7.6, 1.5 Hz, 1H), 7.21 (dd, J = 7.8, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6, 33.6, 36.9, 63.4, 65.1, 116.8, 120.8, 125.4, 127.4, 129.2, 129.3, 131.4, 154.5; IR ($CHCl_3$) 3368 cm^{-1}; HRMS for $C_{13}H_{14}O_2$ calcd 202.0994, found 202.0996. Alcohol **65** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 1.59 (br s, 1H), 2.21 (dd, J = 17.6, 8.8 Hz, 1H), 2.37−2.43 (m, 1H), 2.44−2.52 (m, 1H), 3.14−3.19 (m, 1H), 4.03 (t, J = 10.6 Hz, 1H), 4.04−4.06 (m, 1H), 4.16 (ddd, J = 10.8, 4.0, 1.2 Hz, 1H), 5.82−5.88 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.86 (td, J = 7.2, 1.2 Hz, 1H), 7.07−7.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.8, 38.4, 64.4, 64.7, 116.6, 120.2, 126.0, 127.4, 127.8, 128.4, 128.7, 153.6; IR ($CHCl_3$) 3359 cm^{-1}; HRMS for $C_{13}H_{14}O_2$ calcd 202.0994, found 202.0999.

Compound 36 (entry 13).



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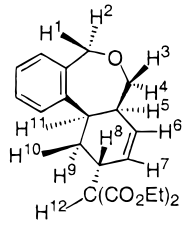
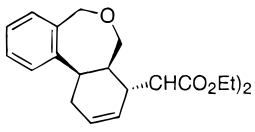
The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield an off-white solid: mp 63−65 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 2.05 (ddd, J = 14.2, 11.7, 4.2 Hz, 1H, H^8), 2.28 (dtd, J = 14.1, 3.6, 0.9 Hz, 1H, H^7), 2.79−2.84 (m, 1H, H^3), 3.36 (dt, J = 11.7, 4.5 Hz, 1H, H^9), 3.84 (dd, J = 11.1, 9.9 Hz, 1H, H^1), 4.16 (ddd, J = 11.1, 3.6, 0.9 Hz, 1H, H^2), 4.73 (dd, J = 8.1, 4.2 Hz, 1H, H^6), 5.96 (ddd, J = 10.2, 4.5, 0.6 Hz, 1H, H^4), 6.13 (dddd, J = 10.2, 4.5, 1.8, 0.9 Hz, 1H, H^5), 6.83 (dd, J = 8.1, 0.9 Hz, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.95 (dd, J = 7.8, 0.9 Hz, 2H), 6.98 (dt, J = 7.2, 0.9 Hz, 1H), 7.10 (dd, J = 7.8, 1.5 Hz, 1H), 7.15 (dd, J = 7.5, 1.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.0, 33.5, 33.7, 65.2, 68.8, 116.0, 116.8, 120.8, 121.1, 125.2, 127.5, 128.4, 129.3, 129.6, 130.7, 154.5, 157.6; IR ($CHCl_3$) 1238, 1065, 1049 cm^{-1}; HRMS for $C_{19}H_{18}O_2$ calcd 278.1307, found 278.1304. Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.61; H, 6.81.

Compound 37 (entry 14). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.00 (ddd, J = 14.4, 11.7, 3.9 Hz, 1H), 2.29 (dt, J = 14.1, 3.3 Hz, 1H), 2.81−2.89 (m, 1H), 3.52 (dt, J = 11.7, 4.5 Hz, 1H), 3.82 (t, J = 10.2 Hz, 1H), 4.17 (ddd, J = 10.8, 3.6, 0.6 Hz, 1H), 4.73 (dd, J = 8.1, 3.9 Hz, 1H), 5.98 (dd, J = 9.9, 4.2 Hz, 1H), 6.16 (dddd, J = 9.9, 4.5, 1.5, 0.9 Hz, 1H), 6.58 (td, J = 8.4, 0.9 Hz, 2H), 6.91 (td, J = 9.9, 1.5 Hz, 1H), 6.99 (dd, J = 8.1, 1.5 Hz, 1H), 7.12 (td, J = 7.8, 1.5 Hz, 1H), 7.20−7.28 (m, 2H), 7.57 (dd, J = 7.8, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.9, 33.7, 65.0, 71.4 (2C), 114.2, 116.6, 116.8, 120.8, 122.7, 125.2, 127.5, 127.9, 128.4, 129.4, 131.4, 133.6, 154.4, 154.5; IR ($CHCl_3$) 1242, 1070, 1045 cm^{-1}; HRMS for $C_{19}H_{17}BrO_2$ calcd 356.0412, found 356.0417.

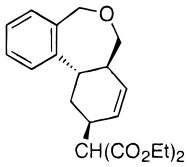
Compounds 38 and 66−68 (entry 15).



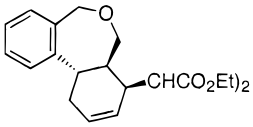
38



66



67



68

The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a white solid consisting of an inseparable 66: 13:14:7 mixture of **38**, **66**, **67**, and **68**: ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 2.89H), 1.23−1.31 (m, 5.0H), 2.18−2.29 (m, 1.99H), 2.43−2.57 (m, 1.26H), 2.60 (d, J = 3.6 Hz, 0.07H), 2.63−2.69 (m, 0.93H), 2.70−2.76 (m, 0.16H), 2.89 (dd, J = 16.0, 4.4 Hz, 0.30H), 3.06 (dd, J = 16.0, 11.2 Hz, 0.30H), 3.12−3.22 (m, 1.20H), 3.48 (d, J = 10.4 Hz, 1.0H), 3.51−3.56 (m, 0.50H), 3.60−3.78 (m, 0.62H), 3.89−4.05 (m, 2.16H), 4.09−4.26 (m, 4.91 H), 4.34 (dd, J = 11.2, 4.0 Hz, 0.30 H), 4.67−4.76 (m, 2.48H), 5.55−5.59 (m, 1.01H), 5.72−5.79 (m, 0.40H), 5.85−5.89 (m, 1.0H), 7.08 (d, J = 7.2 Hz, 1.16H), 7.13−7.26 (m, 4.48H); ^{13}C NMR ($CDCl_3$) δ 13.3, 13.9, 13.98, 14.05, 27.9, 29.3, 34.8, 37.3, 38.8, 39.2, 41.1, 42.3, 43.6, 43.9, 49.9, 56.62, 56.66, 56.72, 61.1, 61.4, 61.5, 63.8, 73.2, 73.8, 74.5, 75.8, 76.6, 125.3, 126.3, 127.3, 127.5, 127.7, 127.9, 128.0, 128.5, 128.6, 128.70, 128.72, 128.79, 128.82, 128.87, 128.93, 130.3, 130.4, 130.8, 139.2, 139.3, 139.6, 139.8, 142.8, 143.4, 167.9, 168.1, 168.3, 169.7; IR ($CHCl_3$) 1748, 1729 cm^{-1}; HRMS for $C_{21}H_{26}O_5$ calcd 358.1780, found 358.1782. After recrystallization of the mixture of **38** plus **66**−**68**, compound **38** was obtained in an almost pure form: mp 100−104 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 6.8 Hz, 3H), 1.29 (t, J = 5.4 Hz, 3H), 2.23 (t, J = 4.6 Hz, 1H, H^{10}), 2.25 (td, J = 18.0, 4.8 Hz, 1H, H^5), 2.53 (ddq, J = 18.4, 11.6, 2.0 Hz, 1H, H^9), 2.66 (dd, J = 10.4, 2.4 Hz, H^8), 3.14−3.18 (m, 1H, H^{11}), 3.48 (d, J = 10.4 Hz, 1H, H^{12}), 3.89−4.01 (m, 2H, H^3 and H^4), 4.09−4.25 (m, 4H), 4.69 (d, J = 14.0 Hz, 1H, H^2), 4.74 (d, J = 14.0 Hz, 1H, H^1), 5.56−5.59 (m, 1H, H^7), 5.86−5.90 (m, 1H, H^6), 7.09 (d, J = 7.2 Hz, 1H), 7.16 (td, J = 7.2, 2.4 Hz, 1H), 7.19−7.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 29.4, 37.3, 38.9, 41.2, 56.7, 61.5, 61.6, 73.8, 74.5, 125.4, 126.3, 127.8, 128.7, 129.0, 130.4, 139.6, 142.9,

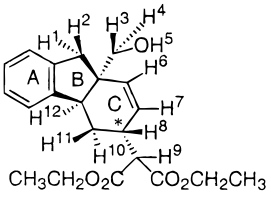
168.0 (one carbon missing as a result of overlap). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.52; H, 7.39.

Compound 39 (entry 16). The reaction mixture was chromatographed using 1:1 EtOAc/hexanes to yield a light yellow solid: mp 111−113 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 2.33−2.38 (m, 2H), 2.51−2.56 (m, 6H), 3.50−3.56 (m, 1H), 3.66 (t, J = 4.2 Hz, 4H), 3.81 (dd, J = 12.0, 3.9 Hz, 1H), 4.08 (br s, 1H), 4.71 (s, 2H), 5.66−5.72 (m, 1H), 5.95−6.02 (m, 1H), 7.10−7.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 29.9, 38.8, 40.6, 50.3, 60.8, 67.4, 73.6, 75.0, 125.9, 126.2, 127.5, 128.3, 128.7, 129.4, 129.6, 139.7; IR ($CHCl_3$) 1118, 1005 cm^{-1}; HRMS for $C_{18}H_{23}NO_2$ calcd 285.1729, found 285.1733. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.81; H, 8.20; N, 4.88.

Compound 40 (entry 17). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.90 (ddd, J = 14.0, 11.0, 4.0 Hz, 1H), 2.36 (dtd, J = 13.6, 4.4, 0.8 Hz, 1H), 2.71−2.74 (m, 1H), 2.98 (d, J = 16.0 Hz, 1H), 3.28 (d, J = 8.8 Hz, 1H), 3.43 (d, J = 16.0 Hz, 1H), 3.74 (s, 3H), 3.89 (t, J = 4.0 Hz, 1H), 4.17 (qd, J = 7.2, 0.8 Hz, 2H), 4.23 (qd, J = 7.2, 2.8 Hz, 2H), 5.62 (dt, J = 10.4, 1.2 Hz, 1H), 5.69 (ddd, J = 10.0, 2.4, 1.2 Hz, 1H), 7.15−7.18 (m, 2H), 7.20−7.21 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 26.0, 31.0, 43.1, 44.6, 52.2, 53.6, 56.2, 61.3 (2C), 123.0, 124.8, 126.7, 126.9, 130.1, 130.2, 140.3, 142.7, 168.07, 168.14, 175.0; IR ($CHCl_3$) 1730 cm^{-1}; HRMS for $C_{22}H_{26}O_6$ calcd 386.1729, found 386.1728.

Compound 41 (entry 18). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.08 (ddd, J = 13.4, 10.0, 4.2 Hz, 1H), 2.62 (dtd, J = 13.2, 6.8, 1.0 Hz, 1H), 3.00 (d, J = 15.9 Hz, 1H), 3.45 (d, J = 15.9 Hz, 1H), 3.76 (s, 3H), 3.96 (t, J = 3.9 Hz, 1H), 5.10 (ddt, J = 9.9, 5.7, 1.5 Hz, 1H), 5.69 (ddd, J = 10.2, 1.8, 1.2 Hz, 1H), 5.78 (ddd, J = 10.2, 1.5, 1.2 Hz, 1H), 7.16−7.29 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.2, 27.8, 43.0, 44.3, 52.4, 53.7, 66.7, 123.0, 124.8, 127.0, 127.1, 129.2, 131.5, 139.8, 142.2, 170.6, 174.6; IR ($CHCl_3$) 1735 cm^{-1}; HRMS for $C_{15}H_{14}O_2$ ($M^+ - C_2H_4O_2$) calcd 226.0994, found 226.0996.

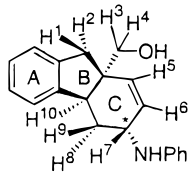
Compound 42 (entry 19).



42

The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H, CH_3), 1.29 (t, J = 6.8 Hz, 3H, CH_3), 1.88−1.95 (m, 2H, H^5 and H^{10}), 2.17 (dt, J = 13.2, 5.6 Hz, 1H, H^{11}), 2.72 (d, J = 15.6 Hz, 1H, H^2), 2.73−2.79 (m, 1H, H^8), 2.94 (d, J = 15.6 Hz, 1H, H^1), 3.39 (d, J = 8.0 Hz, 1H, H^{12}), 3.41 (br s, 1H, H^9), 3.62 (d, J = 10.8 Hz, 1H, H^3), 3.68 (d, J = 10.8 Hz, 1H, H^4), 4.16−4.25 (m, 4H, 2 CH_2), 5.56 (dd, J = 10.0, 2.4 Hz, 1H, H^6), 5.75 (dd, J = 10.0, 2.4 Hz, 1H, H^7), 7.14−7.18 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.02, 14.07, 27.1, 31.7, 41.1, 44.0, 49.6, 56.0, 61.32, 61.34, 68.6, 123.2, 124.9, 126.4, 126.0, 130.8, 132.9, 141.4, 144.6, 168.37, 168.38; IR ($CHCl_3$) 3510, 1728 cm^{-1}; HRMS for $C_{21}H_{26}O_5$ calcd 358.1780, found 358.1789.

Compound 43 (entry 20).



43

The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a white solid: mp 114−116 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.92 (ddd, J = 13.0, 8.0, 4.4 Hz, 1H, H^8), 2.27 (dtd, J = 13.2, 5.6, 1.6 Hz, 1H, H^9), 2.77 (d, J = 16 Hz, 1H, H^1), 2.92 (d, J = 16 Hz, 1H, H^2), 3.42 (dd, J = 6.0, 4.4 Hz, 1H, H^{10}), 3.59 (d, J = 10.8 Hz, 1H, H^3), 3.65 (d, J = 10.8 Hz, 1H, H^4), 3.85−3.89 (m, 1H, H^7), 5.61 (dd, J = 10.0, 1.2 Hz, 1H, H^5), 5.91 (dd, J = 10.0, 2.8 Hz, 1H, H^6), 6.58 (dd, J = 8.8, 0.8 Hz, 2H), 6.69 (tt, J = 7.6, 0.8 Hz, 1H), 7.13−7.21 (m, 6H), missing OH and NH; ^{13}C NMR ($CDCl_3$) δ 30.7, 40.9, 43.1, 45.6, 49.3, 68.6, 113.4, 117.5, 123.4, 125.0, 126.6, 126.7, 129.3, 131.4, 133.2, 141.3, 144.8, 147.0; IR ($CHCl_3$) 3530, 3407 cm^{-1}; HRMS for $C_{20}H_{21}NO$ calcd 291.1623, found 291.1624. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 83.08; H, 7.54; N, 4.75.

Compound 44 (entry 21). The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.76 (dt, J = 14.4, 3.6 Hz, 1H), 2.04 (ddd, J = 14.2, 11.2, 5.2 Hz, 1H), 2.58−2.62 (m, 1H), 2.90−2.95 (m, 1H), 3.02−3.06 (m, 1H), 3.04 (dd, J = 11.2, 9.2 Hz, 1H), 3.25 (dd, J = 11.2, 3.6 Hz, 1H), 3.48 (d, J = 10.0 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 5.75−5.82 (m, 2H), 6.52 (dd, J = 8.0, 0.8 Hz, 1H), 6.69 (td, J = 7.4, 0.8 Hz, 1H), 6.98 (td, J = 7.6, 1.2 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), missing NH; ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 31.5, 31.9, 33.6, 33.8, 43.5, 56.7, 61.4, 61.5, 114.6, 117.9, 124.2, 126.9, 129.1, 129.4, 130.6, 144.5, 168.2, 168.4; IR ($CHCl_3$) 3412, 1729 cm^{-1}; HRMS for $C_{20}H_{25}NO_4$ calcd 343.1784, found 343.1782.

Compound 45 (entry 22). The reaction mixture was chromatographed using 1:3 EtOAc/hexanes to yield a light yellow, viscous liquid: ^{1}H NMR ($CDCl_3$) δ 1.84 (ddd, J = 14.0, 6.8, 4.0 Hz, 1H), 2.13 (ddd, J = 14.2, 8.0, 6.0 Hz, 1H), 2.41 (s, 3H), 2.45−2.50 (m, 1H), 2.81 (dt, J = 8.4, 4.0 Hz, 1H), 2.99 (dd, J = 11.2, 6.4 Hz, 1H), 3.17 (dd, J = 11.2, 3.2 Hz, 1H), 3.72 (br s, 1H), 4.22 (d, J = 16.4 Hz, 1H), 4.39−4.44 (m, 1H), 4.70 (d, J = 16.4 Hz, 1H), 5.17 (dt, J = 10.0, 2.6 Hz, 1H), 5.79 (dt, J = 10.0, 2.6 Hz, 1H), 6.42 (d, J = 8.4 Hz, 1H), 6.56−6.62 (m, 2H), 6.93 (td, J = 7.4, 1.6 Hz, 1H), 7.24−7.29 (m, 3H), 7.34 (t, J = 7.4 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 32.3, 33.2, 33.4, 44.1, 48.1, 51.9, 114.6, 118.1, 122.4, 126.9, 127.0, 127.2, 127.5, 127.6, 128.1, 128.4, 129.7, 134.4, 137.9, 139.1, 143.1, 144.1; IR ($CHCl_3$) 3408, 1335, 1158 cm^{-1}; HRMS for $C_{27}H_{28}N_2O_2S$ calcd 444.1872, found 444.1868.

Compounds 46a and 46b (entry 23). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow liquid as an inseparable mixture of two isomers (65:35): ^{1}H NMR ($CDCl_3$) δ 1.18−1.35 (m, 6H), 1.77 (dt, J = 14.1, 3.3 Hz, 0.65H), 2.00−2.13 (m, 1H), 2.19−2.34 (m, 0.35H), 2.66−2.76 (m, 1H), 2.92−3.27 (m, 3.65H), 3.36−3.53 (m, 1.35H), 4.09−4.31 (m, 4H), 4.41−4.58 (m, 1H), 4.47 (s, 1H), 5.54−5.58 (m, 0.35H), 5.71−5.84 (m, 1.65H), 6.50−6.60 (m, 1.35H), 6.66 (td, J = 7.5, 0.9 Hz, 0.65H), 6.96−7.02 (m, 1.35H), 7.08 (dd, J = 6.6, 0.9 Hz, 0.65H), 7.20−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 14.2, 30.0, 32.1, 32.4, 33.1, 33.4, 33.7, 36.9, 50.0, 51.1, 54.5, 55.4, 56.8, 57.2, 61.36, 61.44, 61.49, 61.54, 110.6, 111.6, 115.5, 116.6, 124.7, 124.8, 125.9, 126.4, 126.6, 126.8, 127.1, 127.2, 127.7, 128.4, 128.54, 128.57, 129.1, 129.5, 130.4, 138.4, 138.7, 143.7, 145.2, 168.0, 168.2, 168.4 (four carbons missing as a result of overlap); IR ($CHCl_3$) 1747, 1728 cm^{-1}; HRMS for $C_{27}H_{31}NO_4$ calcd 433.2253, found 433.2259.

Compound 47 (entry 24). The reaction mixture was chromatographed using 1:15 EtOAc/hexanes to yield a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.93−2.04 (m, 1H), 2.10 (dt, J = 13.5, 3.0 Hz, 1H), 2.69−2.77 (m, 1 H), 3.10−3.27 (m, 3H), 3.83 (br s, 1H), 4.00−4.02 (m, 1H), 4.49 (s, 2H), 5.86 (dd, J = 9.9, 1.2 Hz, 1H), 5.94 (dd, J = 9.9, 1.2 Hz, 1H), 6.55−6.74 (m, 5H), 6.95−7.04 (m, 2H), 7.16−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 31.7, 33.4, 34.8, 46.9, 50.4, 55.4, 111.5, 113.1, 116.6, 117.4, 125.2, 126.6, 126.8, 127.2, 128.6, 129.3, 129.4 (2C), 131.1, 138.7, 145.1, 146.9; IR ($CHCl_3$) 3402 cm^{-1}; HRMS for $C_{26}H_{26}N_2$ calcd 366.2096, found 366.2099.

Compound 48 (entry 25). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless

liquid consisting of a 2.3:1 mixture of compound **48** and diethyl malonate: ^{1}H NMR ($CDCl_3$) δ 1.24−1.31 (m, 6H), 1.58 (ddd, J = 13.0, 11.1, 4.2 Hz, 1H), 1.67 (d, J = 1.2 Hz, 3H), 1.84 (dt, J = 13.2, 0.9 Hz, 1H), 2.26 (d, J = 15.9 Hz, 1H), 2.85−2.95 (m, 2H), 3.24 (d, J = 9.3 Hz, 1H), 3.43 (br s, 1H), 3.69 (s, 3H), 4.16−4.25 (m, 4H), 5.12 (d, J = 0.9 Hz, 1H), 5.60 (dd, J = 10.2, 2.4 Hz, 1H), 5.70 (dt, J = 10.2, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.98, 14.0, 16.5, 28.0, 31.6, 45.8, 47.9, 52.0, 52.4, 56.3, 61.2, 61.4, 126.4, 129.0, 131.1, 138.3, 168.2, 168.3, 175.8; IR ($CHCl_3$) 1753, 1730 cm^{-1}; HRMS for $C_{19}H_{26}O_6$ calcd 350.1729, found 350.1729.

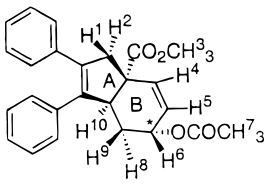
Compound 49 (entry 26). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.65 (ddd, J = 13.0, 10.2, 4.2 Hz, 1H), 1.71 (d, J = 0.9 Hz, 3H), 2.16 (dt, J = 12.9, 4.2 Hz, 1H), 2.29 (d, J = 16.2 Hz, 1H), 2.93 (dd, J = 16.2, 1.2 Hz, 1H), 3.45−3.50 (m, 1H), 3.59 (br s, 1H), 3.72 (s, 3H), 3.99−4.04 (m, 1H), 5.18 (s, 1H), 5.63 (dd, J = 10.2, 1.5 Hz, 1H), 5.87 (d, J = 10.2 Hz, 1H), 6.61 (d, J = 7.5 Hz, 2H), 6.69 (t, J = 7.5 Hz, 1H), 7.16 (dd, J = 8.4, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.6, 31.2, 45.6, 46.0, 47.9, 52.2, 52.6, 113.5, 117.4, 126.3, 129.3, 130.9, 131.0, 138.6, 147.0, 175.9; IR ($CHCl_3$) 3395, 1728 cm^{-1}; HRMS for $C_{18}H_{21}NO_2$ calcd 283.1572, found 283.1572.

Compound 50 (entry 27). The reaction mixture was chromatographed using 1:20 EtOAc/hexanes to yield a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.70 (d, J = 0.9 Hz, 3H), 2.04 (ddd, J = 13.2, 10.2, 4.5 Hz, 1H), 2.25−2.35 (m, 2H), 2.92 (d, J = 16.2 Hz, 1H), 3.59 (br s, 1H), 3.74 (s, 3H), 4.79−4.85 (m, 1H), 5.17 (s, 1H), 5.73 (d, J = 10.2 Hz, 1H), 5.99 (d, J = 10.2 Hz, 1H), 6.70 (td, J = 7.5, 0.9 Hz, 1H), 6.83 (dd, J = 8.1, 0.9 Hz, 1H), 7.26 (td, J = 7.8, 1.5 Hz, 1H), 7.77 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 30.3, 45.5, 48.2, 52.3, 52.5, 71.8, 88.1, 114.1, 122.7, 126.1, 128.6, 129.2, 132.3, 138.6, 139.7, 156.6, 175.4; IR ($CHCl_3$) 1727, 1241, 1063 cm^{-1}; HRMS for $C_{18}H_{19}IO_3$ calcd 410.0379, found 410.0378.

Compound 51 (entry 28). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a very viscous, light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 1.60−1.70 (m, 1 H), 1.73−1.81 (m, 1H), 2.66−2.74 (m, 1H), 3.04 (dd, J = 16.2, 2.1 Hz, 1H), 3.17 (d, J = 9.3 Hz, 1H), 3.32 (dd, J = 16.2, 2.4 Hz, 1H), 3.75 (s, 3H), 3.87−4.17 (m, 5H), 5.82 (dd, J = 10.2, 1.8 Hz, 1H), 5.88 (dd, J = 10.2, 1.8 Hz, 1H), 7.04−7.26 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 13.8, 13.9, 26.2, 31.4, 47.8, 49.0, 50.6, 52.3, 56.2, 61.1, 126.8, 127.8, 128.2, 128.5, 129.8, 130.3, 134.7, 136.47, 136.53, 138.7, 167.9, 168.0, 175.6 (three carbons missing as a result of overlap); IR ($CHCl_3$) 1729 cm^{-1}; HRMS for $C_{30}H_{32}O_6$ calcd 488.2199, found 488.2205.

Compound 52 (entry 29). The reaction mixture was chromatographed using 1:1 EtOAc/hexanes to yield a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.72 (ddd, J = 13.1, 11.1, 4.2 Hz, 1H), 1.88 (dtd, J = 13.2, 4.2, 1.2 Hz, 1H), 2.22−2.40 (m, 4 H), 2.89−2.95 (m, 1H), 3.02 (dd, J = 16.5, 2.1 Hz, 1H), 3.27 (dd, J = 16.5, 3.0 Hz, 1H), 3.54−3.67 (m, 4H), 3.76 (s, 3H), 4.11 (br s, 1H), 5.83 (dd, J = 10.2, 2.1 Hz, 1H), 5.91 (d, J = 10.2 Hz, 1H), 7.04−7.27 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.7, 47.9, 48.7, 49.3, 50.7, 52.2, 56.0, 67.2, 126.8, 127.8, 128.26, 128.35 (2C), 128.4, 131.2, 131.5, 134.6, 136.4, 136.6, 138.6, 175.5; IR ($CHCl_3$) 1730, 1116 cm^{-1}; HRMS for $C_{27}H_{29}NO_3$ calcd 415.2147, found 415.2146.

Compound 53 (entry 30).



53

The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield white crystals: mp 108−110 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.87 (ddd, J = 13.5, 9.3, 1.5 Hz, 1H, H^8), 1.96 (s, 3H, H^7), 2.00−2.08 (m, 1H, H^9), 3.04 (dd, J = 16.5, 2.1 Hz, 1H, H^1), 3.34 (dd, J = 16.5, 2.4 Hz, 1H, H^2), 3.77 (s, 3H, H^3), 4.05 (br s, 1H, H^{10}), 5.08 (dd, J = 9.0, 5.4 Hz, 1H, H^6), 5.91 (br s, 2H, H^4 and H^5), 7.03−7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.1, 27.8, 47.6, 48.7, 50.7, 52.5, 66.4, 127.0, 127.1, 127.9, 128.2, 128.45, 128.47, 128.5, 131.9, 134.6, 136.3, 136.4, 138.7, 170.4, 175.2; IR ($CHCl_3$) 1729 cm^{-1}; HRMS for $C_{25}H_{24}O_4$ calcd 388.1675, found 388.1670. Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 77.11; H, 6.34.

Compound 54 (entry 31). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.65 (ddd, J = 13.2, 11.1, 4.2 Hz, 1H), 1.92 (dt, J = 13.2, 4.5 Hz, 1H), 2.44 (d, J = 16.2 Hz, 1H), 2.85−2.95 (m, 2H), 3.25 (d, J = 9.0 Hz, 1H), 3.46 (br s, 1H), 3.71 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 5.53−5.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0, 27.7, 31.7, 44.1, 45.7, 52.0, 52.1, 56.3, 61.3, 128.8, 129.2, 130.9, 133.1, 168.17, 168.26, 175.7 (two carbons missing as a result of overlap); IR ($CHCl_3$) 1735 cm^{-1}; HRMS for $C_{18}H_{24}O_6$ calcd 336.1573, found 336.1570.

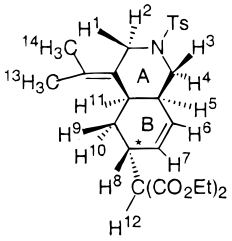
Compound 55 (entry 32). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.72 (ddd, J = 13.0, 10.2, 4.5 Hz, 1H), 2.21 (dt, J = 12.9, 4.2 Hz, 1H), 2.46 (ddd, J = 16.2, 3.6, 2.4 Hz, 1H), 2.97 (ddd, J = 16.2, 5.1, 2.7 Hz, 1H), 3.47−3.52 (m, 1H), 3.58 (br s, 1H), 3.73 (s, 3H), 3.97−4.03 (m, 1H), 5.58−5.73 (m, 3H), 5.88 (dt, J = 10.2, 1.2 Hz, 1H), 6.60 (dd, J = 8.4, 0.9 Hz, 2H), 6.70 (tt, J = 7.2, 1.2 Hz, 1H), 7.16 (dd, J = 8.4, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 30.8, 44.0, 45.6, 45.8, 52.2, 52.3, 113.4, 117.5, 129.0, 129.3, 130.8, 131.0, 133.1, 146.9, 175.8; IR ($CHCl_3$) 3395, 1726 cm^{-1}; HRMS for $C_{17}H_{19}NO_2$ calcd 269.1416, found 269.1412.

Compound 56 (entry 33). The reaction mixture was chromatographed using 1:9 EtOAc/hexanes to yield an off-white solid: mp 160−162 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.40−1.56 (m, 2H), 1.70 (d, J = 12.6 Hz, 2H), 1.84−1.94 (m, 1H), 1.98−2.12 (m, 3H), 2.47−2.61 (m, 2H), 3.38 (t, J = 11.1 Hz, 1H), 3.77 (br s, 1H), 3.83 (dd, J = 11.4, 4.8 Hz, 1H), 3.96−4.05 (m, 2H), 5.49 (t, J = 3.3 Hz, 1H), 5.74 (dd, J = 9.9, 4.5 Hz, 1H), 5.91 (dd, J = 9.9, 5.1 Hz, 1H), 6.62 (d, J = 7.8 Hz, 2H), 6.69 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.6, 25.3, 29.6, 29.7, 34.8, 37.4, 47.0, 66.9, 71.6, 112.9, 117.2, 124.2, 128.9, 129.3, 129.9, 138.5, 146.8; IR ($CHCl_3$) 3335 cm^{-1}; HRMS for $C_{19}H_{23}NO$ calcd 281.1780, found 281.1780. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.23; H, 8.38; N, 5.00.

Compound 57 (entry 34). The reaction mixture was chromatographed using 1:12 EtOAc/hexanes to yield a colorless liquid consisting of a 2.9:1 mixture of compound **57** and diethyl malonate: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6H), 1.34 (ddd, J = 13.6, 11.2, 4.4 Hz, 1H), 1.46 (d, J = 1.2 Hz, 3H), 1.59 (d, J = 1.6 Hz, 3H), 2.08 (dtd, J = 13.6, 4.0, 0.8 Hz, 1H), 2.42 (dt, J = 14.8, 1.2 Hz, 1H), 2.87−2.95 (m, 1H), 2.99 (d, J = 15.6 Hz, 1H), 3.26 (d, J = 9.2 Hz, 1H), 3.64−3.68 (m, 1H), 3.67 (s, 3H), 4.15−4.21 (m, 4H), 5.73 (dt, J = 10.2, 1.6 Hz, 1H), 5.95 (ddd, J = 10.2, 2.8, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.1, 19.3, 27.2, 31.9, 40.6, 41.3, 43.0, 52.0, 56.4, 61.28, 61.30, 125.8, 126.4, 129.48, 129.55, 168.2, 168.3, 175.4 (one carbon missing as a result of overlap); IR ($CHCl_3$) 1730 cm^{-1}; HRMS for $C_{20}H_{28}O_6$ calcd 364.1886, found 364.1890.

Compound 58 (entry 35). The reaction mixture was chromatographed using 2:1 EtOAc/hexanes to yield a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.43−1.50 (m, 1H), 1.45 (d, J = 0.8 Hz, 3H), 1.59 (d, J = 1.6 Hz, 3H), 2.14 (dtd, J = 13.2, 4.0, 1.2 Hz, 1H), 2.39 (dt, J = 14.8, 1.2 Hz, 1H), 2.52−2.61 (m, 4H), 2.99 (dd, J = 14.8, 1.2 Hz, 1H), 3.19−3.23 (m, 1H), 3.69 (s, 3H), 3.70 (t, J = 4.8 Hz, 4H), 3.73 (br s, 1H), 5.89 (d, J = 10.4 Hz, 1H), 5.98 (ddd, J = 10.4, 2.4, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.4, 23.0, 41.1, 41.8, 42.7, 49.0, 52.1, 57.0, 67.5, 125.4, 126.9, 130.2, 131.3, 175.5; IR ($CHCl_3$) 1729 cm^{-1}; HRMS for $C_{17}H_{25}NO_3$ calcd 291.1834, found 291.1839.

Compounds 59a and 59b (entry 36).



59a

The reaction mixture was chromatographed using 1:5 EtOAc/hexanes to yield a white solid consisting of an inseparable mixture of two isomers (60:40): ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 14.2 Hz, 0.6H), 1.16−1.24 (m, 6H), 1.64 (s, 3H), 1.69 (s, 1.2H), 1.71 (s, 1.8H), 1.65−1.71 (m, 1H), 1.74−1.78 (m, 1H), 2.13 (t, J = 12 Hz, 0.6H), 2.29−2.46 (m, 0.4H), 2.38 (s, 1.2H), 2.39 (s, 1.8H), 2.43 (t, J = 11.6 Hz, 0.4H), 2.58−2.64 (m, 1H), 2.76−2.97 (m 2H), 3.30 (d, J = 10.4 Hz, 0.4H), 3.35 (d, J = 11.2 Hz, 0.6H), 3.48 (dd, J = 11.2, 4.4 Hz, 0.4H), 3.63 (ddd, J = 12.0, 4.4, 1.6 Hz, 0.6H), 4.09−4.18 (m, 4H), 4.36 (d, J = 13.6 Hz, 0.4H), 4.48 (d, J = 13.2 Hz, 0.6H), 5.45−5.49 (m, 0.4H), 5.58−5.69 (m, 1.6H), 7.23−7.28 (m, 2H), 7.59−7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.08, 14.11, 19.7, 19.8, 20.5, 20.6, 21.6, 24.2, 25.0, 29.7, 30.0, 34.4, 35.2, 36.1, 37.2, 43.1, 44.4, 45.8, 46.6, 56.7, 57.4, 61.6, 61.7, 124.6, 126.4, 127.4, 127.6, 127.7, 127.9, 128.1, 129.1, 129.66, 129.70, 130.1, 133.6, 133.9, 143.3, 143.5, 167.86, 167.92, 167.97, 168.2 (six carbons missing as a result of overlap); IR ($CHCl_3$) 1747, 1728, 1337, 1163 cm^{-1}; HRMS for $C_{26}H_{35}NO_6S$ calcd 489.2185, found 489.2185. The mixture was recrystallized from EtOAc/hexanes to afford pure **59a** as white crystals: mp 172−174 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 14.4 Hz, 1H, H^9), 1.23 (t, J = 6.8 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.68 (s, 3H, H^{13}), 1.69−1.77 (m, 1H, H^{10}), 1.75 (s, 3H, H^{14}), 2.17 (t, J = 12.0 Hz, 1H, H^3), 2.33−2.40 (m, 1H, H^5), 2.44 (s, 3H), 2.68 (d, J = 13.2 Hz, 1H, H^1), 2.83 (dt, J = 13.6, 3.8 Hz, 1H, H^{11}), 2.91 (dt, J = 10.4, 5.2 Hz, 1H, H^8), 3.40 (d, J = 11.2 Hz, 1H, H^{12}), 3.68 (ddd, J = 11.6, 4.0, 1.6 Hz, 1H, H^4), 4.13−4.23 (m, 4H), 4.53 (d, J = 13.6 Hz, 1H, H^2), 5.66−5.74 (m, 2H, H^6 and H^7), 7.32 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.6, 20.5, 21.5, 24.9, 30.0, 34.3, 35.2, 44.3, 46.5, 56.6, 61.5, 126.4, 127.7, 127.8, 129.0, 129.6, 130.1, 133.6, 143.4, 167.9, 168.1 (two carbons missing as a result of overlap). Anal. Calcd for $C_{26}H_{35}NO_6S$: C, 63.78; H, 7.20; N, 2.86. Found: C, 63.80; H, 7.29; N, 2.84.

Compounds 60a and 60b (entry 37). The reaction mixture was chromatographed using 1:7 EtOAc/hexanes to yield an off-white solid consisting of an inseparable mixture of two isomers (62:38): mp 178−188 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 1.86H), 1.62 (s, 1.14H), 1.68 (s, 3H), 1.48−1.74 (m, 1.38H), 1.81−1.85 (m, 0.62H), 2.10−2.21 (m, 1H), 2.40 (s, 1.14H), 2.42 (s, 1.86H), 2.37−2.50 (m, 1H), 2.69 (d, J = 13.2 Hz, 0.62H), 2.94−2.98 (m, 1H), 3.10 (d, J = 13.6 Hz, 0.38H), 3.55−3.62 (m, 0.76H), 3.69−3.73 (m, 1.62H), 3.91 (s, 0.62H), 4.37 (d, J = 14.0 Hz, 0.38H), 4.52 (d, J = 13.6 Hz, 0.62H), 5.67−5.88 (m, 2H), 6.51 (d, J = 8.0 Hz, 0.76H), 6.54 (d, J = 8.0 Hz, 1.24H), 6.65 (t, J = 7.2 Hz, 0.62H), 6.70 (t, J = 7.2 Hz, 0.38H), 7.11 (t, J = 8.0 Hz, 1.24H), 7.16 (t, J = 8.0 Hz, 0.76H), 7.27 (d, J = 8.0 Hz, 0.76H), 7.31 (d, J = 8.0 Hz, 1.24H), 7.66 (d, J = 8.0 Hz, 1.24H), 7.67 (d, J = 8.0 Hz, 0.76H); ^{13}C NMR ($CDCl_3$) δ 19.6, 20.0, 20.47, 20.49, 21.6, 24.3, 27.0, 29.1, 29.6, 35.4, 36.9, 43.3, 44.3, 44.5, 46.1, 47.2, 49.9, 112.9, 113.2, 117.50, 117.55, 124.8, 126.3, 126.4, 127.4, 127.67, 127.72, 127.75, 129.28, 129.36, 129.45, 129.54, 129.7, 131.0, 133.6, 134.0, 143.4, 143.5, 146.5, 146.8 (two carbons missing as a result of overlap); IR ($CHCl_3$) 3390, 1335, 1159 cm^{-1}; HRMS for $C_{25}H_{30}N_2O_2S$ calcd 422.2028, found 422.2030. Anal. Calcd for $C_{25}H_{30}N_2O_2S$: C, 71.06; H, 7.16; N, 6.63. Found: C, 69.89; H, 7.24; N, 6.40.

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Supporting Information Available: Procedures for the preparation of all starting materials; discussion of the 2D (COSY, HMQC, and NOESY) spectral results for compounds **27**, **34**, **36**, **38**, **42**, **43**, **53**, **59a**, and **59b**; copies of the COSY, HMQC, and NOESY spectra for the above compounds; a table summarizing the spectral data for the above compounds; and copies of the ^{1}H and ^{13}C NMR spectra for compounds **26**, **31**, **35a** and **35b**, **64**, **65**, **37**, **38** and **66**−**68**, **40**−**42**, **44**−**52**, **54**, **55**, **57**, **58**, **59a and 59b**, **and 60a and 60b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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