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Toward the Total Synthesis of FR901483: Concise Synthesis of the Azatricyclic Skeleton

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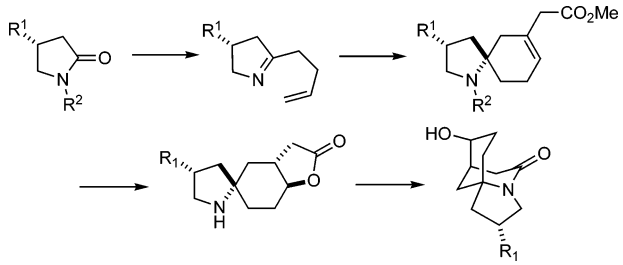

A concise synthesis of the azatricyclic core of FR901483 has been accomplished using a novel strategy that involves a nucleophilic addition to an *N*-acyl iminium ion, a ring-closing metathesis, a diastereoselective hydroboration, and a lactone−lactam rearrangement that worked well in a preliminary model study. Extension of this approach to the synthesis of a more highly functionalized intermediate that could be transformed into (−)-FR901483 first required the development of a new protecting group, the 1-ethylallyloxycarbamate group, for amines that may be removed under mild conditions. However, because the stereoselectivity in a key step in which a functionalized allyl zinc reagent was added to an intermediate hydroxy-substituted imine was low, this route to (−)-FR901483 is no longer being pursued.

Introduction

(−)-FR901483 (**1**) is a potent immunosuppressant that was isolated in 1996 from the fermentation broth of the fungal strain *Cladobotryum* sp. No. 11231 by scientists at the Fujisawa Pharmaceutical Company in Japan.[1] The structure and relative stereochemical relationships of **1** were initially determined by NMR spectroscopy, but the absolute configuration was elucidated by Snider and Lin,[2] who reported the first total synthesis of **1**. From a medicinal perspective, (−)-FR901483 is of considerable interest because it prolongs graft survival time in the rat skin allograft model by inhibiting purine nucleotide synthesis, a mechanism of action that differs from that of more commonly used immunosuppressants such as cyclosporin A and tacrolimus (FK-506).[1] Owing to its intriguing structure and its biological activity, FR901483 has received considerable attention from members of the synthetic community, and since its first total synthesis by Snider and Lin,[2] several total syntheses and numerous approaches to **1** have been reported.[3,4] Most of the total syntheses of FR901483 employ a strategy that drew inspiration from its putative biosynthesis and thus feature an intramolecular aldol reaction to generate the azatricyclic core, although other approaches involve construction of this core via cyclizations of iminium ions.[3f,4b]

(1) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44.

(2) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786.

(3) For total syntheses of FR901483, see: (a) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593−4596. (b) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534−7538. (c) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765−767. (d) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125−1128. (e) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 2729−2731. (f) Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907−916.

(4) For approaches to FR901438, see: (a) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391−1402. (b) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280−8281. (c) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442−6443. (d) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667−4670. (e) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353−2356. (f) Brummond, K. M; Lu, J. *Org. Lett.* **2001**, *3*, 1347−1349. (g) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387−8390. (h) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755−2759. (i) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046−2055. (j) Kaden, S.; Reissig, H.-S. *Org. Lett.* **2006**, *8*, 4763−4766. (k) Gotchev, D. B.; Comins, D. L. *J. Org. Chem.* **2006**, *71*, 9393−9402. (l) Asari, A.; Angelov, P.; Auty, J. M.; Hayes, C. J. *Tetrahedron Lett.* **2007**, *48*, 2631−2634.

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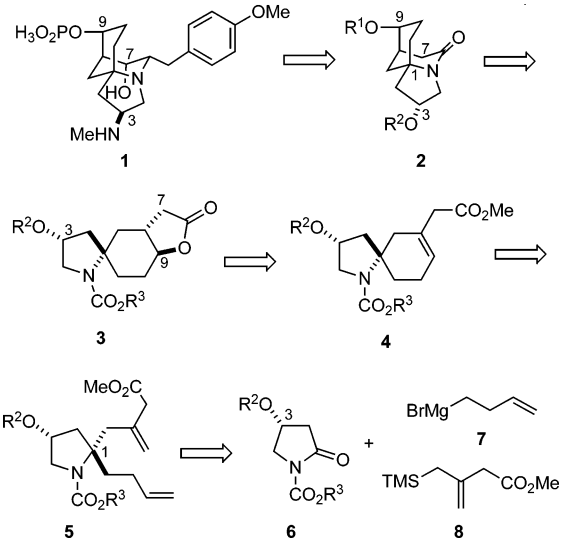
We were attracted to the synthesis of (−)-FR901483 (**1**) in the more general context of our longstanding interest in developing novel and general approaches to alkaloid natural products. For example, we have been interested in discovering new reactions of iminium ions that may be implemented for constructing heterocyclic frameworks common to different families of alkaloids.[5] In another area, we have been interested in applications of transition-metal-catalyzed transformations including ring-closing metathesis (RCM) and Pauson−Khand reactions that may be used to form nitrogen heterocycles.[6,7] Herein, we describe a novel approach, which differs from all of the prior art, for the synthesis of **1**, and the details of our studies on the facile construction of the tricyclic core.[8] During the course of these studies, it was necessary to develop a new nitrogen protecting group that may be removed under very mild conditions.

The essential elements of our plan for the synthesis of (−)-FR901483 are outlined in retrosynthetic format in Scheme 1. The endgame, which is related to that reported recently by Weinreb,[4i] was envisioned to entail the stereoselective elaboration of the advanced intermediate **2** via α-hydroxylation of an amide enolate, introduction of the *p*-methoxybenzyl group, and a Mitsunobu reaction involving the hydroxyl group at C(3) (Scheme 1).[9] The azatricycle **2** would be formed by the base-

SCHEME 1

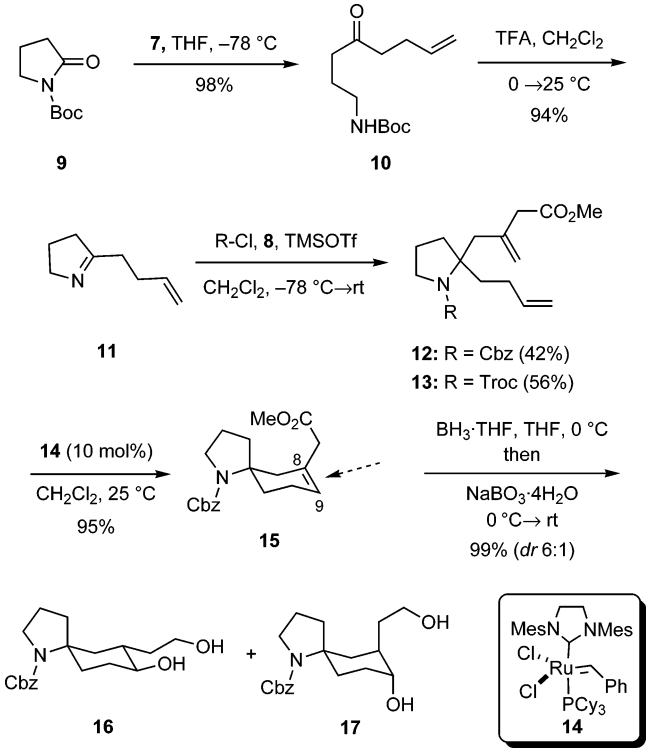


promoted lactone−lactam rearrangement of the secondary amine formed upon deprotection of **3**, which would be produced by lactonization of the equatorial alcohol obtained by the selective hydroboration−oxidation of the β,γ-unsaturated ester **4**.[10] The synthesis of spirocycle **4** would be achieved by the RCM of the diene **5**,[11] which would be derived from the stereoselective geminal dialkylation of the lactam carbonyl group in **6** with the Grignard reagent **7** and the allylsilane **8**. We anticipated that the stereochemistry of this geminal alkylation would be in accord with the findings of Woerpel et al.[12] Namely, we predicted that the allylsilane **8** would add to an intermediate imine or *N*-acyl iminium ion from the same face as the protected hydroxyl group, giving the requisite stereochemistry at C(1) of **5**.

Results and Discussion

Preliminary Model Studies. To establish the underlying feasibility of our strategy to access the tricyclic skeleton of **1**, we first conducted a model study on a pyrrolidinone substrate lacking the hydroxyl function at C(3). The Grignard reagent **7** was added to the Boc-protected lactam **9** to provide the protected linear aminoketone **10** in 98% yield (Scheme 2).[13] The Boc

SCHEME 2



protecting group was removed using trifluoroacetic acid (TFA), and cyclization of the intermediate aminoketone formed in situ gave the known imine **11**[14] in 94% yield. Although this transformation could also be effected by using iodotrimethylsilane (TMSI) in a shorter reaction time (1 h) and in quantitative yield, TFA was both more convenient and less expensive. The imine **11** was then treated with benzyl chloroformate (CbzCl) and the known allylsilane **8**[15] in the presence of a stoichiometric amount of trimethylsilyl triflate (TMSOTf) to deliver the desired diene **12** in 42% yield. When 2,2,2-trichloroethylchloroformate (TrocCl) was employed as the acylating reagent, **13** was isolated in 56% yield. Silver and scandium triflates could also be used

(5) For example, see: (a) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895−904. See also: (b) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003−8010. (c) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918−5924. (d) Reichelt, A.; Bur, S. K.; Martin, S. F. *Tetrahedron* **2002**, *58*, 6323−6328. (e) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541−4550. (f) Amorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett.* **2005**, *7*, 2031−2033.

(6) For selected examples, see: (a) Martin, S. F.; Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 8584−8592. (b) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523−3525. (c) Neipp, C.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867−8878. (d) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301−7314. (e) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733−5735. (f) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547−6561.

(7) Miller, K. A.; Martin, S. F. *Org. Lett.* **2007**, *9*, 1113−1116.

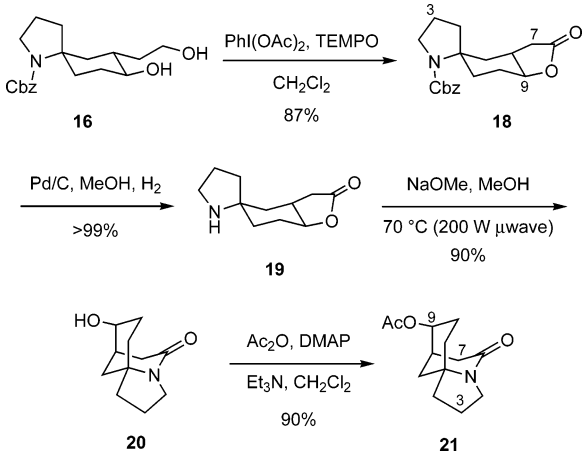
(8) For a preliminary account of portions of this work, see: Simila, S. T. M.; Reichelt, A.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 2933−2936.

as promoters to provide **12** or **13** in similar yields, but because TMSOTf was easier to handle than these Lewis acids, it was employed in further experiments. It is noteworthy that nucleophilic addition to **11** did not proceed to any significant degree in the absence of a Lewis acid promoter.[16] We briefly explored the possibility of converting **9** into **12** in a one-pot procedure. However, when the lactam **9** was treated sequentially with the Grignard reagent **7** and then the allylsilane **8** in the presence of Lewis acids, the ketone **10** was isolated as the only product. Under more forcing conditions, we observed protiodesilylation of the allylsilane **8** and cleavage of the Boc group from **10** as well as complex mixtures of compounds. Even though **13** was obtained in higher yields than **12**, we decided to use **12** in subsequent studies because of the relative ease of removal of the *N*-carbobenzyloxy group from more advanced intermediates. Accordingly, cyclization of **12** via RCM using the Grubbs second-generation catalyst **14**[17] delivered the azaspirane **15** in 95% yield.

At this juncture, the remaining challenge was to induce the stereoselective hydroboration of the azaspirane **15**, a reaction for which there was little precedent in spirocyclic systems.[18] However, there were several reports of hydroborations of conformationally constrained cyclohexenes that led to equatorial alcohols as the major products.[10] It was thus our hope that a borane reagent would react preferentially with the conformer of **15** in which the *N*-carbamate moiety was in an equatorial orientation via a transition state in which the boron atom would be delivered preferentially from an equatorial trajectory to establish the requisite stereochemistry at C(8) and C(9). We also anticipated that the hydroboration of the trisubstituted olefin would be faster than the reduction of the ester and thus chemoselective,[19] but all attempts to effect this selective transformation using reagents including BH_3·THF, BH_3·DMS, 9-BBN, thexylborane, and dicyclohexylborane were unsuccessful; concomitant reduction of the ester was invariably observed as a side reaction. Somewhat surprisingly, the salt of the corresponding carboxylic acid, which should have been inert,[20,21] underwent reduction when BH_3·THF was employed as the hydroborating reagent. Ultimately, we discovered that the simultaneous hydroboration and reduction of the ester by the reaction of **15** with BH_3·THF (3 equiv) followed by oxidation of the alkylborane intermediate with $NaBO_3$·$4H_2O$[22] furnished a diastereomeric mixture (6:1) of **16** and **17** in 99% combined yield. Oxidation of the intermediate alkylborane using the more conventional method of H_2O_2/NaOH was lower yielding (~60 to 70%). Although the diastereomeric diols were easily separable by column chromatography, it was not possible to unequivocally determine the relative stereochemistry of the major diastereomer at this stage.

The unavoidable reduction of the ester functionality upon hydroboration of **15** was merely an inconvenience as we were able to selectively oxidize the primary alcohol moiety of **16** to give the γ-lactone **18** in 87% yield using $PhI(OAc)_2$ and catalytic TEMPO (Scheme 3).[23] The Cbz group of **18** was then easily removed by catalytic hydrogenation to provide the amine **19** in virtually quantitative yield. The subsequent NaOMe-promoted lactone−lactam rearrangement in MeOH using conventional heating techniques was incomplete, even after 2 days of heating under reflux. However, heating a solution of **19** in methanolic NaOMe in a microwave reactor (200 W, 250 psi, 70 °C, three 45-min cycles) delivered the azatricycle **20** in 90% yield.[24] The formation of the hydroxy lactam **20** from the amino lactone **19** verified our tentative assignment of the relative stereochemistry of the major diol diastereomer **16** in which the nitrogen atom and the primary alcohol side chain were cis. The free hydroxyl group at C(9) of **20** was then acetylated to provide **21**, which was amenable to full structural characterization.

SCHEME 3



Enantioselective Synthesis of the Tricyclic Core of (−)-FR901483. Setting the Stage for Geminal Dialkylation of the Imine. Having established the feasibility of accessing the azatricyclic skeleton of FR901483 by the strategy set forth

(9) The numbering is based on the accepted numbering for (−)-FR901483.

(10) For examples of the hydroboration−oxidation of conformationally constrained cyclohexenes to give equatorial alcohols preferentially, see: (a) LaLonde, R. T.; Tobias, M. A. *J. Am. Chem. Soc.* **1963**, *85*, 3771−3775. (b) Brown, H. C.; Pfaffenberger, C. D. *Tetrahedron* **1975**, *31*, 925−928. (c) Brown, H. C.; Liotta, R.; Brener, L. *J. Am. Chem. Soc.* **1977**, *99*, 3427−3432.

(11) For a review, see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238 and references therein.

(12) (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209. (b) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149−14152. (c) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879−10884.

(13) (a) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228−234. (b) Rudolph, A.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895−4898.

(14) ^{1}H NMR spectrum of **11** was consistent with the one reported in the literature: Tehrani, K. A.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 3099−3108.

(15) The methyl ester was prepared by methylating (K_2CO_3, MeI, DMF 82% yield) the corresponding acid that was prepared according to a literature procedure: Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1983**, *61*, 2530−2539.

(16) Yamaguchi, R.; Hatano, B.; Nakayasu, T.; Kozima, S. *Tetrahedron Lett.* **1997**, *38*, 403−406.

(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(18) Hartung, R.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 1597−1604.

(19) Brown, H. C.; Korytnyk, W. *J. Am. Chem. Soc.* **1960**, *82*, 3866−3869.

(20) Brown, H. C.; Rao, S. *J. Am. Chem. Soc.* **1960**, *82*, 681−686.

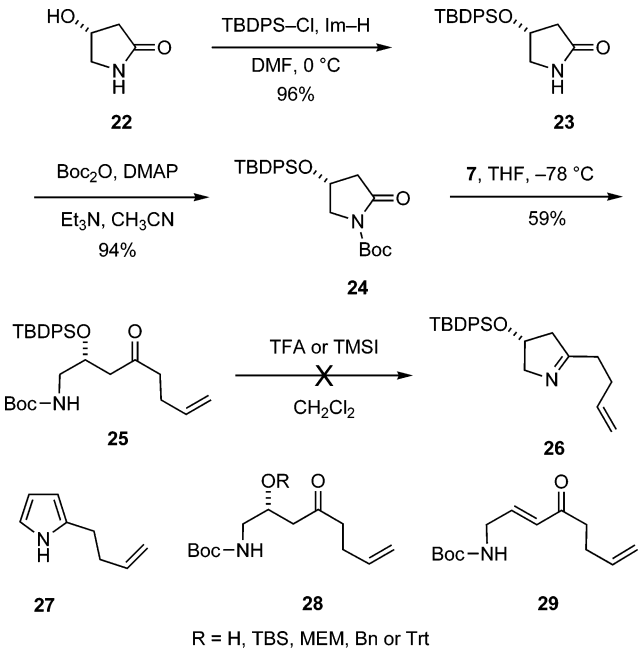
(21) The reduction of carboxylic acid salts in the presence of 2 equiv of diborane has been reported to occur rapidly. See: Yoon, N. M.; Cho, B. T. *Tetrahedron Lett.* **1982**, *23*, 2475−2478.

(22) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930−5933.

(23) (a) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977. (b) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57−59.

in Scheme 1, we turned our attention to its application to the enantioselective synthesis of (−)-FR901483. Toward this goal, commercially available (*R*)-4-hydroxy-2-pyrrolidinone (**22**) was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether to provide **23**, which was then converted into the *N*-Boc lactam **24** in 90% overall yield (Scheme 4). When **24** was treated with the Grignard reagent **7**, the ketone **25** was isolated in 59% yield.

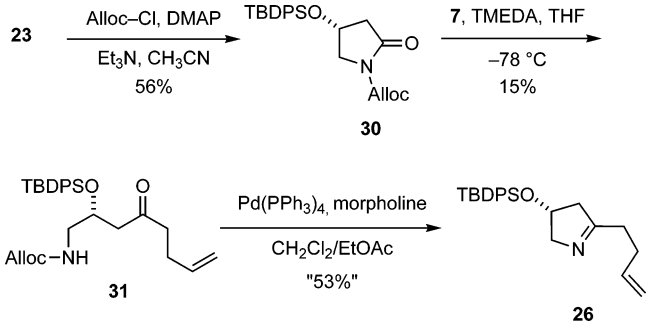
SCHEME 4



Attempts to improve the yield of this reaction by longer reaction times or use of several equivalents of the Grignard reagent **7** were unavailing, and we discovered that **25** was prone to β-elimination of the protected hydroxyl group to give the conjugated ketone **29** under more forcing conditions. Owing to the observed instability of **25**, it did not elicit surprise that removal of the *N*-Boc protecting group from **25** under acidic conditions to give the chiral imine **26** proved to be troublesome. Indeed, when **25** was treated with various Lewis and protic acids to deprotect the nitrogen atom, the sole isolated product was the pyrrole **27**,[25] resulting perhaps from β-elimination of the protected hydroxyl group of the desired **26** and subsequent tautomerization. A variety of hydroxyl protecting groups including TBS, MEM, benzyl, and trityl for the lactam **24** and ketone **25** were examined as was the corresponding unprotected hydroxy lactam, but each of the derived ketones **28** was highly susceptible to β-elimination to provide the conjugated ketone **29** as the only isolable product. The only protected β-hydroxyketone that could be isolated after the Grignard reaction was the TBDPS ether **25**, which exhibited modest stability, perhaps because the steric bulk of the TBDPS group somehow retards elimination.[26]

At this juncture, it was apparent that the chiral ketone **25** and the derived imine **26** were highly acid-sensitive and prone to β-elimination. It was thus deemed essential to employ a nitrogen protecting group that could be cleaved under very mild, non-acidic conditions, and it occurred to us that an *N*-allylcarbamate (Alloc) protecting group might be suitable. To investigate the worthiness of this alternative, the lactam **23** was protected as its Alloc derivative **30**, which was subjected to reaction with the Grignard reagent **7** following the procedure previously established for preparing **25** (Scheme 5). However, we found that extensive cleavage of the Alloc group occurred under these conditions to give **23** as the major product. We had previously discovered that competing nucleophilic attack by organometallic reagents on the carbonyl group of *N*-carbamoyl-2-pyrrolidinones could be minimized by either using hindered carbamates (e.g., Boc) or conducting the reaction in the presence of TMEDA as an additive.[27] In the event, the reaction of **30** with the butenyl Grignard reagent **7** in presence of an equivalent of TMEDA provided the ketone **31** in 15% yield. Unfortunately, we were unable to improve the yield of this reaction by simple operational changes, but we were able to secure sufficient quantities of **31** to determine whether the Alloc group could indeed be cleaved under sufficiently mild conditions to avoid deleterious pyrrole formation. Gratifyingly, treatment of **31** with $Pd(PPh_3)_4$ (20 mol %) in the presence of morpholine gave **26** in good yield along with *N*-allylmorpholine, which was inseparable from **26**.

SCHEME 5



Development of a New N-Protecting Group. It was apparent at this stage that a different protecting group strategy would be necessary. The Alloc group could be removed from **31** under sufficiently mild conditions as not to incur material loss through β-elimination, but the yield of **31** from the addition of **7** to **30** was poor. Our previous work with lactams related to **30** suggested that increased steric bulk was needed on the *N*-carbamoyl lactam moiety.[27] However, there is little precedent for substituted allyloxy carbonyl protecting groups in the literature,[28] especially those with additional branching on the carbinol carbon atom. The isopropylallylcarbamate protecting group has been introduced as a protecting group in peptide synthesis, but the reported preparation of the thiopyrimidincarbonate reagent used to introduce this protecting group involves four tedious synthetic steps as well as the somewhat forcing

(24) For related applications of lactone−lactam rearrangements in alkaloid synthesis, see: Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905−8914. See also ref 5d.

(25) Patterson, J. M.; Brasch, J.; Drenchko, P. *J. Org. Chem.* **1962**, *27*, 1652−1659.

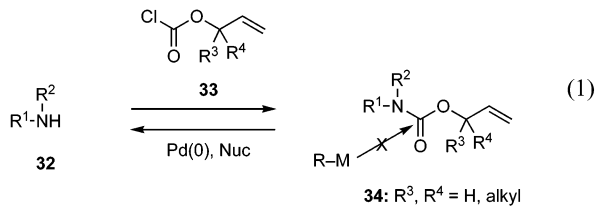
(26) The precise origin of the enhanced stability of **25** is unknown as some β-hydroxy aldehydes and ketones do undergo facile β-elimination. For example, see: Paquette, L. A.; Chang, S.-K. *Org. Lett.* **2005**, *7*, 3111−3114.

(27) (a) Rudolf, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895−4898. (b) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301−7314.

(28) The *N*-cinnamylcarbamate group may be removed under the same conditions as the Alloc group, but this protecting group lacks the requisite steric bulk. See: Kinoshita, H.; Inomata, K.; Kameda, T.; Kotake, H. *Chem. Lett.* **1985**, 515−518.

cleavage conditions rendered this protecting group unattractive for our needs.[29] We were able to prepare 1-isopropylallylchloroformate, but the yields were low and irreproducible. There was thus an opportunity to design a new Alloc-derived protecting group for primary amines.

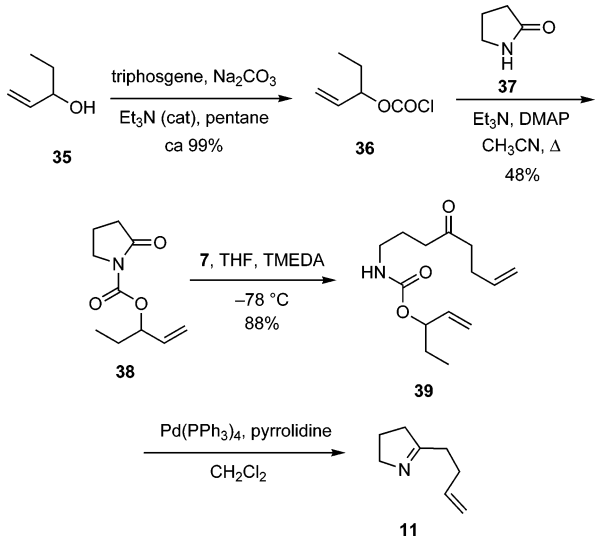
The criteria for this new carbamate protecting group for an amine **32** were somewhat demanding (eq 1). First, the alkyl chloroformate **33** required for preparing the carbamate **34** in a single operation should be accessible from commercially available materials in a single step. Second, the alkyl group on the carbamate had to be sufficiently bulky that the carbonyl group would not undergo attack by strong nucleophilic bases such as Grignard and alkyllithium reagents. Finally, it was essential that the protecting group could be cleaved under mild conditions, such as the palladium-catalyzed process used to remove the Alloc group from **31**. Our attention was thus focused upon substituted Alloc groups of the general type **33**. We were initially inspired by the Boc protecting group and thus envisioned that the tertiary allylic carbamate **34** ($R^3 = R^4 = Me$) would satisfy our requirements. However, we quickly discovered that **33** ($R^3 = R^4 = Me$), like other tertiary alkyl chloroformates, was unstable.[30,31] On the other hand, we were able to prepare a number of branched allyl chloroformates **33** ($R^3 = H$; $R^4 =$ Me, Et, Pr, and *i*-Bu) from the corresponding allylic alcohols in excellent yields by reaction with triphosgene in pentane in the presence of Na_2CO_3 and a catalytic amount of Et_3N.[32,33] Because each of these groups incorporates a stereocenter that might complicate characterization of chiral amines, we also tried to prepare **33** ($R^3 = H$; $R^4 = CH{=}CH_2$) but were unsuccessful as the product was simply too unstable.



(1)

Having prepared the chloroformates **33** ($R^3 = H$; $R^4 =$ Me, Et, Pr, and *i*-Bu), we initiated a series of exploratory experiments to examine the potential of the corresponding carbamates as amine protecting groups. For example, we found that reaction of **36**, which was prepared in virtually quantitative yield by the reaction of commercially available **35** with triphosgene, with 2-pyrrolidinone (**37**) in the presence of Et_3N and DMAP gave **38** in good yield. Attempts to improve this yield under other mild conditions were unfruitful, and the use of stronger bases such as NaHMDS gave complex mixtures. Subsequent reaction of **38** with 3-butenylmagnesium bromide (**7**) in the presence of TMEDA gave **39** in 88% yield (Scheme 6); when the reaction was conducted in the absence of TMEDA, the yield of **39** was only 64%. The yields for preparing protected 2-pyrrolidinones related to **38** using other chloroformates **33** ($R^3 = H$; $R^4 =$ Me, Pr, and *i*-Bu) were comparable (41−48%), whereas the yields of the corresponding ring opened products were either lower or no better than for the preparation of **39**. Inasmuch as the allylic alcohol required to prepare **36** is less expensive than the other commercially available alcohols, we elected to use the ethylallyloxycarbonyl (Etalloc) protecting group in subsequent studies.

SCHEME 6



We then screened conditions for removing the Etalloc group from **39** to prepare the imine **11**. Removal of Alloc-type protecting groups is typically performed in the presence of a palladium catalyst that forms a π-allyl palladium complex that is then trapped with a suitable nucleophile, thereby releasing the amine.[34] Because we would ultimately employ this protecting group in a situation that mandated the use of neutral or slightly basic conditions, our initial focus was on screening secondary amine nucleophiles, rather than the more commonly used protocols using carboxylic acids. We thus discovered that the reaction of **39** with pyrrolidine in CH_2Cl_2 in the presence of $Pd(PPh_3)_4$ (10 mol %) led to the rapid cleavage of the Etalloc protecting group and the formation of an inseparable mixture (1:1) of **11** and *N*-(2-penten-1-yl)pyrrolidine. The cleavage reaction was slower in the presence of morpholine and when other solvents such as CH_3CN, THF, and Et_2O were used.

Although pyrrolidine proved to be an excellent nucleophile for effecting the removal of the Etalloc group from **39**, we discovered that the alkyl pyrrolidine byproduct interfered with the subsequent reaction of **11** with **8**, giving **12** in significantly lower yields (eq 2). In searching for an alternative nucleophile, we discovered that the palladium-catalyzed deprotection of **39** with benzotriazole in CH_2Cl_2 proceeded rapidly.[35] Gratifyingly, the alkylated benzotriazole byproduct did not affect the subsequent reaction. Thus, when **39** was allowed to react with benzotriazole (1.0 equiv) in the presence of $Pd(PPh_3)_4$ (10 mol %), the deprotection step was complete within 45 min (eq 2). Subsequent treatment of the crude mixture (ca. 1:1) of **11** and the alkylated benzotriazole with CbzCl, allylsilane **8**, and TMSOTf provided **12** in 40% yield, a yield comparable to that observed previously (cf. Scheme 2).

Utilization of the Etalloc Protecting Group To Prepare the Tricyclic Core of (−)-FR901483. The utility of any new protecting group must be assessed on the basis of its merits for

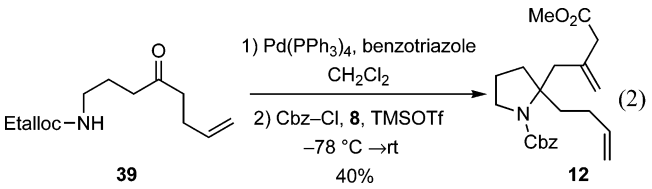
(29) Minami, I.; Yukara, M.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 2737−2740.

(30) Choppin, A. R.; Rogers, J. W. *J. Am. Chem. Soc.* **1948**, *70*, 2967−2967.

(31) Kevill, D. N.; Weitl, F. L. *J. Am. Chem. Soc.* **1968**, *90*, 6416−6420.

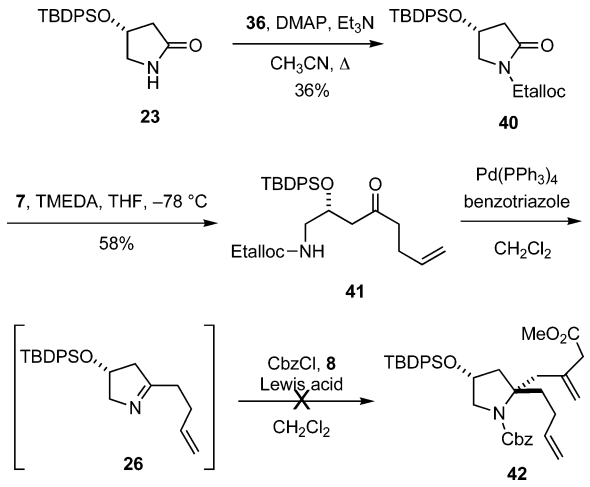
(32) Deshmukh, A. R. A. S.; Gumaste, V. K. U.S. Patent US006919471B2, 2005.

(33) All allylic chloroformates were heat- and moisture-sensitive and were used immediately after preparation.



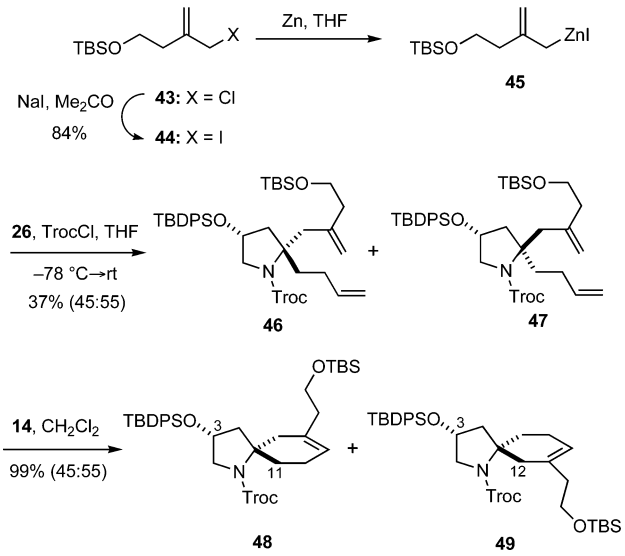
the preparation of a particular target. Toward this goal, the chiral lactam **23** was treated with the chloroformate **36** in the presence of DMAP and Et_3N to give **40** in an unoptimized 36% yield (96% based upon recovered starting material) (Scheme 7). Reaction of **40** with 3-butenylmagnesium bromide (**7**) in the presence of TMEDA gave the ketone **41** in 58% yield. Although the palladium-catalyzed removal of the Etalloc group in the presence of benzotriazole proceeded smoothly, all attempts to isolate and purify the resultant chiral imine **26** were unsuccessful owing to its acid sensitivity and facile transformation to the pyrrole **27**. The crude reaction mixture was therefore simply filtered through a short pad of basic alumina, and the volume of the collected fractions was reduced so the concentration of **26** was about 0.1 M. However, when the **26** thus obtained was treated with CbzCl and **8** in the presence of Lewis acids such as TMSOTf or $Sc(OTf)_3$, none of the desired product **42** was observed; pyrrole **27** was the major product.

SCHEME 7



Owing to the low reactivity of the allylsilane **8**, it was necessary to use a Lewis acid to promote the geminal dialkylation. It was thus apparent that such conditions were incompatible with the acid-sensitive nature of **26**, and we thus reasoned that a more nucleophilic reaction partner that did not require Lewis acid additives was needed. Inasmuch as zinc reagents were known to add efficiently to imines,[36] it occurred to us that a functionalized allylic zinc species might be employed to solve the problem at hand. To explore this possibility, the known allyl chloride **43**[37] was first converted into the iodide **44** in 84% yield by a Finkelstein reaction,[38] and **44** was then allowed to react

SCHEME 8



with zinc in THF[39,40] to form **45** (Scheme 8). The chiral imine **26**, which was generated in situ by the Pd-catalyzed deprotection of **41**, was then treated with the functionalized zinc reagent **45** in the presence of TrocCl to give an inseparable mixture (45:55) of **46** and **47** in 37% yield. When CbzCl was used as the acylating agent, the yield was lower. The mixture of **46** and **47** thus obtained was then subjected to RCM using Grubbs second-generation catalyst **14** to give a separable mixture of **48** and **49** in nearly quantitative yield. On the basis of NMR experiments and especially an NOE interaction between the proton at C(3) and a proton on C(12) of the major product, we tentatively assigned the structure of the major diastereoisomer as being **49**, which has the incorrect stereochemistry at the spirocenter. Similarly, an NOE interaction was observed between the proton at C(3) and one of the protons on C(11) of the minor diastereoisomer as would be expected for **48**, which has the desired stereochemistry at the spirocenter.

The lack of diastereoselectivity in the addition reaction was a little surprising, as we had anticipated a higher level of stereochemical control based upon Woerpel's studies on stereoelectronic effects in nucleophilic additions to five-membered oxocarbenium ions.[12] It would thus appear that those observations may not be applicable to additions to derivatives of five-membered imines, although further work is required before any firm conclusions can be drawn. For example, we do not know whether the imine or an *N*-acyl iminium ion is the reactive intermediate that undergoes addition. The steric bulk associated with the TBDPS protecting group may also be a factor. In any case, the poor stereoselectivity in a key step of our approach to (−)-FR901483 was clearly a major disappointment. This, together with the recent findings of the Weinreb group, which had encountered a number of problems with an endgame strategy related to ours,[4i] persuaded us to conclude these studies and pursue more fruitful endeavors.

Summary

We have thus explored a novel route to the immunosuppressant agent FR901483. As a prelude to working on the natural

(34) For a review on allylic protecting groups and their removal, see: Guibé, F. *Tetrahedron* **1998**, *54*, 2967−3042.

(35) For a recent example of the use of benzotriazole as a nucleophile in allylic allylations, see: Oliveira, R. N.; Mendonca, F. J. B., Jr.; de Melo, S. J.; Srivastava, R. M. *Synlett* **2006**, *18*, 3049−3052.

(36) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186−195.

(37) Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6691−6693.

(38) Finkelstein, H. *Ber.* **1910**, *43*, 1528−1528.

(39) Knochel, P.; Almena, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8319 and references therein.

(40) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. *Synlett* **2005**, *18*, 2701−2719.

product, we completed a preliminary model study featuring the nucleophilic addition of a functionalized allylsilane to an *N*-acyl iminium ion, a ring closing metathesis, a stereoselective hydroboration, and a lactone−lactam rearrangement to elaborate the tricyclic core of the target. Application of this chemistry toward the enantioselective synthesis of (−)-FR901483 required that we first develop a new amine protecting group, the Etalloc group, which is more stable to organometallic reagents than the Alloc group and may be easily removed under mild conditions. Further investigations for the general utilization of this protecting group will be reported in due course. Unfortunately, the diastereoselectivity in a key addition of a functionalized allyl zinc reagent to the imine **26** was low, and pleasing solutions to this vexing problem were not apparent. This result reflects our poor understanding of the structural factors that govern the stereoselectivities of nucleophilic additions to five-membered imine derivatives, whereas our ability to predict the stereochemistry of such additions to six-membered imines is significantly better.

Experimental Section[41]

2-(But-3-enyl)-2-(2-methoxycarbonylmethylallyl)-pyrrolidine-1-carboxylic Acid Benzyl Ester (12). A mixture of CbzCl (238 μL, 1.58 mmol) and **11** (150 mg, 1.22 mmol) in CH_2Cl_2 (2 mL) containing 4 Å molecular sieves was stirred at −78 °C for 10 min, whereupon **8** (682 mg, 3.66 mmol) in CH_2Cl_2 (2 mL) was added at −78 °C and stirring was continued for 1 h. TMSOTf (221 μL, 1.22 mmol) was then added, and the mixture was stirred for 16 h, letting the mixture to warm slowly to 25 °C. The molecular sieves were removed by filtration, and the crude reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (5:95) to give 190 mg (42%) of **12** as a clear oil. ^{1}H NMR (DMSO-d_6, 100 °C) δ 7.37−7.27 (comp, 5 H), 5.75 (ddt, J = 16.8, 10.4, 6.8 Hz, 1 H), 5.09 (d, J = 12.5 Hz, 1 H), 5.05 (d, J = 12.5 Hz, 1 H), 4.99−4.88 (comp, 4 H), 3.59 (s, 3 H), 3.46−3.35 (m, 2 H), 3.00 (d, J = 16.0 Hz, 2 H), 2.80 (d, J = 14.0 Hz, 1 H), 2.31 (d, J = 14.0 Hz, 1 H), 2.08−1.96 (comp, 3 H), 1.89−1.83 (comp, 2 H), 1.74−1.67 (m, 3 H); ^{13}C NMR (DMSO-d_6, 100 °C) δ 170.1, 152.7, 138.9, 137.9, 136.7, 130.0, 127.6, 126.9, 116.9, 113.5, 65.1, 61.0, 50.5, 47.8, 42.3, 41.4, 36.8, 33.8, 27.2, 20.9; IR (neat) ν 2935, 1742, 1697, 1442, 1398, 1353, 1154; mass spectrum (CI$^+$) m/z 372.2182 [$C_{22}H_{29}O_4N$ + H requires 372.2175].

7-Methoxycarbonylmethyl-1-azaspiro[4.5]dec-7-ene-1-carboxylic Acid Benzyl Ester (15). Grubbs second-generation catalyst **14** (19 mg, 0.02 mmol) was added to a solution of **12** (84 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) at 25 °C, and the mixture was stirred for 20 h, whereupon the solvent was removed in vacuo. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (2:98) to give 74 mg (95%) of **15** as a clear oil. ^{1}H NMR (DMSO-d_6, 100 °C) δ 7.37−7.27 (comp, 5 H), 5.48 (br s, 1 H), 5.08 (d, J = 12.5 Hz, 1 H), 5.05 (d, J = 12.5 Hz, 1 H), 3.59 (s, 3 H), 3.57−3.53 (m, 1 H), 3.40−3.35 (m, 1 H), 2.98−2.96 (m, 2 H), 2.92−2.86 (m, 1 H), 2.46−2.44 (m, 1 H), 2.16−2.05 (m, 2 H), 1.83−1.68 (comp, 5 H), 1.35 (dd, J = 10, 4.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 100 °C) δ 170.6, 153.0, 136.9, 129.8, 127.7, 127.0, 126.8, 122.9, 64.9, 61.8, 50.6, 47.2, 41.6, 36.1, 35.6, 29.2, 23.3, 20.8; IR (neat) ν 2938, 1730, 1694, 1437, 1352, 1143; mass spectrum (CI$^+$) m/z 344.1786 [$C_{20}H_{25}O_4N$ + H requires 344.1784].

8-Hydroxy-7-(2-hydroxyethyl)-1-azaspiro[4.5]decane-1-carboxylic Acid Benzyl Ester (16). A 1.0 M solution of BH_3·THF (360 μL, 0.36 mmol) was added to a solution of **15** (43 mg, 0.12 mmol) in THF (0.5 mL) dropwise at 0 °C. The mixture was stirred for 3 h, whereupon water (0.2 mL) was added with stirring. $NaBO_3$·$4H_2O$ (61 mg, 0.36 mmol) and water (0.8 mL) were then added sequentially, keeping the mixture at 0 °C. The mixture was stirred for 3 h at 25 °C, whereupon it was poured into a separatory funnel containing ice-cold water (5 mL). The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography eluting with EtOH/CH_2Cl_2 (3:97) to give 36 mg (86%) of **16** and 5 mg (13%) of **17** as a clear oil (combined yield: 99%). ^{1}H NMR (DMSO-d_6, 100 °C, major diastereomer **16**) δ 7.37−7.27 (comp, 5 H), 5.08 (d, J = 13.0 Hz, 1 H), 5.05 (d, J = 13.0 Hz, 1 H), 3.49−3.31 (comp, 5 H), 2.71 (dd, J = 13.5, 6.0 Hz 1 H), 2.60−2.51 (m, 2 H), 1.97−1.83 (m, 2 H), 1.79−1.68 (comp, 3 H), 1.64−1.60 (comp, 2 H), 1.54 (p, J = 7.0 Hz, 1 H), 1.42 (p, J = 7.0 Hz, 1 H), 1.24−1.19 (m, 1 H), 1.16−1.08 (comp, 2 H); ^{13}C NMR (DMSO-d_6, 100 °C, major diastereomer **16**) δ 152.7, 137.1 127.7, 126.9, 126.8, 68.0, 64.7, 62.9, 59.6, 46.7, 43.2, 37.4, 36.0, 33.9, 27.4, 27.3, 21.1; IR (neat) ν 3389, 2928, 1683, 1401, 1352, 1178, 1105, 1028; mass spectrum (CI$^+$) m/z 334.2021 [$C_{19}H_{27}O_4N$ + H requires 334.2018].

2,3,3a,6,7,7a-Hexahydro-2-oxospiro[benzofuran-5(4*H*),2′-pyrrolidin]-1′-carboxylic Acid Benzyl Ester (18). Iodobenzene diacetate (150 mg, 0.47 mmol) and TEMPO (4 mg, 0.023 mmol) were added to a solution of **16** (39 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) at 25 °C, and the mixture was stirred for 20 h. CH_2Cl_2 (5 mL) and aqueous 0.5 N $Na_2S_2O_3$ (1 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL), and the combined organic layers were washed with $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to give 34 mg (87%) of **18** as a clear oil. ^{1}H NMR δ 7.36−7.27 (comp, 5 H), 5.11 (d, J = 12.5 Hz, 1 H), 5.06 (d, J = 12.5 Hz, 1 H), 3.91 (dt, J = 11.0, 6.5 Hz, 1 H), 3.55−3.47 (m, 2 H), 2.77−2.72 (m, 1 H), 2.51−2.44 (m, 3 H), 2.31−2.26 (m, 1 H), 2.11−2.01 (m, 2 H), 1.92−1.87 (m, 1 H), 1.82−1.72 (comp, 3 H), 1.62−1.58 (m, 1 H), 1.39−1.33 (m, 1 H); ^{13}C NMR δ 176.7, 154.4, 136.7, 128.5, 128.0, 127.9, 82.9, 66.6, 62.5, 47.8, 43.9, 40.1, 38.2, 36.1, 31.2, 25.4, 21.6; IR (neat) ν 2922, 1781, 1701, 1454, 1402, 1354, 1203, 1104, 1027; mass spectrum (CI$^+$) m/z 330.1696 [$C_{19}H_{23}O_4N$ + H requires 330.1705].

3a,6,7,7a-Tetrahydrospiro[benzofuran-5(4*H*),2′-pyrrolidin]-2(3*H*)-one (19). A mixture of **18** (25 mg, 0.076 mmol) in MeOH (1 mL) containing 10% Pd/C (5 mg) was stirred under a hydrogen atmosphere (1 atm) at 25 °C for 24 h. The mixture was filtered through a pad of Celite, and the pad was washed with MeOH (3 mL). The combined filtrate and washings were concentrated in vacuo to give 15 mg (99%) of **19** as a clear oil. ^{1}H NMR (Cd_3Od) δ 3.99 (dt, J = 11.0, 4.0 Hz, 1 H), 3.41−3.36 (m, 2 H), 2.52 (dd, J = 16.0, 6.5 Hz, 1 H), 2.45−2.39 (m, 1 H), 2.26−2.01 (comp, 6 H), 1.95 (t, J = 7.5 Hz, 2 H), 1.92−1.78 (comp, 4 H); ^{13}C NMR (Cd_3Od) δ 177.9, 84.1, 68.3, 46.8, 41.9, 39.5, 37.3, 35.7, 33.7, 27.7, 23.9; IR (neat) ν 2919, 1772, 1449, 1190, 1026; mass spectrum (CI$^+$) m/z 196.1333 [$C_{11}H_{17}O_2N$ + H requires 196.1338].

9-Hydroxy-5-azatricyclo[6.3.1.0^{1,5}]dodecan-6-one (20). A solution of NaOMe (6 mg, 0.12 mmol) and **19** (14 mg, 0.072 mmol) in CH_3OH (1 mL) was heated with stirring in a microwave reactor at 70 °C (200 W, 250 psi) for 3 × 45 min. The mixture was concentrated in vacuo, and the residue was triturated with benzene (2 × 3 mL) to give 13 mg (90%) of **20** as a clear oil. ^{1}H NMR (C$_6d_6$) δ 3.00 (dt, J = 4.0, 8.4 Hz, 1 H), 2.74−2.65 (m, 2 H), 2.19−2.13 (comp, 2 H), 1.69−1.52 (m, 2 H), 1.48−1.40 (comp, 3 H), 1.33−1.26 (comp, 3 H), 1.18 (t, J = 8 Hz, 2 H), 1.05 (dt, J = 13.0, 4.5 Hz, 1 H), 0.90 (t, J = 13.0 Hz, 1 H); ^{13}C NMR (C$_6d_6$) δ 173.9, 74.3, 60.9, 46.3, 42.6, 39.8, 39.2, 39.1, 35.9, 32.7, 25.5; IR (neat) ν 3239, 2923, 1663, 1410, 1303, 1168; mass spectrum (CI$^+$) m/z 196.1329 [$C_{11}H_{17}O_2N$ + H requires 196.1338].

Acetic Acid 6-Oxo-5-azatricyclo[6.3.1.0^{1,5}]dodec-9-yl Ester (21). Acetic anhydride (12 μL, 0.128 mmol), Et_3N (15 μL, 0.104

(41) All new and known compounds were judged to be >95% pure by ^{1}H NMR spectroscopy.

mmol), and DMAP (0.6 mg, 0.052 mmol) were added to a solution of **20** (5 mg, 0.026 mmol) in CH_2Cl_2 (0.5 mL), and the mixture was stirred at 25 °C for 6 h. CH_2Cl_2 (5 mL) and saturated NH_4Cl (5 mL) were added, and the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (2:98) to give 5.5 mg (90%) of **21** as a clear oil. ^{1}H NMR δ 4.70 (dt, J = 4.0, 8.0 Hz, 1 H), 3.48−3.44 (m, 1 H), 3.40−3.35 (m, 1 H), 3.10 (dd, J = 14.0, 6.2 Hz, 1 H), 2.77 (dt, J = 12.8, 3.8 Hz, 1 H), 2.67 (m, 1 H), 2.07 (s, 3 H), 1.99−1.95 (m, 1 H), 1.89−1.78 (comp, 3 H), 1.75−1.61 (comp, 4 H), 1.23−1.16 (comp, 2 H); ^{13}C NMR δ 172.6, 170.8, 71.8, 64.1, 49.1, 39.6, 34.8, 33.8, 26.9, 25.2, 24.9, 22.7, 21.4; IR (neat) ν 2926, 1732, 1644, 1407, 1246, 1088, 1027; mass spectrum (CI$^+$) m/z 238.1436 [$C_{13}H_{19}O_3N$ + H requires 238.1443].

1-Ethylallyl Chloroformate (36). Et_3N (21 μL, 0.15 mmol) was added to a solution of triphosgene (328 mg, 1.10 mmol) and Na_2CO_3 (318 mg, 3.0 mmol) in pentane (5 mL) at 0 °C, and the mixture was stirred for 30 min. A solution of pent-1-en-3-ol (308 μL, 3.0 mmol) in pentane (5 mL) was added dropwise at 0 °C, the mixture was allowed to warm to 25 °C, and stirring was continued for 16 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give 445 mg (99%) of **36** as a clear oil. ^{1}H NMR (C_6d_6) δ 5.31 (ddd, J = 17.2, 10.8, 7.2 Hz, 1 H), 4.99 (dt, J = 17.2, 1.2 Hz, 1 H), 4.86 (dt, J = 10.8, 1.2 Hz, 1 H), 4.84−4.81 (m, 1 H), 1.37−1.18 (comp, 2 H), 0.54 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (C_6d_6) δ 149.6, 134.1, 119.2, 85.2, 26.9, 8.9; IR (neat) ν 2973, 1779, 1165, 824; mass spectrum (CI$^+$) m/z 149.0289 [$C_6H_9O_2Cl$ + H requires 149.0291].

2-Oxopyrrolidine-1-carboxylic Acid 1-Ethylallyl Ester (38). 1-Ethylallyl chloroformate **36** (175 mg, 1.18 mmol) was added to a solution of 2-pyrrolidinone (66 mg, 0.78 mmol), Et_3N (164 μL, 1.18 mmol), and DMAP (96 mg, 0.78 mmol) in CH_3CN (1 mL) at 0 °C, and the mixture was stirred at 80 °C for 18 h. Saturated $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:5) to give 71 mg (48%) of **38** as a clear oil. ^{1}H NMR δ 5.77 (ddd, J = 17.2, 10.8, 6.8 Hz, 1 H), 5.31 (dt, J = 17.2, 1.2 Hz, 1 H), 5.20−5.17 (m, 1 H), 5.16 (dt, J = 10.8, 1.2 Hz, 1 H), 3.76 (t, J = 7.6 Hz, 2 H), 2.48 (t, J = 7.6 Hz, 2 H), 1.99 (p, J = 7.6 Hz, 2 H), 1.73−1.63 (comp, 2 H), 0.89 (t, J = 6.8 Hz, 3 H); ^{13}C NMR δ 173.9, 151.0, 135.5, 117.5, 78.4, 46.2, 32.7, 27.0, 17.4, 9.1; IR (neat) ν 3409, 2970, 1789, 1715, 1369, 1287; mass spectrum (CI$^+$) m/z 198.1134 [$C_{10}H_{15}O_3N$ + H requires 198.1130].

***tert*-Butyl-(3-iodomethylbut-3-enyloxy)dimethylsilane (44).** NaI (1.28 g, 8.55 mmol) was added to a solution of *tert*-butyl-(3-chloromethylbut-3-enyloxy)dimethylsilane (**43**)[37] (400 mg, 1.71 mmol) in acetone (15 mL), and the mixture was heated under reflux for 5 h. The solvent was removed in vacuo, Et_2O (100 mL) was added, and the resultant white solid was removed by filtration. The filtrate was washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes to give 480 mg (86%) of **44** as a pale yellow oil. ^{1}H NMR δ 5.25 (s, 1 H), 4.92 (d, J = 1.2 Hz, 1 H), 3.95 (s, 2 H), 3.74 (t, J = 6.8 Hz, 2 H), 2.42 (t, J = 6.8 Hz, 2 H), 0.87 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR δ 144.3, 115.2, 61.9, 37.2, 25.9, 18.3, 11.3, −5.3; IR (neat) ν 2954, 2857, 1471, 1388, 1256, 1098, 836; mass spectrum (CI$^+$) m/z 327.0643 [$C_{11}H_{23}$-OSiI + H requires 327.0641].

2-(But-3-enyl)-2-[4-(*tert*-butyldimethylsilanyloxy)-2-methylenebutyl]-(*R*)-4-(*tert*-butyldiphenylsilanyloxy)pyrrolidine-1-carboxylic Acid 2,2,2-Trichloroethyl Esters (46) and (47). A solution of benzotriazole (25 mg, 0.21 mmol), $Pd(PPh_3)_4$ (48 mg, 0.041 mmol), and **41** (106 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) was stirred for 1 h at 25 °C, whereupon it was quickly filtered through a short pad of basic alumina and washed with CH_2Cl_2 (ca. 1 mL). After concentration in vacuo to a volume of about 1 mL, THF (1 mL) was added, and the mixture was cooled to −78 °C. TrocCl (58 μL, 0.41 mmol) was added, and the mixture was stirred at −78 °C for 20 min. In another flask, **44** (202 mg, 0.62 mmol) was added dropwise to a solution of zinc (49 mg, 0.74 mmol) in THF (0.6 mL) at room 25 °C, and the mixture was stirred for 20 min. This solution of allyl zinc iodide was transferred via a cannula to the above solution of the imine at −78 °C, and stirring was continued for 18 h while allowing the cooling bath to warm to room temperature. Saturated NH_4Cl/H_2O (1:1, 10 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:99 to 2:98) to give 58 mg (37%) of an inseparable mixture (45:55) of **46** and **47** as a clear oil. ^{1}H NMR (DMSO-d_6, 100 °C) δ 7.62−7.58 (comp, 4 H), 7.48−7.39 (comp, 6 H), 5.84−5.74 (m, 0.55 H), 5.71−5.62 (m, 0.45 H), 5.01−4.64 (comp, 6 H), 4.53 (p, J = 6.8 Hz, 1 H), 3.70 (t, J = 6.8 Hz, 1 H), 3.57−3.50 (comp, 2 H), 3.34−3.31 (m, 1 H), 2.84−2.62 (comp, 3 H), 2.25 (t, J = 6.8 Hz, 1 H), 2.19−1.94 (comp, 6 H), 1.04 (s, 9 H), 0.87 (s, 4.05 H), 0.83 (s, 4.95 H), 0.03 (s, 2.7 H), −0.02 (s, 3.3 H); ^{13}C NMR (DMSO-d_6, 100 °C) δ 143.0, 137.8, 134.6, 132.8, 129.3, 127.2, 125.6, 117.2, 113.8, 96.0, 69.5, 61.3, 59.8, 59.4, 55.0, 41.3, 40.3, 27.4, 27.3, 26.4, 26.2, 25.2, 18.0, 17.1, −3.8; IR (neat) ν 2930, 2858, 1721, 1403, 1105, 835, 702; mass spectrum (CI$^+$) m/z 752.2890 [$C_{38}H_{56}O_4NSi_2Cl_3$ + H requires 752.2892].

7-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-3-(*tert*-butyldiphenylsilanyloxy)-1-azaspiro[4.5]dec-7-ene-1-carboxylic Acid 2,2,2-Trichloroethyl Esters (48 and 49). A solution of **46** and **47** (36 mg, 0.048 mmol) in CH_2Cl_2 (0.5 mL) containing Grubbs' catalyst **14** (8 mg, 0.005 mmol) at 25 °C was stirred for 20 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (0.5:99.5 to 2:98) to give 15 mg (45%) of **48** and 19 mg (54%) of **49** as clear oils. ^{1}H NMR (major diastereomer **49**, major carbamate rotamer) δ 7.62−7.59 (m, 4 H), 7.43−7.31 (comp, 6 H), 5.30−5.29 (m, 1 H), 4.86−4.26 (m, 2 H), 4.25 (p, J = 5.2 Hz, 1 H), 3.70−3.30 (comp, 4 H), 3.19−3.00 (m, 1 H), 2.59−2.49 (m, 2 H), 2.20−1.76 (comp, 6 H), 1.31−1.28 (m, 1 H), 1.03 (s, 9 H), 0.86 (s, 9 H), −0.01 (s, 6 H); ^{13}C NMR (major diastereomer **49**, major carbamate rotamer) δ 151.8, 135.7, 133.9, 133.4, 129.9, 127.8, 121.0, 96.1, 74.3, 70.4, 63.6, 62.2, 56.2, 44.7, 41.4, 36.8, 30.8, 29.7, 26.9, 25.9, 23.9, 19.0, −5.2; ^{1}H NMR (minor diastereomer **48**, major carbamate rotamer) δ 7.62−7.59 (m, 4 H), 7.43−7.31 (comp, 6 H), 5.33−5.32 (m, 1 H), 4.82−4.57 (m, 2 H), 4.27 (p, J = 5.2 Hz, 1 H), 3.68−3.45 (comp, 4 H), 3.03−2.85 (m, 1 H), 2.59−2.49 (m, 2 H), 2.09−1.76 (comp, 6 H), 1.31−1.29 (m, 1 H), 1.03 (s, 9 H), 0.86 (s, 9 H), −0.00 (s, 6 H); ^{13}C NMR (minor diastereomer **48**, major carbamate rotamer) δ 151.7, 135.6, 133.6, 133.4, 129.9, 127.8, 121.4, 96.1, 74.3, 69.6, 63.2, 62.1, 56.2, 44.6, 41.1, 38.0, 31.9, 29.7, 26.8, 25.9, 24.3, 19.0, −5.2; IR (neat) ν 2926, 1719, 1400, 1104, 835, 701; mass spectrum (CI$^+$) m/z 724.2579 [$C_{36}H_{52}O_4NSi_2Cl_3$ + H requires 724.2579].

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Supporting Information Available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and a copy of ^{1}H NMR spectrum for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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