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Synthetic Studies on Perophoramidine and the Communesins: Construction of the Vicinal Quaternary Stereocenters

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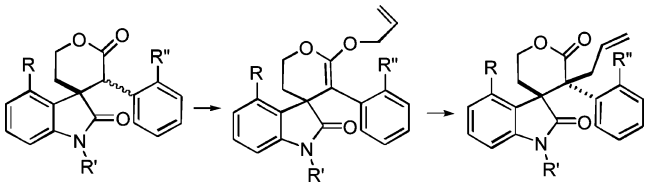

An efficient synthetic strategy for installation of the two vicinal quaternary carbon centers of the communesins is reported. Key steps include the O-allylation/Claisen rearrangement of spirolactone systems, which are formed by tandem intramolecular Heck cyclization/carbonylation. Substituent and solvent effects on the stereochemical outcome of the Claisen rearrangements have been examined. The stereochemical assignment of the allyl spirolactone previously reported as **17** has now been revised to **31**, which has the communesin relative configuration at the quaternary carbons. Key *C*-allyl spirolactone **59** bearing functional handles required for the communesin core has been constructed with a 9.8:1 diastereomer ratio.

Introduction and Background

About a decade ago, Numata et al. reported two unusual natural products isolated from a *Penicillium* mold found growing on the marine alga *Enteromorpha intestinalis*.[1] The unique structures of these two compounds, communesin A (**1**) and communesin B (**5**), were established by spectroscopic analysis (Figure 1). An interesting feature of these complex, highly functionalized polycyclic compounds is the two contiguous quaternary centers at C-7,8. Communesins A and B were found to have in vitro cytotoxic activity against P-388 lymphoid leukemia cells. In 2001, Hemscheidt and co-workers described a metabolite called nomofungin, which was isolated from an unidentified fungus growing on the bark of *Ficus microcarpa* in Hawaii.[2] This material was found to have cytotoxic activity against LoVo and KB cells, which was shown to be due to the ability of the metabolite to cause microfilament disruption. The metabolite was initially proposed to have structure **9**, but it was later found that this assignment was in error, and that nomofungin is actually communesin B (**5**). It should be noted, however, that the Hemscheidt work did serve to establish both the configuration at C-21 of **5** as well as the absolute configuration of the molecule, which were not originally determined by the Numata group. Recently, several other modified communesin derivatives have been isolated,[3] including communesin C (**6**),[4] D (**7**), E (**2**), F (**8**), G (**3**), and H (**4**) (Figure 1). Some of these new compounds were found to have significant biological activity. For example, communesins D, E, and F are

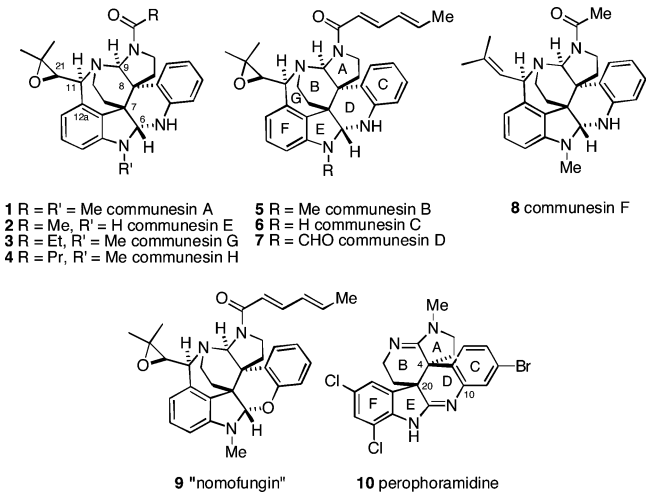

FIGURE 1. Structures of the communesins and perophoramidine.

(1) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355.

(2) (a) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2001**, *66*, 8717. (b) For the retraction of the nomofungin structure, see: Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2003**, *68*, 1640.

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insecticidal,[3b] and communesins C and D are moderately active against various leukemia cell lines.[3a]

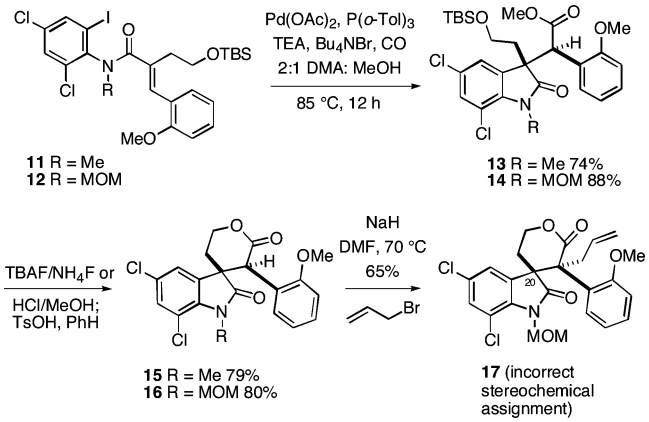
In 2002, Ireland reported the isolation of a congeneric compound, perophoramidine, from the marine ascidian *Perophora namei* collected in the Philippines.[5] Based mainly upon NMR spectral analysis, this metabolite was assigned the hexacyclic structure **10**, which contains some unique features, including two amidine units, two chlorines, and a bromine. Like the communesins, perophoramidine has two adjacent quaternary carbons at C-4,20, but interestingly, the natural products have the opposite relative stereochemistry at these centers. Perophoramidine has cytotoxicity against the HCT116 colon carcinoma cell line and also induces apoptosis via PARP cleavage.

Perophoramidine and the communesins have closely related structures and presumably arise via a common biogenetic pathway.[6] Some model studies on biogenetically patterned synthesis of the communesin/perophoramidine ring system by the Stoltz[7] and Qin[8] groups have appeared, as well as a model hetero-Diels−Alder-based approach by Crawley and Funk.[9] Moreover, Fuchs and Funk have completed an elegant, biogenetically inspired total synthesis of racemic perophoramidine.[10] In addition, Rainier and co-workers recently described a nice total synthesis of dehaloperophoramidine.[11]

In 2003, we disclosed some preliminary results on a Heck-based strategy for total synthesis of these alkaloids.[12] In this work, it was found that acrylamides **11** and **12** underwent tandem intramolecular Heck cyclization/carbonylation[13] to afford E/F-lactam esters **13** and **14**, respectively, in good yields (Scheme 1).

These compounds could then be cleanly cyclized to lactones **15** and **16** after removal of the TBS protecting groups. As part of these studies, we reported that lactone **16** could be deprotonated and alkylated with allyl bromide to afford a single product to which we assigned the perophoramidine relative

SCHEME 1



stereochemistry at the quaternary centers as shown in **17** via ^{1}H NMR NOESY experiments. On the basis of the subsequent studies discussed in this paper, we have found that the configurational assignment of this alkylation product is in fact incorrect (vide infra).

Results and Discussion

Because we believed that we had been able to efficiently access the requisite perophoramidine C-4,20 quaternary carbon stereochemistry, work was undertaken on synthesis of a Heck substrate bearing the appropriate C-ring substituents. Using a two-step procedure developed by Coe[14] heating commercially available 4-bromo-2-nitrotoluene (**18**) in the presence of *N*,*N*-dimethylformamide dimethyl acetal and pyrrolidine in DMF generated the known enamine **19**,[15] which was oxidatively cleaved using $NaIO_4$ in THF/H_2O to afford the desired benzaldehyde **20** in 93% yield over two steps (Scheme 2). Wittig olefination of the aldehyde **20** with readily available ylide **21**[16] in refluxing toluene generated the benzylidene lactone **22** in excellent yield. Ring opening of this unsaturated lactone with the aluminum amide reagent[17] derived from the commercially available aniline **23** produced the nitro acrylamide **24** in quantitative yield. Subsequent protection of the primary alcohol moiety of **24** as its TBS ether and alkylation of the amide nitrogen using NaH/MOMCl resulted in the *N*-MOM acrylamide **25** in 84% yield over the two steps.

To continue the synthesis, the Heck reaction/carbonylation sequence with substrate **25** was examined, leading to the desired lactam ester **28** as a mixture of diastereomers along with the reductive Heck product **27**[18] and ester **26** derived from uncyclized starting iodide (Scheme 3). The ratios of these products

(3) (a) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod*. **2004**, *67*, 78. (b) Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci. Biotechnol. Biochem*. **2004**, *68*, 753. (c) Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod*. **2005**, *68*, 258.

(4) Some structurally different compounds were initially designated as the same communesins due to simultaneous publication by two groups (see refs 3a and 3b). However, the current communesin nomenclature can be found in ref 3c.

(5) (a) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124. (b) For another related alkaloid see: Verotta, L.; Pilati, T.; Tato, M.; Elisabetsky, E.; Amador, T. A.; Nunes, D. S. *J. Nat. Prod*. **1998**, *61*, 392.

(6) For recent labeling studies on the biosynthesis of the communesins, see: Wigley, L. J.; Mantle, P. G.; Perry, D. A. *Phytochemistry* **2006**, *67*, 561.

(7) (a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett*. **2003**, *44*, 1203. (b) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262.

(8) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett*. **2006**, *8*, 2187.

(9) Crawley, S. L.; Funk, R. L. *Org. Lett*. **2003**, *5*, 3169.

(10) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc*. **2004**, *126*, 5068.

(11) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed*. **2006**, *45*, 4317.

(12) (a) Artman, G. D., III; Weinreb, S. M. *Org. Lett*. **2003**, *5*, 1523. (b) Artman, G. D., III. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 2004.

(13) (a) Grigg, R.; Millington, E. L.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605. (b) Brown, S.; Clarkson, S.; Grigg, R.; Thomas, W. A.; Sridharan, V.; Wilson, D. M. *Tetrahedron* **2001**, *57*, 1347. (c) Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 1361. (d) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88. (e) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (f) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919.

(14) (a) Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219. (b) Coe, J. W.; Vetelino, M. G.; Bradlee, M. J. *Tetrahedron Lett.* **1996**, *37*, 6045.

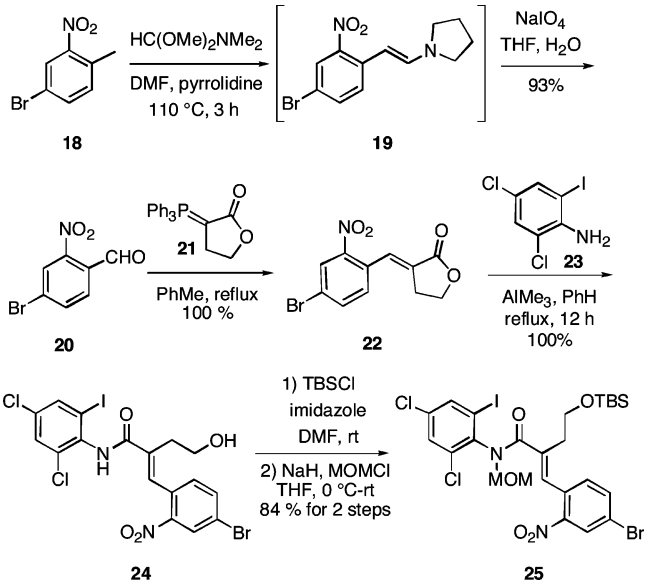
(15) Schumacher, R. W.; Davidson, B. S. *Tetrahedron* **1999**, *55*, 935.

(16) (a) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1992**, *48*, 9373. (b) McCort, G.; Hoornaert, C.; Aletru, M.; Denys, C.; Duclos, O.; Cadilhac, C.; Guilpain, E.; Dellac, G.; Janiak, P.; Galzin, A.-M.; Delahaye, M.; Guilbert, F.; O'Connor, S. *Bioorg. Med. Chem.* **2001**, *9*, 2129.

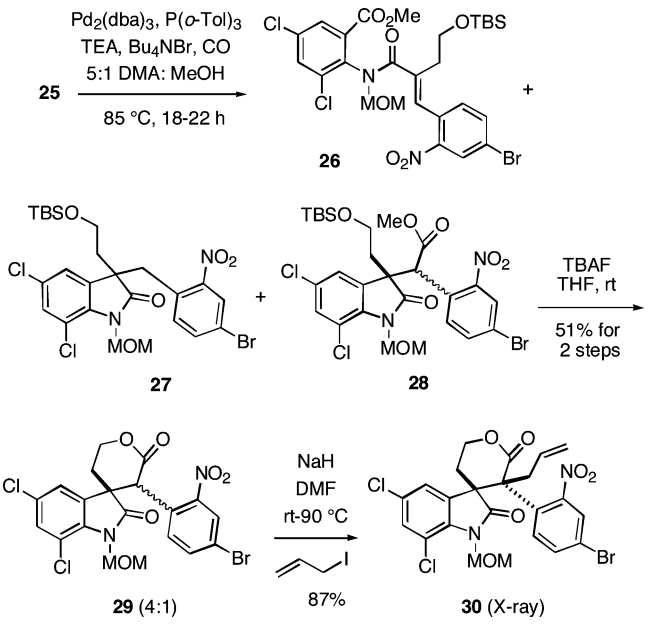
(17) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth*. **1979**, *59*, 49.

(18) For some examples of reductive Heck reactions, see: (a) Denmark, S. E.; Schnute, M. E. *J. Org. Chem*. **1995**, *60*, 1013. (b) Diaz, P.; Gendre, F.; Stella, L.; Charpentier, B. *Tetrahedron* **1998**, *54*, 4579. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379 and references cited therein. (d) For a recent example of MeOH acting as a hydride transfer agent, see: Sajiki, H.; Ikawa, T.; Yamada, H.; Tsubouchi, K.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 171.

SCHEME 2



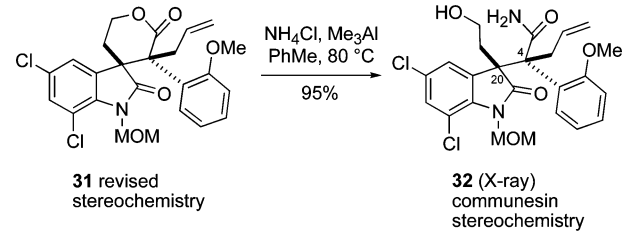
SCHEME 3



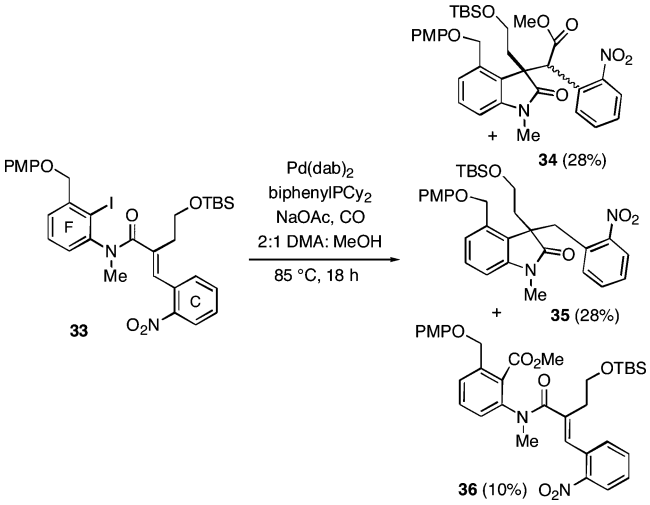
varied widely depending upon the specific reaction conditions (Pd source, ligand, solvent, base, etc.) used for the Heck/carbonylation step. However, the formation of the desired cyclization products **28** was optimal under the conditions shown in the scheme. Although compounds **26**−**28** could be separated by chromatography and characterized spectrally (see Experimental Section), it was found best to simply expose the crude reaction mixture to TBAF, leading to lactone **29** (4:1 diastereomeric mixture) in 51% isolated overall yield from substrate **25**.

This mixture of lactones was deprotonated with sodium hydride in DMF at room temperature, upon which allyl iodide was added, and the mixture was heated in an oil bath at 90 °C. This reaction produced a single crystalline alkylation product in excellent yield whose structure was established unambiguously by X-ray analysis. We were quite surprised to find, however, that the allylated lactone has the communesin stereochemistry shown in **30** rather than the expected perophoramidine configuration at the quaternary centers.

SCHEME 4



SCHEME 5



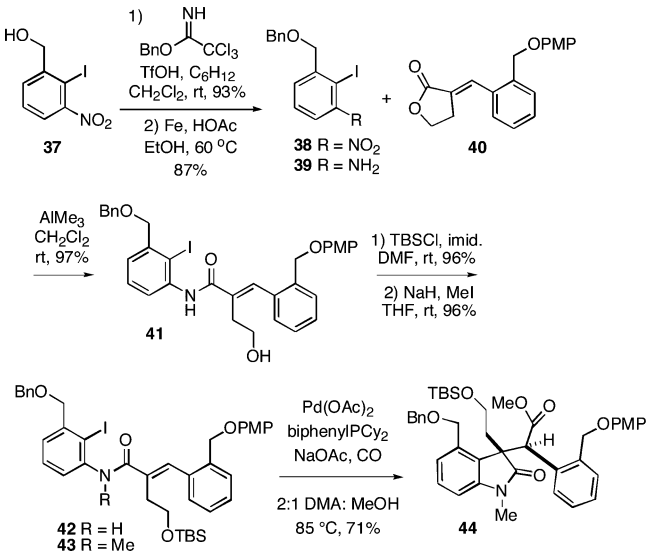
In view of this unexpected stereochemical result, we decided to reexamine the model system shown in Scheme 1.[12] Thus, the lactone product from C-allylation of **16**[19] was exposed to the reagent derived from ammonium chloride and trimethylaluminum[20] to afford hydroxy amide **32** (Scheme 4). This material provided crystals suitable for X-ray analysis, which established that the allylation product of **16** in fact has the communesin stereochemistry shown in **31** and is not the perophoramidine diastereomer **17** which had originally been assigned.

Since the experiments outlined above suggested that we might be able to access the quaternary carbons of the communesins stereoselectively, we turned to an investigation of systems bearing useful C and F aromatic ring substituents for synthesis of this group of metabolites. Using methodology similar to that described above, Heck substrate **33** was prepared in a few steps. It was found, however, that under most conditions, the Heck/carbonylation sequence led to the reduced compound **35** as the major or sole product rather than the desired ester **34** (Scheme 5). After substantial experimentation, it was possible at best to produce equal amounts of **34** and **35** along with a small quantity of ester **36** using the conditions shown in the scheme. It should be noted that a similar tendency for intramolecular reductive Heck reactions has been observed by Denmark and Schnute when using nitroolefins.[18a] The rationale presented for these results would also apply to our cases involving nitroarenes **25** and **33**. Since the desired transformation of Heck substrate **33**

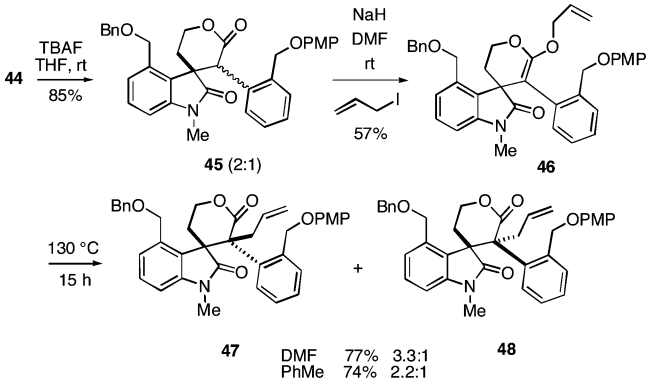
(19) For preparation of lactones **16** and **31**, see Supporting Information in ref 12a.

(20) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

SCHEME 6



SCHEME 7



to ester **34** was not synthetically useful, we turned to an alternative system lacking the nitro group which was expected to be more amenable to the requisite Heck/carbonylation process.

One solution we considered was to install the required C-ring nitrogen via a late-stage Curtius rearrangement of a system bearing a suitable carbon substituent. Thus, Heck substrate **43** was constructed via the chemistry outlined in Scheme 6. Known benzyl alcohol **37**[21] was first converted to the benzyl ether **38**, and the nitro group was subsequently reduced to afford aniline **39**. Conversion of this amine to the corresponding aluminum amide[17] followed by reaction with benzylidene lactone **40**[2222] then led to amide **41** in high yield. The alcohol functionality of **41** was protected as the TBS ether **42**, and the amide nitrogen was methylated to yield the desired substrate **43**. This compound underwent smooth tandem Heck cyclization/carbonylation to produce the desired lactam ester **44** as a single stereoisomer

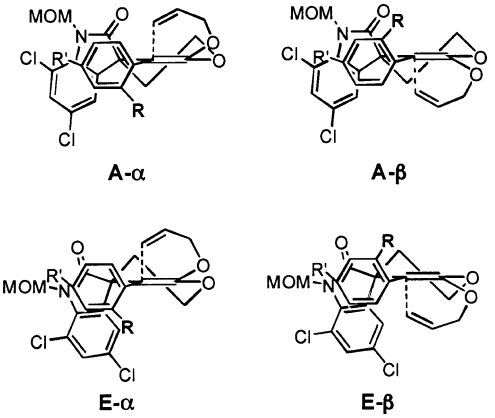


FIGURE 2. Models for allylation of lactones **16** and **29**.

whose configuration was not proven, but by analogy with **13**/**14**[12] is assumed to be as shown.

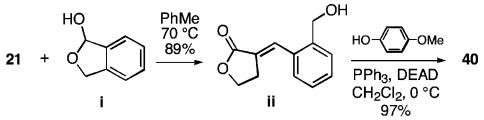
Treatment of silyl ether ester **44** with TBAF led to desilylation and in situ cyclization to lactone **45**, which was produced as a 2:1 mixture of diastereomers (Scheme 7). During work with spirolactone **45**, it was discovered that allylation of the corresponding enolate does not actually involve a direct C-alkylation. Thus, treatment of **45** with sodium hydride in DMF along with allyl iodide at room temperature affords the chromatographically isolable ketene acetal **46** in 57% yield (71% based on recovered lactone, formed via hydrolysis of **46** during purification). Ketene acetal **46** appears to exist as a 2:1 mixture of atropisomers, as can be seen by ^{1}H NMR. It was found that heating ketene acetal **46** at 130 °C in either DMF or toluene led to a Claisen rearrangement producing a separable mixture of diastereomeric C-allylation products **47** and **48**, with a slightly better stereoselectivity in the former solvent. The stereochemistry of the minor isomer was established by ^{1}H NMR NOESY analysis to have the configuration shown in **48** (see Supporting Information). It should be noted that, although we cannot isolate the ketene acetals in the two alkylations described above, we believe these processes also involve an initial O-allylation followed by a Claisen rearrangement (vide infra).

In view of the disappointing level of stereoselectivity in the alkylation of lactone **45**, we decided to explore an alternative system with different substitution in the F-ring with the hope of improving this key step. Known, easily prepared phenol **49**[23] was therefore first converted to the carbamate **50**, and the nitro group was reduced to yield the aniline **51** (Scheme 8). Condensation of this intermediate with benzylidene lactone **40** then produced amide **52** in excellent overall yield. The alcohol functionality of **52** was protected as the MOM ether **53**, and the amide nitrogen was methylated to afford **54**. The tandem Heck cyclization/carbonylation of this substrate proceeded cleanly to generate the requisite lactam ester **55** as a single stereoisomer assumed to be as indicated.

The MOM protecting group of **55** was next removed with methanolic HCl to give the desired spirolactone **57** along with some of the uncyclized hydroxy ester **56** (Scheme 9). O-Allylation of the spirolactone as was done with **45** gave the ketene acetal **58**, which in this case was again a 2:1 mixture of atropisomers. Heating **58** in DMF at 110 °C did not show improved stereoselectivity over the system in Scheme 7, leading to a 2.3:1

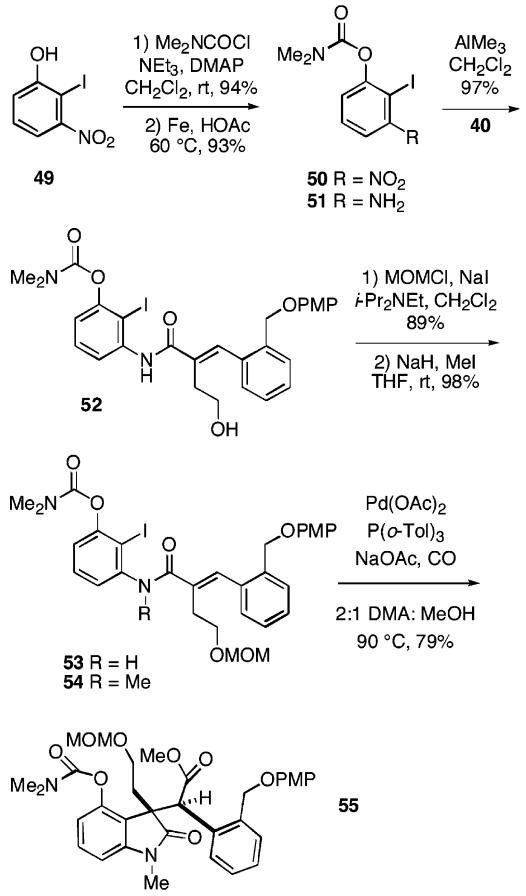
(21) (a) Seno, K.; Hagishita, S.; Sato, T.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2013. (b) Ozlu, Y.; Cladingboel, D. E.; Parsons, P. J. *Tetrahedron* **1994**, *50*, 2183.

(22) Prepared by reaction of Wittig reagent **21**[16] with known lactol **i** (Mikami, K.; Ohmura, H. *Org. Lett*. **2002**, *4*, 3355) to afford benzylidene lactone **ii**, which was then protected as shown:

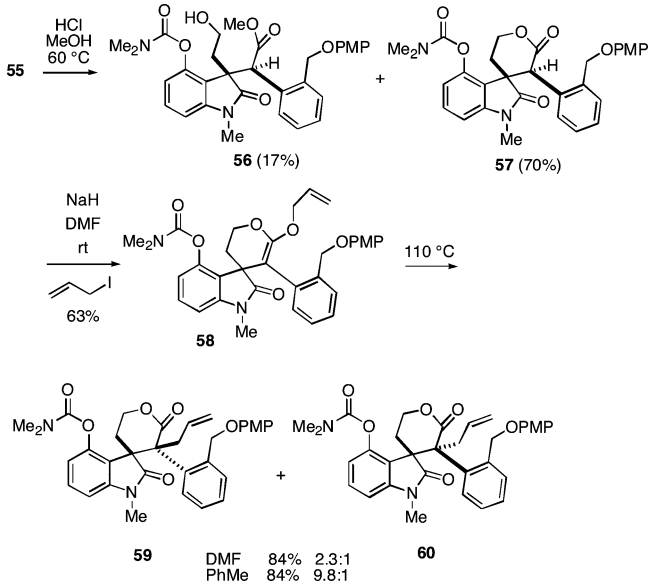


(23) Dai, W.-M.; Lai, K. W. *Tetrahedron Lett*. **2002**, *43*, 9377.

SCHEME 8



SCHEME 9



mixture of stereoisomers **59** and **60** in good yield. We have been unable to definitively establish the configurations of these diastereomers, but by analogy with the three cases described above, we believe the major isomer has the communesin configuration shown in **59**. We were pleased to find, however, that heating ketene acetal **58** in toluene induced a Claisen rearrangement, which led to a synthetically useful 9.8:1 mixture of **59**:**60**.

To rationalize the high stereoselectivity shown in the first two lactone allylations (cf. Schemes 3 and 4), we considered

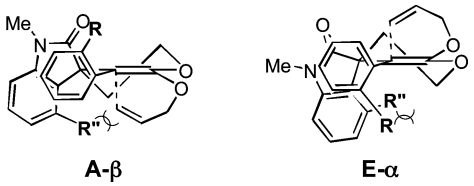


FIGURE 3. Transition state models for Claisen rearrangement of ketene acetals **46** and **58**.

four possible half-chair transition state conformations for the Claisen rearrangement of the corresponding ketene acetal intermediates (Figure 2). The carbonyl group of the oxy-indole moiety (EF-rings) could occupy either pseudoaxial (**A**) or pseudoequatorial (**E**) positions. In addition, each transition state has two possible atropisomers (α and ***β***) derived from the position of the substituent (R) at C(10) in the C-ring aryl moiety. It seems reasonable that the allyl group approaches the ketene acetal double bond from the face opposite to this substituent in order to avoid severe steric interactions.[24] Since axial attack of the allyl group is more favorable stereoelectronically,[25] transition states **A-*β*** and **E-α** are expected to be preferable to conformations **A-α** and **E-*β***. In addition, it appears from inspection of models that the aryl group of the oxy-indole moiety blocks attack of the allyl substituent more effectively than does the carbonyl group, and therefore transition state **E-α** would seem to be favored over **A-*β***. Steric interactions and/or electronic repulsions between the carbonyl group and the substituent R (OMe or NO_2) may additionally destabilize conformation **A-*β***.

On the other hand, allylation of the lactones bearing substituents (R″) at the C-12a position of the oxy-indole moiety showed lower stereoselectivity than did the above two cases (cf. Schemes 7 and 9). As shown in Figure 3, substituent R″ causes substantial steric interactions not only with substituent R in **E-α** but also with the allyl group in **A-*β***. As noted above, NMR analysis shows that there is little preference for one atropisomer in ketene acetals **46** and **58** at room temperature. These steric interactions presumably slow the Claisen rearrangements of the latter two ketene acetals, making these species more easily isolable, and also lead to generally low stereoselectivities. At this point, however, we are unable to explain why we observe high stereoselectivity in the rearrangement of ketene acetal **58** in toluene.

In conclusion, we have developed a concise strategy to construct systems bearing the two quaternary centers of the communesins. Key steps in this approach involve an intramolecular tandem Heck cyclization/carbonylation, followed by a stereoselective O-allylation/Claisen rearrangement of a spirolactone enolate. We are currently attempting to utilize this methodology in a total synthesis of the communesins.

Experimental Section

3-(4-Bromo-2-nitrophenyl)-2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-*N*-(2,4-dichloro-6-iodophenyl)-*N*-methoxymethylacrylamide (25). *N*,*N*-Dimethylformamide dimethyl acetal (7.25 mL, 54.6 mmol) and pyrrolidine (4.50 mL, 53.9 mmol) were added to 4-bromo-2-nitrotoluene (**18**, 9.66 g, 44.7 mmol, TCI) in DMF (25

(24) Similar facial selectivity controlled by the conformation of an α-substituent has been proposed for the alkylation of six-membered lactone enolates: Tomioka, K.; Kawasaki, H.; Yasuda, K.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 3597.

(25) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 274−284.

mL). The reaction mixture was heated at 110 °C for 4 h to give a dark red solution. The reaction mixture was cooled to room temperature, and the volatile organics were removed under reduced pressure resulting in the known enamine **19**[15] as a mass of red crystals.

The above enamine was dissolved in THF (30 mL) and added slowly to $NaIO_4$ (28.9 g, 135 mmol) in 50% aqueous THF (200 mL) while maintaining the temperature below 20 °C. The reaction mixture was rapidly stirred for an additional 2 h, and the insoluble salts were removed by filtration and washed with EtOAc. The combined organic filtrate was washed with water, dried ($MgSO_4$), and concentrated. The crude product was purified by flash silica gel chromatography (1:9 EtOAc:hexanes) to afford the desired 4-bromo-2-nitrobenzaldehyde (**20**, 9.58 g, 93%) as a yellow solid (mp 93−95 °C; lit. mp 95 °C[26]): IR (KBr) 3085, 2912, 2863, 1812, 1691, 1525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.38 (d, J = 0.6 Hz, 1H), 8.26 (d, J = 1.7 Hz, 1H), 7.93 (ddd, J = 8.3, 1.8, 0.6 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 150.1, 137.4, 131.1, 129.9, 128.4, 127.8.

3-(Triphenyl-λ^5-phosphanylidene)dihydrofuran-2-one (**21**, 4.62 g, 13.3 mmol)[16] was added to nitrobenzaldehyde **20** (3.07 g, 13.3 mmol) in toluene (70 mL). The reaction mixture was heated at reflux for 2 h and cooled to room temperature. The volatile organics were removed under reduced pressure. The crude product was absorbed onto silica gel and purified by flash silica gel column chromatography (1:2 EtOAc:hexanes) to afford the benzylidene lactone **22** (3.96 g, 100%) as a light brown solid (mp 129−131 °C): IR (KBr) 2929, 2867, 1762, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 1.8 Hz, 1H), 7.82 (dd, J = 8.3, 1.8 Hz, 1H), 7.78 (t, J = 2.9 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 4.46 (t, J = 7.2 Hz, 2H), 3.07 (dd, J = 7.2, 3.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 148.8, 136.7, 131.3, 129.3, 129.0, 128.4, 123.5, 65.7, 26.9.

2,4-Dichloro-6-iodoaniline (**23**, 11.1 g, 39 mmol, TCI) was dissolved in benzene (60 mL) and slowly added via syringe to $AlMe_3$ (2.0 M in hexanes, 21 mL, 42 mmol) in benzene (10 mL) at 0 °C. After stirring the mixture for an additional 45 min, the benzylidine lactone **22** (10.4 g, 35 mmol) dissolved in CH_2Cl_2 (60 mL) was slowly added via syringe. The reaction mixture was heated at 65 °C for 15 h then cooled to 0 °C. Then, 1 N HCl (50 mL) was slowly added dropwise, and the reaction mixture was stirred for an additional 30 min. The organic layer was removed, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude oil was absorbed onto silica gel and purified by flash silica gel chromatography (1:2 EtOAc:hexanes) to afford the bromo dichloro acrylamide **24** (16.5 g, 81%) as a foam: ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 2.0 Hz, 1H), 8.05 (s, 1H), 7.80−7.83 (m, 2H), 7.67 (s, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 3.73−3.80 (br m, 2H), 2.63 (t, J = 5.8 Hz, 2H), 2.48 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 148.2, 137.6, 137.3, 137.0, 135.1, 134.8, 133.2, 132.8, 132.4, 130.3, 128.4, 122.8, 100.2, 61.5, 31.4.

TBSCl (5.11 g, 33.9 mmol) was added in a single portion to acrylamide **24** (16.3 g, 27.8 mmol) and imidazole (4.20 g, 61.7 mmol) in DMF (30 mL), and the mixture was stirred at room temperature for 60 min. Water was added, and the aqueous phase was extracted with ether. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired TBS ether (19.5 g, 100%) as an oil, which was used without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.28 (d, J = 2.0 Hz, 1H), 7.74−7.77 (m, 2H), 7.70 (s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 2.2 Hz, 1H), 3.75 (t, J = 5.6 Hz, 2H), 2.67 (t, J = 5.6 Hz, 2H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 148.4, 137.9, 137.7, 136.9, 135.9, 134.7, 133.6, 133.4, 132.8, 130.7, 130.4, 128.4, 122.7, 100.8, 62.8, 31.8, 26.3, 18.7, −5.0; HRMS-APCI $[M + H]^+$ calcd for $C_{23}H_{26}BrCl_2IN_2O_4Si$, 698.9340; found, 698.9366.

NaH (60% dispersion in mineral oil, 1.33 g, 33.2 mmol) was added to the TBS ether (19.5 g, 27.8 mmol) in THF (140 mL) at 0 °C. The solution was stirred for an additional 20 min at this temperature before MOMCl (3.10 mL, 41.6 mmol) was introduced. The reaction solution was warmed to room temperature and stirred for 12 h. Saturated aqueous $NaHCO_3$ (100 mL) was slowly added, and the organic layer was removed. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography (1:4 EtOAc:hexanes) to afford the *N*-MOM amide **25** (17.4 g, 84%) as an oil, which solidified upon standing: ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (m, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.75−7.78 (m, 2H), 7.65 (s, 1H), 7.54 (d, J = 2.1 Hz, 1H), 5.10 (AB_q, J = 67.1, 10.5 Hz, 2H), 3.81−3.85 (m, 2H), 3.28 (s, 3H), 2.71 (br m, 2H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 150.8, 137.4, 135.6, 135.1, 133.8, 130.7, 129.3, 128.9, 128.1, 123.3, 121.8, 116.9, 72.0, 59.5, 56.6, 52.8, 40.2, 39.6, 26.1, −5.4; HRMS-APCI $[M + H]^+$ calcd for $C_{25}H_{30}BrCl_2IN_2O_5Si$, 742.9602; found, 742.9572.

(4-Bromo-2-nitrophenyl)-{3-[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-5,7-dichloro-1-methoxymethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl}-acetic Acid Methyl Ester (28). To a solution of *N*-MOM amide **25** (27.4 mg, 0.037 mmol) in DMA (2.0 mL) and MeOH (0.4 mL) were added $Pd_2(dba)_3$ (3.4 mg, 0.004 mmol), P(*o*-Tol)$_3$ (4.5 mg, 0.015 mmol), *n*-Bu_4NBr (23.7 mg, 0.074 mmol), and NEt_3 (26 μL, 0.187 mmol). The mixture was stirred at 85 °C under a CO atmosphere (1 atm) for 21 h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was used for the next step without further purification. For analytical purposes, the compounds were separated by preparative TLC (1:5 EtOAc:hexanes). More polar major diastereomer of **28** (pale yellow oil): IR (film) 2946, 2860, 1735, 1536, 1461, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 2.1 Hz, 1H), 7.70 (dd, J = 8.5, 2.1 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 5.37, 5.30 (ABq, J = 10.5 Hz, 2H), 5.09 (s, 1H), 3.65 (s, 3H), 3.42 (s, 3H), 3.24 (td, J = 6.2, 2.6 Hz, 2H), 2.25 (td, J = 6.2, 3.7 Hz, 2H), 0.72 (s, 9H), −0.17 (d, J = 2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 170.2, 151.3, 138.3, 135.6, 133.5, 133.0, 130.9, 128.5, 128.4, 126.8, 124.0, 123.2, 117.2, 72.6, 59.4, 57.1, 53.1, 52.8, 50.4, 37.2, 26.1, 18.6, −5.3, −5.4; HRMS-ES $[M + H]^+$ calcd for $C_{27}H_{34}BrCl_2N_2O_7Si$, 675.0696; found, 675.0712. Less polar minor diastereomer of **28** (pale yellow oil): IR (film) 2946, 2860, 1735, 1536, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 2.1 Hz, 1H), 7.56 (dd, J = 8.5, 2.1 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 5.24, 5.19 (ABq, J = 10.5 Hz, 2H), 5.16 (s, 1H), 3.64 (s, 3H), 3.29 (t, J = 6.2 Hz, 2H), 3.22 (s, 3H), 2.22−2.12 (m, 2H), 0.72 (s, 9H), −0.17 (d, J = 2.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 170.4, 151.4, 138.3, 135.7, 133.7, 133.5, 131.2, 129.0, 128.1, 127.0, 124.3, 123.0, 116.9, 72.3, 59.3, 56.8, 53.3, 53.2, 51.0, 39.3, 26.1, 18.6, −5.3, −5.4; HRMS-ES $[M + H]^+$ calcd for $C_{27}H_{34}BrCl_2N_2O_7Si$, 675.0696; found, 675.0672.

3-(4-Bromo-2-nitrobenzyl)-3-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-5,7-dichloro-1-methoxymethyl-1,3-dihydroindol-2-one (27). Pale yellow oil: IR (film) 2935, 2860, 1730, 1536, 1461, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.3, 2.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 5.19 (s, 2H), 3.80, 3.41 (ABq, J = 13.7 Hz, 2H), 3.37 (m, 2H), 3.32 (s, 3H), 2.32 (dt, J = 13.8, 6.9 Hz, 1H), 2.08 (dt, J = 13.8, 5.5 Hz, 1H), 0.75 (s, 9H), −0.14 (d, J = 3.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 150.8, 137.3, 135.7, 135.1, 133.8, 130.6, 129.3, 128.9, 128.1, 123.4, 121.8, 116.9, 72.0, 59.5, 56.5, 52.8, 40.3, 39.6, 26.1, 18.5,

(26) Imming, P.; Imhof, I.; Zentgraf, M. *Synth. Commun.* **2001**, *31*, 3721.

−5.36, −5.37; HRMS-ES [M + H]$^+$ calcd for $C_{25}H_{32}BrCl_2N_2O_5Si$, 617.0641; found, 617.0659.

2-{[2-(4-Bromo-2-nitrobenzylidene)-4-(*tert*-butyldimethylsilanyloxy)-butyryl]-methoxymethylamino}-3,5-dichlorobenzoic Acid Methyl Ester (26). Yellow solid (mp 125−126 °C): IR (film) 2946, 2860, 1730, 1665, 1531, 1278 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, 5:1 atropisomer mixture) δ 8.30 (d, J = 1.8 Hz, 1H, *major*), 8.09 (d, J = 1.7 Hz, 1H, *minor*), 7.89 (d, J = 2.4 Hz, 1H, *major*), 7.85 (d, J = 2.4 Hz, 1H, *minor*), 7.77 (d, J = 1.8 Hz, 1H, *minor*), 7.75−7.69 (m, 3H, *major*), 7.67 (m, 1H, *minor*), 7.46 (s, 1H, *major*), 7.22 (d, J = 8.2 Hz, 1H, *minor*), 7.00 (s, 1H, *minor*), 5.23, 4.85 (ABq, J = 10.5 Hz, 2H, *minor*), 5.20, 4.79 (ABq, J = 10.2 Hz, 2H, *major*), 3.92 (s, 3H, *minor*), 3.89 (s, 3H, *major*), 3.84 (t, J = 6.0 Hz, 2H, *major*), 3.74 (m, 2H, *minor*), 3.46 (s, 3H, *minor*), 3.21 (s, 3H, *major*), 2.68 (m, 2H, *major)*, 2.41 (m, 2H, *minor*), 0.90 (s, 9H, *major*), 0.83 (s, 9H, *minor*), 0.07 (s, 6H, *major*), −0.02 (s, 6H, *minor*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 164.7, 148.5, 137.6, 136.6, 136.4, 136.2, 134.9, 134.1, 133.8, 133.1, 130.9, 130.5, 129.4, 128.2, 122.4, 83.3, 61.0, 56.8, 53.3, 33.4, 26.3, 18.7, −5.0; HRMS-ES [M + H]$^+$ calcd for $C_{27}H_{34}BrCl_2N_2O_7Si$, 675.0696; found, 675.0665.

Synthesis of Spirolactone 29. To a stirred solution of the above crude mixture of Heck/carbonylation adducts in THF (3.0 mL) was added TBAF (0.072 mL, 1.0 M in THF, 0.072 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was diluted with EtOAc and saturated aqueous NH_4Cl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (1:4 EtOAc:hexanes) to give the spirolactone **29** (9.9 mg, 51% over two steps) as a pale yellow oil: IR (film) 2924, 1725, 1531, 1455, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 4:1 diastereomeric mixture) δ 7.95 (s, 1H, *minor*), 7.79 (d, J = 1.9 Hz, 1H, *major*), 7.61 (dd, J = 8.5, 1.9 Hz, 1H, *major*), 7.45 (dd, J = 8.6, 1.8 Hz, 1H, *minor*), 7.41 (d, J = 8.5 Hz, 1H, *major*), 7.34 (s, 1H, *minor*), 7.25 (d, J = 1.8 Hz, 1H, *major*), 7.22 (s, 1H, *minor*), 7.12 (d, J = 1.7 Hz, 1H, *major*), 6.68 (d, J = 8.5 Hz, 1H, *minor*), 5.50 (br s, 1H, *minor*), 5.44 (s, 1H, *major*), 5.30 (s, 1H, *minor*), 5.21, 5.18 (ABq, J = 10.3 Hz, 2H, *major*), 5.13 (s, 1H, *minor*), 5.06 (dt, J = 11.5, 4.2 Hz, 1H, *major*), 4.85 (m, 1H, *minor*), 4.72 (m, 1H, *minor*), 4.64 (dt, J = 11.7, 4.7 Hz, 1H, *major*), 3.23 (s, 3H, *major*), 2.99 (s, 3H, *minor*), 2.59−2.52 (m, 1H, *major and minor*), 2.26 (m, 1H, *minor*), 2.19 (dt, J = 14.6, 4.0 Hz, 1H, *major*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 168.8, 150.6, 136.3, 136.2, 134.5, 132.5, 131.8, 130.5, 127.9, 126.6, 123.1, 122.7, 117.6, 72.0, 65.2, 56.8, 52.7, 46.8, 33.2; HRMS-ES [M + Na]$^+$ calcd for $C_{20}H_{15}BrCl_2N_2NaO_6$, 550.9388; found, 550.9388.

Allylation of Spirolactone 29. To a stirred suspension of spirolactone **29** (102 mg, 0.191 mmol) and NaH (9.2 mg, 60% dispersion in mineral oil, 0.230 mmol) in DMF (2.0 mL) was added allyl iodide (0.026 mL, 0.287 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and heated at 90 °C for 7 h. The reaction mixture was cooled to room temperature, diluted with saturated aqueous NH_4Cl, and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the allyl lactone **30** (95 mg, 87%) as a yellow solid (mp 157−158 °C). Recrystallization from EtOAc provided X-ray quality crystals of **30**: IR (film) 2924, 1725, 1536, 1461, 1359 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 8.6, 2.0 Hz, 1H), 7.10 (d, J = 1.9 Hz, 1H), 6.81 (d, J = 1.8 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 5.51−5.34 (m, 4H), 4.99 (d, J = 17.2 Hz, 1H), 4.94 (d, J = 10.4 Hz, 1H), 4.61 (dt, J = 11.6, 4.0 Hz, 1H), 3.44 (s, 3H), 3.35 (dd, J = 15.2, 6.3 Hz, 1H), 2.99 (ddd, J = 15.2, 10.9, 4.3 Hz, 1H), 2.86 (dd, J = 15.4, 7.1 Hz, 1H), 2.16 (dt, J = 14.7, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 168.0, 150.8, 136.1, 134.8, 134.3, 132.7, 132.6, 132.4, 131.1, 129.0, 128.0, 125.1, 122.1, 120.3, 116.9, 72.3, 65.0, 57.1, 54.4, 54.2, 44.1, 31.5; HRMS-ES [M + Na]$^+$ calcd for $C_{23}H_{19}BrCl_2N_2NaO_6$, 590.9701; found, 590.9697.

2-[5,7-Dichloro-3-(2-hydroxyethyl)-1-methoxymethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-2-(2-methoxyphenyl)-pent-4-enoic Acid Amide (32). To a stirred suspension of NH_4Cl (229 mg, 4.28 mmol) in toluene (5 mL) was slowly added Me_3Al (2.30 mL, 2.0 M in hexanes, 4.60 mmol) at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 1.5 h. To a solution of lactone **31** (291 mg, 0.61 mmol) in toluene (15 mL) was added the above aluminum amide reagent at room temperature, and the mixture was heated at 80 °C overnight. The reaction mixture was cooled to room temperature and was carefully quenched with 1 N HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (10:10:1 CH_2Cl_2:EtOAc:MeOH) to give the amide **32** (286 mg, 95%) as a yellow solid (mp 179−180 °C). Recrystallization from EtOAc provided X-ray quality crystals of **32**: IR (film) 3342, 1708, 1672, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.85 (br s, 1H), 7.14 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 6.78 (t, J = 7.6 Hz, 1H), 6.54 (br s, 1H), 5.87 (m, 1H), 5.51 (br s, 1H), 5.17 (d, J = 16.8 Hz, 1H), 5.03 (d, J = 10.0 Hz, 1H), 4.65 (br s, 2H), 3.55−2.89 (m, 10H), 2.42 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 180.2, 174.7, 156.9, 136.9, 134.6, 134.0, 131.1, 129.6, 129.1, 128.2, 127.3, 124.7, 119.4, 118.4, 114.6, 110.7, 71.3, 58.8, 58.4, 57.0, 56.3, 54.1, 37.3, 34.7; HRMS-ES [M + H]$^+$ calcd for $C_{24}H_{27}Cl_2N_2O_5$, 493.1297; found, 493.1285.

1-Benzyloxymethyl-2-iodo-3-nitrobenzene (38). To a stirred solution of (2-iodo-3-nitrophenyl)methanol (**37**)[21] (0.86 g, 3.08 mmol) in CH_2Cl_2 (6 mL) and cyclohexane (10 mL) was added benzyl 2,2,2-trichloroacetimidate (1.14 mL, 6.13 mmol), followed by TfOH (0.03 mL, 0.34 mmol). The mixture was stirred at room temperature for 9 h and then diluted with saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (1:15 EtOAc:hexanes) to give benzyl ether **38** (1.06 g, 93%) as a yellow oil: IR (film) 2871, 1712, 1526, 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1H), 7.58 (dd, J = 7.9, 1.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.44−7.32 (m, 5H), 4.71 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 137.9, 131.6, 129.4, 129.0, 128.4, 128.2, 123.9, 89.1, 76.9, 73.5; HRMS-EI [M]$^+$ calcd for $C_{14}H_{12}INO_3$, 368.9862; found, 368.9866.

3-Benzyloxymethyl-2-iodophenylamine (39). To a solution of the nitrobenzene **38** (1.05 g, 2.83 mmol) in EtOH (10 mL) and glacial acetic acid (10 mL) was added iron powder (0.79 g, 14.15 mmol). The mixture was heated at 60 °C for 3 h and then cooled to room temperature. The mixture was diluted with iced water and carefully neutralized with solid Na_2CO_3. The resulting solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the aniline **39** (0.83 g, 97%) as a colorless oil: IR (film) 3447, 3357, 2859, 1610, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.29 (m, 5H), 7.14 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 6.9 Hz, 1H), 6.72 (dd, J = 7.9, 0.9 Hz, 1H), 4.65 (s, 2H), 4.56 (s, 2H), 4.00 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 141.8, 138.6, 129.2, 128.9, 128.3, 128.1, 119.4, 114.5, 88.6, 77.2, 73.0; HRMS-ES [M + H]$^+$ calcd for $C_{14}H_{15}INO$, 340.0198; found, 340.0195.

***N*-(3-Benzyloxymethyl-2-iodophenyl)-4-hydroxy-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyramide (41).** To a stirred solution of the aniline **39** (0.69 g, 2.03 mmol) and lactone **40**[22] (0.57 g, 1.84 mmol) in CH_2Cl_2 (30 mL) was added $AlMe_3$ (1.80 mL, 2.0 M in hexane, 3.60 mmol) at 0 °C. The mixture was warmed to room temperature, stirred overnight, and then poured into ice cold aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography

(1:1 EtOAc:hexanes) to give the amide **41** (1.16 g, 97%) as a white solid (mp 126.5−127 °C): IR (film) 3368, 2859, 1661, 1509, 1226 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.11 (dd, J = 8.0, 1.5 Hz, 1H), 7.68 (s, 1H), 7.54 (m, 1H), 7.51−7.28 (m, 10H), 6.94−6.89 (m, 2H), 6.84−6.80 (m, 2H), 5.03 (s, 2H), 4.64 (s, 2H), 4.55 (s, 2H), 3.79 (t, J = 5.8 Hz, 2H), 3.74 (s, 3H), 2.77 (t, J = 5.8 Hz, 2H), 2.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 154.6, 153.1, 141.9, 138.64, 138.61, 138.3, 135.5, 135.3, 134.3, 129.9, 129.6, 129.3, 129.00, 128.95, 128.9, 128.3, 125.9, 122.5, 116.3, 115.2, 96.0, 77.1, 73.1, 69.7, 62.5, 56.2, 31.9; HRMS-ES $[M + H]^+$ calcd for $C_{33}H_{33}INO_5$, 650.1404; found, 650.1404.

***N*-(3-Benzyloxymethyl-2-iodophenyl)-4-(*tert*-butyldimethylsilanyloxy)-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyramide (42).** To a solution of the amide **41** (568 mg, 0.87 mmol) and imidazole (178 mg, 2.62 mmol) in DMF (8.7 mL) was added TBSCl (316 mg, 2.09 mmol). The reaction mixture was stirred at room temperature overnight and then diluted with EtOAc. The solution was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the TBS ether **42** (641 mg, 96%) as a colorless oil: IR (film) 2950, 2848, 1678, 1509, 1226, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.2 (dd, J = 8.0, 1.4 Hz, 1H), 7.74 (s, 1H), 7.56 (m, 1H), 7.44−7.29 (m, 9H), 6.94−6.91 (m, 2H), 6.85−6.82 (m, 2H), 5.03 (s, 2H), 4.65 (s, 2H), 4.59 (s, 2H), 3.9 (t, J = 6.1 Hz, 2H), 3.76 (s, 3H), 2.84 (t, J = 6.1 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 154.5, 153.3, 141.8, 139.0, 138.5, 138.3, 135.7, 135.2, 134.1, 129.9, 129.3, 129.2, 128.9, 128.8, 128.5, 128.23, 128.21, 125.6, 122.4, 116.4, 115.1, 95.9, 77.2, 73.1, 69.4, 62.5, 56.1, 31.8, 26.4, 18.8, −4.9; HRMS-ES $[M + H]^+$ calcd for $C_{39}H_{47}INO_5Si$, 764.2268; found, 764.2271.

***N*-(3-Benzyloxymethyl-2-iodophenyl)-4-(*tert*-butyldimethylsilanyloxy)-2-[2-(4-methoxyphenoxymethyl)benzylidene]-*N*-methylbutyramide (43).** To a stirred suspension of NaH (40 mg, 60% dispersion in mineral oil, 1.01 mmol) in THF (8 mL) was added a solution of the amide **42** (641 mg, 0.84 mmol) in THF (3 mL) at 0 °C. The mixture was stirred at room temperature for 30 min and recooled to 0 °C. To the solution was added MeI (0.08 mL, 1.29 mmol), and the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (1:3 EtOAc:hexanes) to give the *N*-methyl amide **43** (630 mg, 96%) as a colorless oil: IR (film) 2950, 2860, 1650, 1509, 1226, 1090 cm^{-1}; ^1H NMR (300 MHz, toluene-d_8, 90 °C) δ 7.38 (m, 1H), 7.28−7.01 (m, 12H), 6.78 (dt, J = 12.8, 3.8 Hz, 2H), 6.72 (dt, J = 12.8, 3.8 Hz, 2H), 4.59 (d, J = 5.5 Hz, 2H), 4.42 (d, J = 7.1 Hz, 2H), 4.38 (s, 2H), 3.94 (m, 2H), 3.45 (s, 3H), 3.22 (s, 3H), 2.75 (m, 1H), 2.57 (m, 1H), 0.95 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, toluene-d_8, 90 °C) δ 170.7, 155.1, 153.6, 148.3, 144.3, 137.5, 129.2, 136.3, 135.1, 131.9, 129.2, 129.1, 128.7, 128.5, 128.1, 127.84, 127.78, 127.7, 127.53, 127.48, 116.9, 115.3, 103.3, 77.1, 73.1, 69.1, 62.5, 55.4, 37.6, 34.0, 26.2, 18.5, −5.2; HRMS-ES $[M + H]^+$ calcd for $C_{40}H_{49}INO_5Si$, 778.2425; found, 778.2397.

{4-Benzyloxymethyl-3-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl}-[2-(4-methoxyphenoxymethyl)phenyl]-acetic Acid Methyl Ester (44). To a solution of *N*-methyl amide **43** (222 mg, 0.286 mmol) in DMA (3.0 mL) and MeOH (1.5 mL) were added $Pd(OAc)_2$ (6.4 mg, 0.029 mmol), biphenyldicyclohexylphosphine (30.1 mg, 0.086 mmol), and NaOAc (46.9 mg, 0.572 mmol). The mixture was stirred at 85 °C under a CO atmosphere (1 atm) for 24 h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (1:5 EtOAc:hexanes) to give the methyl ester **44** (145 mg, 71%) as a colorless oil: IR (film) 2950, 2859, 1740, 1712, 1509, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.17 (m, 9H), 7.12 (dd, J = 14.8, 7.5 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 9.1 Hz, 2H), 6.82 (d, J = 9.2 Hz, 2H), 6.65 (d, J = 7.7 Hz, 1H), 4.93, 4.69 (ABq, J = 11.6 Hz, 2H), 4.63 (s, 1H), 4.41, 4.29 (ABq, J = 11.9 Hz, 2H), 3.89, 3.77 (ABq, J = 11.1 Hz, 2H), 3.78 (s, 3H), 3.59 (s, 3H), 3.19 (m, 2H), 3.10 (s, 3H), 2.56 (dt, J = 14.4, 7.2 Hz, 1H), 2.13 (dt, J = 13.4, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 171.6, 154.5, 153.1, 145.4, 138.2, 136.5, 136.0, 133.4, 130.6, 129.7, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1, 126.1, 123.5, 116.2, 115.1, 107.6, 73.4, 69.2, 68.9, 60.0, 56.1, 55.1, 52.5, 38.0, 26.9, 26.4, 26.2, 18.6, −5.3, −5.4; HRMS-ES $[M + H]^+$ calcd for $C_{42}H_{52}NO_7Si$, 710.3513; found, 710.3521.

Synthesis of Spirolactone 45. To a stirred solution of methyl ester **44** (172 mg, 0.24 mmol) in THF (10 mL) was added TBAF (0.27 mL, 1.0 M in THF, 0.27 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. The mixture was diluted with EtOAc and saturated aqueous NH_4Cl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the lactone **45** (116 mg, 85%) as a separable mixture of diastereomers (2:1). For analytical purposes, the diastereomers were separated by preparative TLC (1:1 EtOAc:hexanes). More polar major diastereomer of **45** (colorless oil): IR (film) 2927, 1752, 1712, 1605, 1509, 1226 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.01 (m, 11H), 6.83−6.74 (m, 4H), 6.54 (d, J = 7.7 Hz, 1H), 5.03 (s, 1H), 4.83 (ddd, J = 11.7, 6.7, 4.9 Hz, 1H), 4.67−4.43 (m, 6H), 4.30 (ddd, J = 11.8, 7.2, 4.6 Hz, 1H), 3.77 (s, 3H), 2.96 (s, 3H), 2.61 (ddd, J = 14.7, 6.8, 4.8 Hz, 1H), 2.27 (ddd, J = 14.6, 7.4, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 171.1, 154.5, 153.0, 144.1, 137.3, 136.5, 134.4, 132.3, 130.8, 129.7, 129.2, 129.1, 128.79, 128.75, 128.7, 128.2, 127.8, 125.1, 116.3, 115.1, 108.6, 73.8, 70.0, 69.7, 64.8, 56.2, 52.6, 47.2, 30.3, 26.5; HRMS-ES $[M + H]^+$ calcd for $C_{35}H_{34}NO_6$, 564.2386; found, 564.2391. Less polar minor diastereomer of **45** (colorless oil): IR (film) 2916, 1746, 1706, 1610, 1509, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.30 (m, 5H), 7.27−7.23 (m, 3H), 7.09 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 6.88−6.84 (m, 3H), 6.63 (d, J = 7.8 Hz, 1H), 6.54 (d, J = 7.4 Hz, 1H), 5.32 (d, J = 11.7 Hz, 1H), 4.98 (s, 1H), 4.80−4.55 (m, 6H), 4.38 (dd, J = 11.7, 5.6 Hz, 1H), 3.79 (s, 3H), 2.91 (s, 3H), 2.73 (td, J = 14.5, 5.8 Hz, 1H), 2.23 (d, J = 14.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 172.6, 154.6, 153.1, 144.2, 138.2, 136.7, 136.0, 131.5, 130.8, 129.8, 129.7, 129.0, 128.9, 128.6, 128.3, 128.2, 127.5, 125.4, 116.6, 115.1, 108.5, 73.6, 70.2, 69.2, 66.1, 56.1, 52.5, 47.1, 31.6, 26.8; HRMS-ES $[M + Na]^+$ calcd for $C_{35}H_{33}NNaO_6$, 586.2206; found, 586.2210.

O-Allylation of Spirolactone 45. To a stirred suspension of spirolactone **45** (20.6 mg, 0.037 mmol) and NaH (2.0 mg, 60% dispersion in mineral oil, 0.050 mmol) in DMF (2 mL) was added allyl iodide (0.010 mL, 0.109 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the *O*-allyl ketene acetal **46** (12.7 mg, 57%, 71% based on recovered starting material) as a colorless oil and unreacted spirolactone **45** (3.9 mg): IR (film) 3470, 2927, 1706, 1509, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 2:1 atropisomeric mixture) δ 7.44−7.22 (m, 7H, *major and minor*), 7.13 (t, J = 7.7 Hz, 1H, *minor*), 7.08−7.01 (m, 1H, *major and minor*), 6.98−6.96 (m, 2H, *major and minor*), 6.91 (d, J = 6.7 Hz, 1H, *minor*), 6.86−6.82 (m, 3H, *major and minor*), 6.77 (t, J = 7.6 Hz, 1H, *major*), 6.58 (d, J = 8.1 Hz, 1H, *major and minor*), 6.35 (d, J = 7.8 Hz, 1H, *minor*), 5.78 (m, 1H, *major and minor*), 5.27 (d, J = 13.3 Hz, 1H, *major*), 5.17−5.06 (m, 3H, *major*, 2H, *minor*), 5.01−4.84 (m, 2H, *major and minor*), 4.77−4.65 (m, 2H, *major*, 3H, *minor*), 4.44−4.24 (m, 4H, *major and minor*), 3.78 (s, 3H, *major and minor*), 3.16 (s, 3H, *minor*), 2.95 (s, 3H, *major*), 2.58 (m, 1H, *major and minor*), 1.98 (d, J = 14.6 Hz, 1H, *major*), 1.85 (d, J = 14.3 Hz, 1H, *minor*); ^{13}C NMR (300 MHz, $CDCl_3$) δ 180.7, 179.4, 157.6, 156.3, 154.0, 153.9, 153.8,

153.6, 144.0, 143.6, 138.32, 138.27, 137.2, 135.2, 134.7, 134.0, 133.7, 133.4, 132.7, 130.9, 130.2, 129.8, 129.6, 129.0, 128.9, 128.81, 128.76, 128.4, 128.34, 128.26, 128.1, 127.5, 127.4, 127.1, 127.0, 126.7, 126.4, 125.2, 124.4, 118.22, 118.16, 116.2, 115.9, 115.0, 114.9, 108.0, 107.9, 87.1, 84.4, 73.8, 73.5, 69.30, 69.26, 68.33, 68.26, 65.5, 64.6, 56.1, 50.5, 50.4, 32.6, 31.4, 26.8, 26.6; HRMS-ES $[M + H]^+$ calcd for $C_{38}H_{37}NO_6$, 604.2699; found, 604.2684.

Thermal Claisen Rearrangement of Ketene Acetal 46. A solution of ketene acetal **46** in DMF or toluene was heated at 130 °C and stirred for 15 h. The solvent was removed under reduced pressure. The residue was purified by preparative TLC (1:1 EtOAc:hexanes) to give the two allyl lactone diastereomers **47** and **48**. More polar major diastereomer **47** (oil): IR (film) 2929, 1704, 1508, 1228 cm^{-1}; ^1H NMR (300 MHz, toluene-d_8, 90 °C) δ 7.56 (d, J = 7.9 Hz, 1H), 7.26−6.98 (m, 9H), 6.90 (t, J = 7.2 Hz, 1H), 6.80−6.67 (m, 4H), 6.38 (d, J = 6.8 Hz, 1H), 6.10 (m, 1H), 5.21 (br s, 1H), 5.13 (td, J = 12.1, 4.4 Hz, 1H), 4.77 (s, 1H), 4.72 (d, J = 8.8 Hz, 1H), 4.52 (br s, 1H), 4.20, 4.13 (ABq, J = 12.1 Hz, 2H), 4.06 (dd, J = 11.0, 7.0 Hz, 1H), 3.47 (s, 3H), 3.16 (m, 1H), 3.15 (s, 2H), 2.85 (m, 1H), 2.81 (s, 3H), 2.53 (dd, J = 15.4, 6.8 Hz, 1H), 1.35 (dd, J = 14.7, 4.6 Hz, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 °C) δ 176.5, 172.4, 155.3, 154.0, 145.1, 139.6, 139.1, 138.6, 137.8, 137.3, 134.1, 132.3, 129.4, 128.7, 128.2, 127.9, 127.5, 126.7, 127.5, 126.7, 125.8, 116.1, 115.7, 107.5, 73.0, 69.6, 69.0, 64.6, 59.1, 57.0, 55.7, 41.2, 27.2, 25.7; HRMS-ES $[M + H]^+$ calcd for $C_{38}H_{38}NO_6$, 604.2699; found, 604.2714. Less polar minor diastereomer **48** (oil): IR (film) 2918, 1704, 1508, 1228 cm^{-1}; ^1H NMR (300 MHz, toluene-d_8, 90 °C) δ 7.83 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 2H), 7.22−6.96 (m, 8H), 6.77 (d, J = 8.8 Hz, 2H), 6.60 (t, J = 7.8 Hz, 1H), 6.36 (br s, 1H), 5.99 (d, J = 7.7 Hz, 1H), 5.77 (m, 1H), 5.52 (td, J = 12.3, 4.1 Hz, 1H), 5.33 (d, J = 11.8 Hz, 1H), 4.98−4.85 (m, 3H), 4.60, 4.57 (ABq, J = 10.3 Hz, 2H), 4.50, 4.44 (ABq, J = 11.9 Hz, 2H), 4.0 (dd, J = 11.1, 6.9 Hz, 1H), 3.47 (s, 3H), 3.39 (dd, J = 14.7, 5.6 Hz, 1H), 2.95 (dd, J = 14.3, 6.7 Hz, 1H), 2.74 (td, J = 14.4, 6.9 Hz, 1H), 2.32 (s, 3H), 1.42 (dd, J = 14.7, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 °C) δ 177.2, 169.9, 155.1, 154.8, 145.9, 139.7, 138.1, 137.4, 137.2, 134.5, 133.9, 129.5, 129.4, 129.3, 128.9, 128.4, 127.5, 127.3, 125.9, 125.6, 117.7, 117.1, 115.6, 107.8, 73.6, 71.2, 70.4, 64.7, 57.9, 57.8, 55.7, 42.0, 26.9, 25.4; HRMS-ES $[M + H]^+$ calcd for $C_{38}H_{38}NO_6$, 604.2699; found, 604.2722.

Dimethylcarbamic Acid 2-Iodo-3-nitrophenyl Ester (50). To a stirred solution of 2-iodo-3-nitrophenol (**49**, 422 mg, 1.59 mmol), NEt_3 (0.33 mL, 2.35 mmol),[23] and DMAP (19.4 mg, 0.16 mmol) in CH_2Cl_2 (20 mL) was added *N*,*N*-dimethylcarbamyl chloride (0.18 mL, 1.96 mmol) at 0 °C. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the carbamoyl-protected phenol **50** (505 mg, 94%) as a white solid (mp 125−126 °C): IR (film) 1713, 1531, 1386, 1359, 1246, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, J = 7.9, 1.4 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.53 (dd, J = 8.1, 1.4 Hz, 1H), 3.35 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 153.9, 153.4, 130.0, 127.3, 122.4, 86.1, 37.5, 37.3; HRMS-ES $[M + Na]^+$ calcd for $C_9H_9IN_2NaO_4$, 358.9505; found, 358.9513.

Dimethylcarbamic Acid 3-Amino-2-iodophenyl Ester (51). To a solution of the nitrobenzene **50** (446 mg, 1.33 mmol) in EtOH (10 mL) and glacial acetic acid (5 mL) was added iron powder (296 mg, 5.30 mmol). The mixture was heated at 60 °C for 4 h and then cooled to room temperature. The mixture was diluted with water and carefully neutralized with solid Na_2CO_3. The resulting solution was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the aniline **51** (375 mg, 93%) as a white solid (mp 113−114 °C): IR (film) 3333, 1714, 1617, 1466, 1386, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (t, J = 7.9 Hz, 1H), 6.80 (dd, J = 8.0, 2.9 Hz, 2H), 4.50 (br s, 2H), 3.42 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 152.7, 149.0, 129.8, 113.0, 112.2, 82.0, 37.3, 37.2; HRMS-ES $[M + H]^+$ calcd for $C_9H_{12}IN_2O_2$, 306.9944; found, 306.9949.

Dimethylcarbamic Acid 3-{4-Hydroxy-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyrylamino}-2-iodophenyl Ester (52). To a stirred solution of aniline **51** (111 mg, 0.362 mmol) and lactone **40**[22] (107 mg, 0.345 mmol) in CH_2Cl_2 (10 mL) was added $AlMe_3$ (0.19 mL, 2.0 M in hexane, 0.380 mmol) at 0 °C. The mixture was warmed to room temperature, stirred overnight, and then carefully diluted with saturated aqueous NH_4Cl at 0 °C, followed by CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (10:1 CH_2Cl_2:MeOH) to give the amide **52** (207 mg, 97%) as a white solid (mp 110−111 °C): IR (film) 3387, 2934, 1725, 1665, 1509, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.06 (dd, J = 8.2, 1.4 Hz, 1H), 7.64 (s, 1H), 7.53−7.51 (m, 1H), 7.40−7.31 (m, 4H), 6.97 (dd, J = 8.1, 1.4 Hz, 1H), 6.92−6.79 (m, 4H), 5.01 (s, 2H), 3.75 (t, J = 5.9 Hz, 2H), 3.74 (s, 3H), 3.18 (s, 3H), 3.03 (s, 3H), 2.74 (t, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 154.6, 154.0, 153.2, 152.4, 140.0, 138.5, 135.6, 135.2, 134.5, 129.9, 129.7, 129.6, 129.0, 128.8, 119.82, 119.76, 116.4, 115.2, 89.4, 69.6, 62.3, 56.2, 37.3, 37.2, 31.8; HRMS-ES $[M + H]^+$ calcd for $C_{28}H_{30}IN_2O_6$, 617.1149; found, 617.1139.

Dimethylcarbamic Acid 2-Iodo-3-{4-methoxymethoxy-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyrylamino}phenyl Ester (53). To a mixture of amide **52** (961 mg, 1.56 mmol), $(i\text{-}Pr)_2NEt$ (0.54 mL, 3.10 mmol), and NaI (467 mg, 3.12 mmol) in CH_2Cl_2 (30 mL) was added MOMCl (0.18 mL, 2.37 mmol) at 0 °C. The mixture was warmed to room temperature, stirred overnight, and then diluted with saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the MOM ether **53** (914 mg, 89%) as a white solid (mp 107−108 °C): IR (film) 3389, 2937, 1729, 1673, 1509, 1385, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.17 (dd, J = 8.3, 1.3 Hz, 1H), 7.67 (s, 1H), 7.57−7.54 (m, 1H), 7.43−7.34 (m, 4H), 6.98 (dd, J = 8.3, 1.3 Hz, 1H), 6.93−6.80 (m, 4H), 5.02 (s, 2H), 4.58 (s, 2H), 3.75 (s, 3H), 3.70 (t, J = 6.3 Hz, 2H), 3.29 (s, 3H), 3.19 (s, 3H), 3.05 (s, 3H), 2.84 (t, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 154.6, 153.9, 153.2, 152.3, 140.2, 138.1, 135.8, 135.1, 134.4, 130.0, 129.5, 129.3, 128.9, 128.6, 119.5, 119.4, 116.4, 115.2, 96.7, 88.8, 69.4, 66.5, 56.2, 55.8, 37.3, 37.2, 29.0; HRMS-ES $[M + H]^+$ calcd for $C_{30}H_{34}IN_2O_7$, 661.1411; found, 661.1397.

Dimethylcarbamic Acid 2-Iodo-3-({4-methoxymethoxy-2-[2-(4-methoxyphenoxymethyl)benzylidene]butyryl}methylamino)-phenyl Ester (54). To a stirred suspension of NaH (11.1 mg, 60% dispersion in mineral oil, 0.278 mmol) in THF (6 mL) was added a solution of lactam **53** (167 mg, 0.253 mmol) in THF (4 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and recooled to 0 °C. To the solution was added MeI (0.019 mL, 0.305 mmol), and the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (10:10:1 CH_2Cl_2:EtOAc:MeOH) to give the *N*-methyl amide **54** (167 mg, 98%) as a colorless oil: IR (film) 2926, 1723, 1616, 1503, 1227, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−6.96 (m, 8H), 6.81 (br s, 4H), 4.68−4.48 (m, 4H), 3.77 (s, 3H), 3.67 (br s, 2H), 3.36 (s, 6H), 3.11 (s, 3H), 3.02 (s, 3H), 2.59 (br s, 1H), 2.43 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 154.4, 153.8, 153.1, 148.8, 136.5, 135.9, 134.4, 133.2, 130.2, 129.1, 128.4, 127.8, 127.0, 122.8, 116.5, 114.9, 97.3, 96.6, 68.5, 66.2, 56.1, 55.7, 37.8, 37.3, 37.1, 30.3; HRMS-ES $[M + H]^+$ calcd for $C_{31}H_{36}IN_2O_7$, 675.1567; found, 675.1562.

[4-Dimethylcarbamoyloxy-3-(2-methoxymethoxyethyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-[2-(4-methoxyphenoxymethyl)phenyl]acetic Acid Methyl Ester (55). To a solution of *N*-methyl amide **54** (280 mg, 0.415 mmol) in DMA (2.6 mL) and MeOH (1.3 mL) were added $Pd(OAc)_2$ (18.6 mg, 0.083 mmol), P(*o*-Tol)$_3$ (75.7 mg, 0.249 mmol), and NaOAc (68.0 mg, 0.829 mmol). The mixture was stirred at 90 °C under a CO atmosphere (1 atm) for 1 day. The reaction mixture was cooled to room temperature and diluted with EtOAc. The solution was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (1:2 EtOAc:hexanes) to give the ester **55** (199 mg, 79%) as a colorless oil: IR (film) 2938, 1729, 1616, 1509, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.50 (m, 1H), 7.32−7.16 (m, 4H), 6.97 (d, J = 8.4 Hz, 1H), 6.88−6.80 (m, 4H), 6.51 (d, J = 7.6 Hz, 1H), 5.08, 4.85 (ABq, J = 11.6 Hz, 2H), 4.68 (s, 1H), 4.32, 4.21 (ABq, J = 6.5 Hz, 2H), 3.78 (s, 3H), 3.61 (s, 3H), 3.19−3.03 (m, 2H), 3.12 (s, 3H), 3.09 (s, 3H), 2.88 (s, 3H), 2.64 (s, 3H), 2.63−2.55 (m, 1H), 2.47−2.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 171.2, 154.5, 153.4, 153.1, 148.7, 146.3, 136.5, 133.5, 130.6, 129.9, 129.6, 128.3, 127.9, 118.6, 116.8, 116.3, 115.0, 104.9, 96.7, 69.2, 64.4, 56.2, 55.4, 54.5, 52.6, 37.2, 36.4, 34.2, 26.9; HRMS-ES [M + H]$^+$ calcd for $C_{33}H_{39}N_2O_9$, 607.2656; found, 607.2645.

Synthesis of Spirolactone 57. To a stirred solution of ester **55** (61.1 mg, 0.101 mmol) in MeOH (5.0 mL) was added concentrated HCl (1 drop) at room temperature. The mixture was warmed to 60 °C and stirred for 4 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give spirolactone **57** (37.5 mg, 70%) as a white solid (mp 213-215 °C) and hydroxy ester **56** (9.5 mg, 17%) as a colorless oil. Spirolactone **57**: IR (film) 1729, 1712, 1622, 1509, 1226, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.5, 1.1 Hz, 1H), 7.27−7.19 (m, 2H), 7.12 (td, J = 7.6, 1.3 Hz, 1H), 7.04 (dd, J = 7.6, 1.4 Hz, 1H), 6.82 (dd, J = 8.4, 0.6 Hz, 1H), 6.78−6.70 (m, 4H), 6.42 (d, J = 7.8 Hz, 1H), 5.01 (ddd, J = 11.4, 6.8, 4.7 Hz, 1H), 4.97 (s, 1H), 4.94 (d, J = 11.9 Hz, 1H), 4.56 (ddd, J = 11.7, 7.5, 4.2 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 3.75 (s, 3H), 3.00 (s, 3H), 2.95 (s, 3H), 2.94 (s, 3H), 2.55 (ddd, J = 14.8, 6.7, 4.4 Hz, 1H), 2.42 (ddd, J = 14.7, 7.7, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 170.8, 154.6, 154.3, 152.9, 148.2, 144.9, 136.5, 132.2, 131.4, 130.6, 129.5, 128.3, 128.0, 121.9, 118.0, 116.7, 115.0, 106.0, 69.8, 65.0, 56.1, 52.1, 46.6, 37.6, 36.8, 30.4, 26.7; HRMS-ES [M + Na]$^+$ calcd for $C_{30}H_{30}N_2NaO_7$, 553.1951; found, 553.1963.

Hydroxy ester **56**: IR (film) 3470, 2927, 1735, 1712, 1616, 1509, 1226, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.52 (m, 1H), 7.28−7.17 (m, 4H), 6.86−6.80 (m, 5H), 6.53 (d, J = 7.7 Hz, 1H), 5.07, 4.83 (ABq, J = 12.9 Hz, 2H), 4.70 (s, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.34 (t, J = 6.3 Hz, 2H), 3.12 (s, 3H), 2.92 (s, 3H), 2.72 (s, 3H), 2.56 (dt, J = 13.8, 6.9 Hz, 1H), 2.34 (dt, J = 12.7, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 171.2, 154.5, 154.4, 153.0, 148.3, 146.2, 136.4, 133.4, 130.6, 130.0, 129.6, 128.2, 128.0, 120.3, 117.2, 116.2, 115.0, 105.5, 69.2, 59.6, 56.2, 54.6, 52.7, 37.4, 37.2, 36.6, 27.0; HRMS-ES [M + H]$^+$ calcd for $C_{31}H_{35}N_2O_8$, 563.2393; found, 563.2392.

O-Allylation of Spirolactone 57. To a stirred suspension of spirolactone **57** (69.1 mg, 0.130 mmol) and NaH (6.2 mg, 60% dispersion in mineral oil, 0.155 mmol) in DMF (2 mL) was added allyl iodide (0.024 mL, 0.262 mmol) at room temperature. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the *O*-allyl ketene acetal **58** (46.6 mg, 63%) as a colorless oil: IR (film) 2916, 1712, 1616, 1509, 1226 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 2:1 atropisomeric mixture) δ 7.40 (d, J = 7.3 Hz, 1H), 7.26−6.95 (m, 7.5H), 6.90−6.77 (m, 4.5 H), 6.73 (s, 2H), 6.46 (d, J = 7.7 Hz, 1H), 6.43 (d, J = 7.8 Hz, 0.5H), 5.80−5.64 (m, 1.5H), 5.24−4.86 (m, 7.5H), 4.38−4.27 (m, 4.5H), 3.78 (s, 3H), 3.76 (s, 1.5H), 3.18 (s, 3H), 3.76 (s, 1.5H), 3.18 (s, 3H), 3.073 (s, 3H), 3.067 (s, 3H), 2.99 (s, 1.5H), 2.95 (s, 3H), 2.49−2.39 (m, 1.5H), 2.08−1.99 (m, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 179.0, 157.1, 156.2, 154.5, 154.3, 153.9, 153.8, 153.5, 148.2, 148.0, 145.1, 145.0, 138.6, 138.1, 134.0, 133.7, 132.9, 132.5, 131.5, 131.1, 129.6, 129.5, 127.5, 127.2, 126.7, 126.4, 126.2, 123.0, 122.5, 118.3, 118.2, 117.9, 117.7, 116.3, 116.2, 115.0, 114.8, 105.5, 105.3, 88.0, 84.6, 69.5, 69.4, 68.5, 68.3, 65.1, 65.0, 56.2, 50.20, 50.15, 37.5, 37.4, 36.9, 31.6, 29.8, 26.9, 26.8; HRMS-ES [M + H]$^+$ calcd for $C_{33}H_{35}N_2O_7$, 571.2444; found, 571.2429.

Claisen Rearrangement of Ketene Acetal 58. A solution of ketene acetal **58** in DMF or toluene was heated at 110 °C and stirred overnight. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:1 EtOAc:hexanes) to give the allyl lactone diastereomers **59** and **60**. More polar major diastereomer **59** (pale yellow oil): IR (film) 2927, 1729, 1712, 1616, 1502, 1226, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 7.23 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.77 (br s, 2H), 6.60−6.56 (m, 2H), 5.64 (m, 1H), 5.04−4.87 (m, 3H), 4.66 (br s, 1H), 4.47 (br s, 1H), 3.79 (s, 3H), 3.22 (br s, 1H), 3.10 (s, 3H), 2.92−2.87 (m, 4H), 2.78−2.70 (m, 4H), 2.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 171.9, 154.0, 153.7, 153.0, 149.3, 145.0, 137.0, 134.9, 134.3, 131.7, 131.4, 130.1, 127.5, 126.8, 120.1, 118.3, 116.9, 115.0, 114.5, 105.2, 68.7, 65.4, 55.7, 55.4, 38.4, 36.9, 36.5, 29.7, 29.4, 24.6; HRMS-ES [M + Na]$^+$ calcd for $C_{33}H_{34}N_2NaO_7$, 593.2264; found, 593.2263. Less polar minor diastereomer **60** (pale yellow oil): IR (film) 2927, 1729, 1712, 1616, 1509, 1226, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.30 (t, J = 8.1 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 7.02−7.00 (m, 2H), 6.90−6.83 (m, 4H), 6.54 (br s, 1H), 6.34 (d, J = 7.7 Hz, 1H), 5.63−5.56 (m, 2H), 5.06−4.96 (m, 3H), 4.79 (br s, 1H), 4.55 (dd, J = 11.3, 6.4 Hz, 1H), 3.81 (s, 3H), 3.61 (dd, J = 15.2, 5.9 Hz, 1H), 3.23 (s, 3H), 3.18−3.02 (m, 2H), 3.11 (s, 3H), 2.58 (s, 3H), 2.01 (dd, J = 14.9, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 171.1, 154.6, 154.1, 154.0, 149.4, 146.4, 138.3, 133.8, 132.4, 130.8, 129.9, 127.8, 125.9, 119.4, 118.4, 118.2, 116.4, 115.0, 113.7, 105.7, 71.1, 65.5, 56.7, 56.2 41.9, 37.5, 37.1, 30.1, 26.1, 24.9; HRMS-ES [M + Na]$^+$ calcd for $C_{33}H_{34}N_2NaO_7$, 593.2264; found, 593.2274.

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Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds along with X-ray data for compounds **30** and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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