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# Anodic Amide Oxidation/Olefin Metathesis Strategies: Developing a Unified Approach to the Synthesis of Bicyclic Lactam Peptidomimetics

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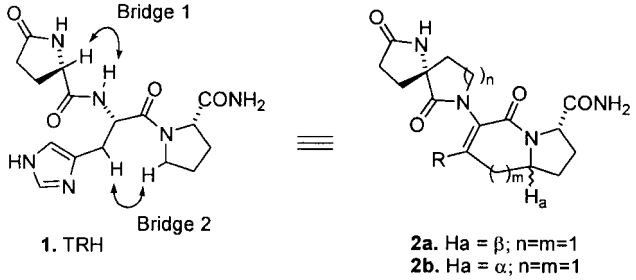
**Abstract**—In connection with efforts to build constrained peptidomimetics for the endocrine hormone TRH, a general strategy for the construction of bicyclic lactam peptide building blocks has been developed. This strategy used an anodic amide oxidation to selectively functionalize proline and then an olefin metathesis to build the desired lactam constraint. The route described provides a single approach for synthesizing both fully functionalized TRH analogs having seven- and eight-membered ring lactam constraints, as well as six- and seven-membered ring lactam analogs without the sidechain on the central amino acid. 

## Introduction

As part of a general effort to develop new strategies for constructing conformationally restricted peptidomimetics,[1,2] we recently synthesized the fully constrained thyroliberin (TRH) analogs **2a** and **2b**.[3,4] These analogs were synthesized in connection with efforts to determine whether the conformation of TRH represented by **1** was a viable proposal for the TRH conformation that binds the endocrine receptor TRH-R.[5–7] Interestingly, analogs **2a** and **2b** were not full agonists of the TRH-R receptor. While neither a bridge added to the pyroglutamate region of the molecule (bridge 1)[8] nor a bridge added to the central region of the molecule (bridge 2)[7] had stopped previous analogs from being full agonists, the fully constrained analog **2a** having both bridges reached only 47% of maximal potency at high concentrations. Analog **2b** reached only 25% of maximal potency. This observation was particularly surprising for **2a** which displayed an affinity for TRH-R that was a factor of 4 better than the unrestricted, and fully potent, 2-cyclohexylAla-TRH.[7] Typically, TRH analogs have displayed an almost linear relationship between affinity for TRH-R and potency. Why was this not true for **2a**? (Scheme 1)

In order to address this question, a number of new analogs were proposed. These suggestions included more flexible analogs like **3** (Scheme 2) which were designed in order to explore whether the partial agonist behavior of **2a** was the result of the analog being too rigid, and analogs like **4** which were designed in order to explore whether the partial agonist behavior of **2a** was the result of the substituent on the central amino acid not being properly positioned. We report here that both families of analogs (**3** and **4**) can be readily synthesized by taking advantage of an anodic amide oxidation–olefin metathesis strategy for constructing bicyclic lactams.

From the start, it was clear that the synthetic methodology developed for the synthesis of **2a** would not allow for the synthesis of analogs like **3** and **4**. Efforts to functionalize seven-membered ring lactams (**7** and **9**/X=H) in analogy to the conversion of **5** to **2a** were not successful, and the anodic oxidation of proline derivatives was not compatible with the presence of either an oxygen or a nitrogen substituent on the carbon alpha to the amide carbonyl (X=OR or $NR_2$).[1a] In addition, intramolecular cyclization reactions of iminium ions like **8** (X=H) did not afford seven-membered ring lactams whenever $R_1$ was an electron donating group. Instead, the cyclization reactions triggered subsequent




**Scheme 1.**

*Keywords*: anodic amide oxidation; TRH-R; bicyclic lactum peptidomimetics.

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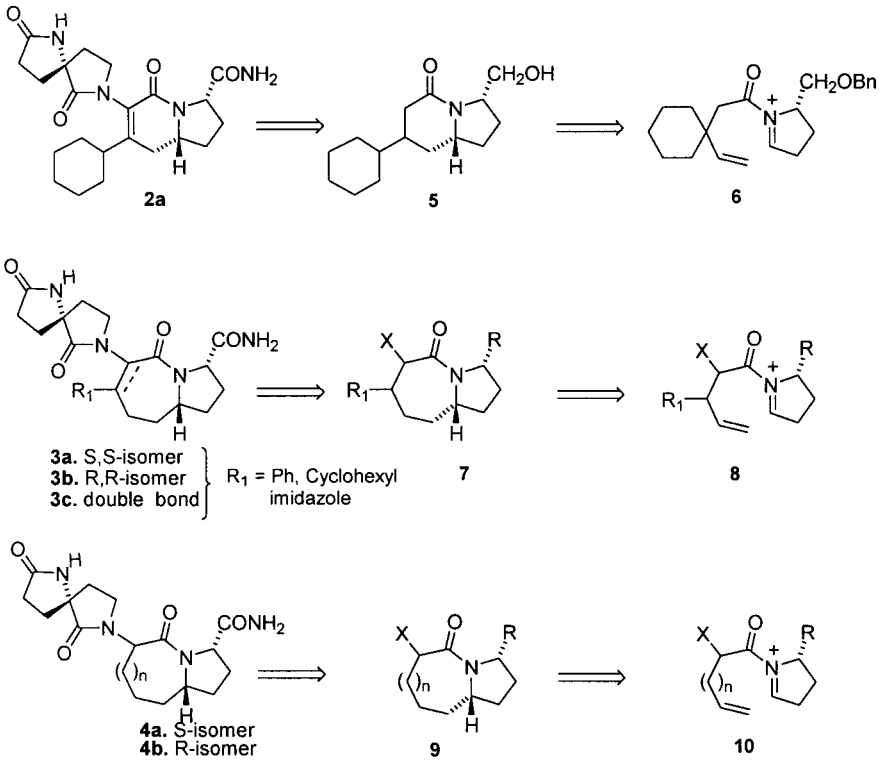
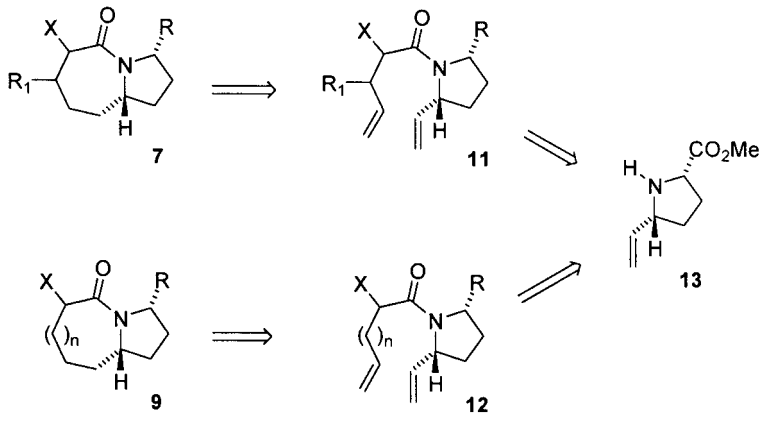



**Scheme 2.**

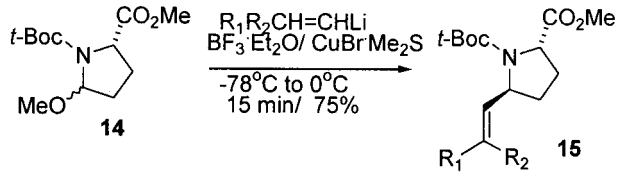
rearrangement reactions that afforded six-membered ring lactam products.[1a,1d] Even if these problems could be resolved, the number of analogs that could be synthesized was limited by the fact that the bridgehead stereochemistry resulting from the intramolecular cyclization reaction was set by the stereochemistry of the groups on the N-terminal side chain.[9] A sidechain with (*S*,*S*) stereochemistry would give rise to a bicyclic lactam with an *R*-configuration at the bridgehead carbon. A cyclization substrate having a side-chain with (*R*,*R*)-stereochemistry would give rise to a bicyclic lactam having an *S*-configuration at the bridgehead carbon. This would be a problem since TRH analogs having *S*-bridgehead stereochemistry are known not to bind or activate TRH-R well.[3,7]

Alternative routes to the six- and seven-membered ring building blocks (**9**) needed for the synthesis of **4a** and **4b** have been reported.[9a,10] However, the application of this chemistry to the TRH problem did not appear practical. First, the existing routes required that separate strategies be taken for making either the six- or the seven-membered ring analogs. Second, a new route would be still required for analogs like **3**, because the existing routes to **9** did not incorporate substituents on the carbon beta to the amide carbonyl.

With this in mind, we began to investigate the route outlined in Scheme 3. In this approach, both families of analogs (**3** and **4**) would be made from a common vinyl-substituted proline derivative **13**.[11] This plan offered several important advantages. First, the problems encountered with function-alization of seven-membered ring lactams and oxidations of substituted prolines would be avoided by functionalizing the proline ring early. Second, the stereochemistry at the



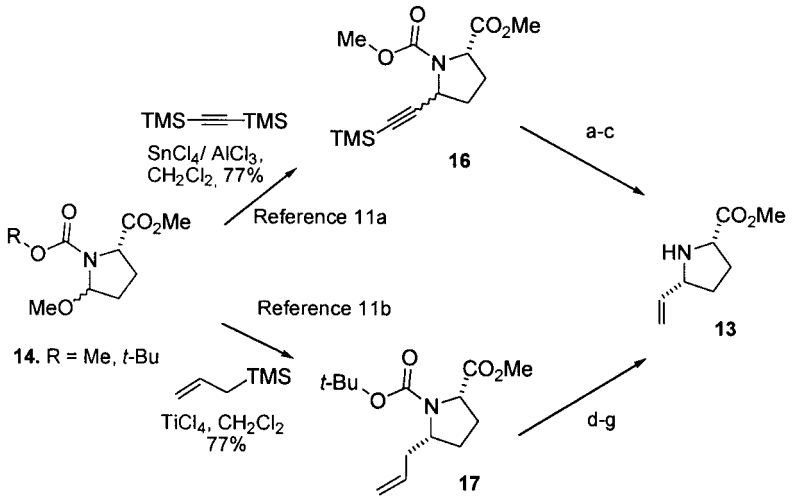

**Scheme 3.**




**Scheme 4.**

geous to use a mixed Lewis acid catalyst (1:1 $AlCl_3$/$SnCl_4$) for the synthesis of **16**. Using the mixed catalyst system improved the consistency of the yield obtained for the addition, and avoided the occasional generation of increased amounts of the *trans*-5-vinylproline product.

On a final note, both the synthesis of **13** and the synthesis of **15** did use an anodic amide oxidation to generate the




**Scheme 5.** *Reagents:* (a) TBAF, THF, −20°C, 95%. (b) Lindlar cat., $H_2$, EtOAc, 95%. (c) TMSI, $CHCl_3$, 50°C, 70%. (d) i. $O_3$, MeOH, $CH_2Cl_2$, −78°C; ii. $NaBH_4$, −78°C to rt, 96%. (e) $(n\text{-}Bu)_3P$, $o\text{-}NO_2(C_6H_4)SeCN$, THF, 85%. (f) i. MCPBA, $CH_2Cl_2$, −70°C, 30 min; ii. $Me_2S$, $Et_3N$, −70°C to rt, 96%. (g) TFA, $CH_2Cl_2$, 65%.

bridgehead carbon would be set during the synthesis of **13**. If a mixture of isomers were to arise, then the *cis*- and *trans*-isomers of **13** could be separated and a sizable amount of the desired isomer obtained with a minimum amount of impact on the synthesis. Finally, the synthesis called for the use of an olefin metathesis reaction to complete the formation of the lactam ring.[12] Since the olefin metathesis reaction was known to be compatible with amino acid functionality, all of the stereocenters in a desired analog would be set in the starting materials (X=NHBOC) before construction of the bicyclic lactam ring skeleton. This would allow for the synthesis of analogs having a variety of stereochemical patterns without altering the bridgehead stereochemistry.

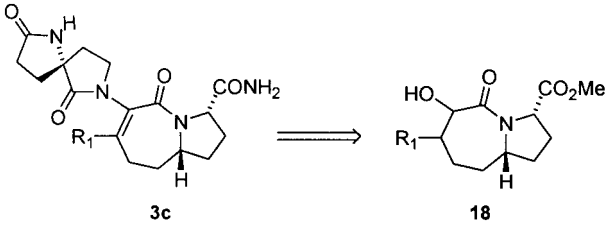
## Synthesis of the vinylproline starting materials

When this work was started, syntheses for both the *trans*- and the *cis*-5-vinylsubstituted prolines had been reported. Several items concerning these syntheses warrant comment here. The pure *trans*-5-vinylproline derivative **15** can be conveniently made by the addition of a vinyl cuprates to the *N*-acyliminium ion generated by $BF_3{\cdot}Et_2O$ treatment of a methoxylated amide **14** (Scheme 4).[13] While this procedure was extremely useful, it did not allow access to the *cis*-5-vinylproline derivative **13** that was required for the synthesis of TRH analogs. In this case, three options were available.[11] Of these options, the two outlined in Scheme 5 have proven to be the most effective for generating multigram quantities of **13**. Of these two, we prefer the route developed by Manfree because it avoids the use of selenium. While for the most part our use of the Manfree procedure has followed the literature,[11a] we have found it advantamethoxylated amide **14**.[14] The use of the anodic amide oxidation ensured that the pathway could take advantage a variety of amino acid based starting materials,[14c] and hence left open the possibility for using the same chemistry to develop peptidomimetics with variations in the C-terminal end of the building block.[1c]

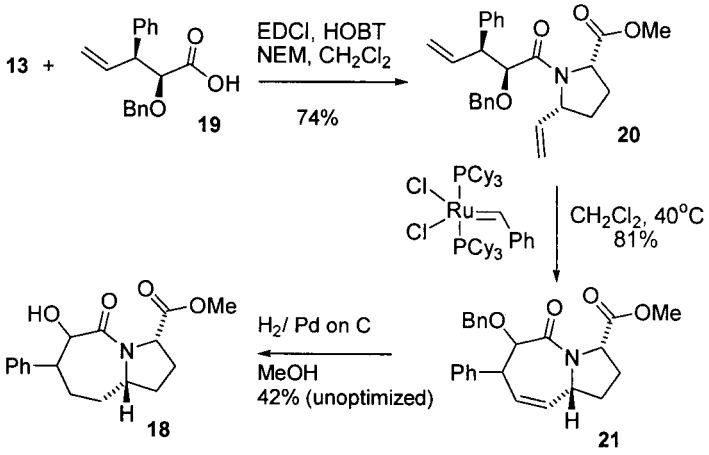
## Building more flexible analogs—an initial approach

At the start, it appeared that the fastest way to constrain the central region of TRH with a seven-membered ring lactam would be to take advantage of the route suggested in Scheme 6. In this route, the metathesis reaction would be used to make **18**, and then **18** converted into a TRH analog using the chemistry developed for **2a**. In this sequence, an α-hydroxyamide was oxidized and the resulting ketone converted into a enamine by treatment with ammonia in methanol. The enamine was then coupled to a pyroglutamate derivative and the C-terminal end of the building block converted into the primary amide.

In practice, the synthesis of alcohol **18** proceeded nicely




**Scheme 6.**




**Scheme 7.**

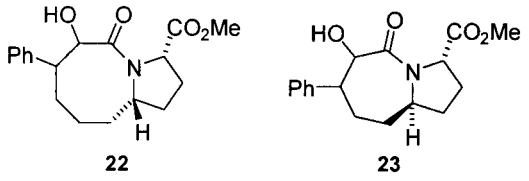



**Figure 1.**

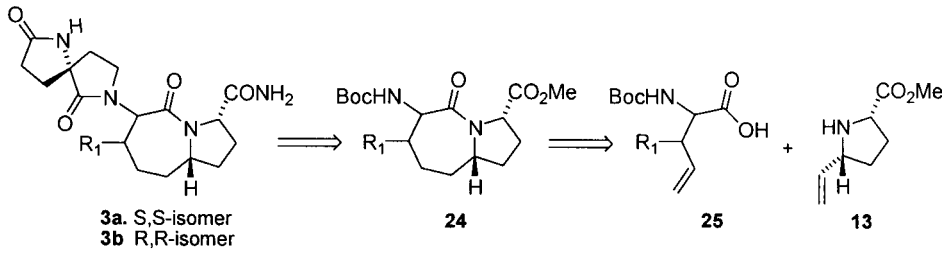
(Scheme 7). The *cis*-vinylproline **13** was coupled to 2-benzyloxy-3-phenyl-4-pentenoic acid **19**, and the olefin metathesis reaction accomplished with the use of the ruthenium based catalyst developed by Grubbs and coworkers.[12] The metathesis reaction led to an 81% isolated yield of the bicyclic lactam derivative **21**. Hydrogenation of the double bond in **21** afforded the desired seven membered building block **18**. The yield of the hydrogenation reaction was not optimized due to subsequent problems with the synthesis (see below).

In addition to **18**, two other building blocks were assembled (Fig. 1). The eight-membered ring analog **22** was made in an identical fashion to **18** except for the use of 5-allylproline **17** in place of **13**. The olefin metathesis reaction led to the 72% yield of the cyclized product. The synthesis of **23** started from the *trans*-vinylproline derivative **15** ($R_1$=$R_2$=H). Every other aspect of the synthesis was identical.

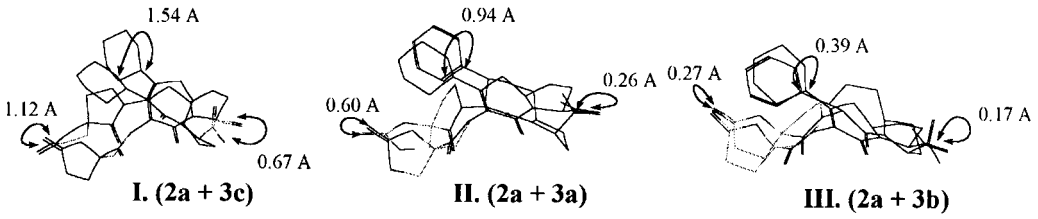
While this synthetic strategy allowed for assembly of the proposed alcohol building blocks, it was not capable of generating the actual TRH analogs. In the case of **18**, neither the oxidation of the alpha keto amide nor the conversion of the resulting ketone into an enamine could be accomplished in an acceptable yield.

## Building more flexible analogs—a second more versatile approach

The difficulty associated with adding in the nitrogen functionality to **18** and the compatibility of the olefin metathesis catalyst with peptide based substrates,[12] prompted us to examine the utility of a synthetic route that would directly generate the cyclic products with the N-terminal amine group already in place (Scheme 8). This route was extremely attractive because molecular modeling suggested that a more flexible seven-membered ring lactam analog would better mimic **2a** if the double bond in **3c** was removed. For example, consider the overlapped structures illustrated in Scheme 9.[16] In each of the three drawings, a potential new analog (**3a**–**3c**) has been overlayed with **2a** in order to illustrate how well the pharmacophoric groups in the new analog overlap with the conformation of the same groups in **2a**. The distance between the pharmacophores for the best possible fit are indicated by the arrows. From structure **I**, it was clear that the conformation of the pharmacophoric groups in **3c** would differ significantly from the conformation found in **2a**. This was a problem because analog **2a** bound TRH-R well. The question being asked was whether or not a more flexible analog having the *same* conformation would be fully potent. An ideal analog would add flexibility to the constraints without altering the conformation of the pharmacophoric groups. To this end, both analogs **3a** and **3b** appeared to be superior to **3c** (structures **II** and **III**). Of these two, analog **3b** looked to be best




**Scheme 8.**



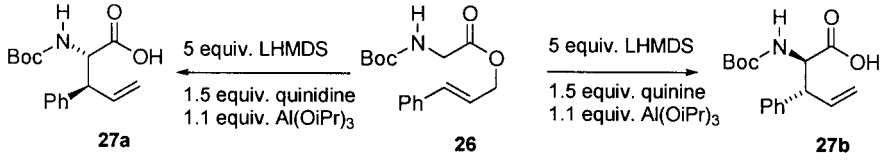

**Scheme 9.**

because it would allow for a close overlap between the pharmacophoric groups while better maintaining the overall conformation of the peptide backbone found in **2a**. In either case, it appeared that our ability to address the biological questions of concern would benefit greatly from the addition of stereocenters into the lactam ring.

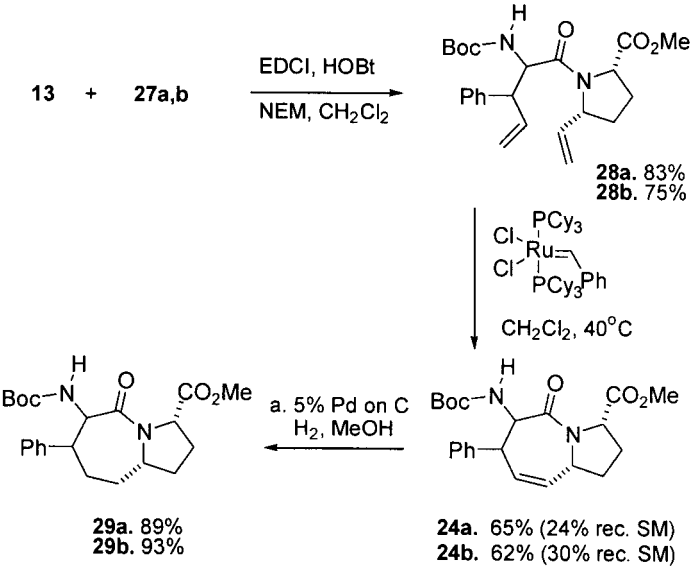
The forward synthesis of the bicyclic building blocks required for making **3a** and **3b** (as well as partially constrained analogs) began with the construction of the known acids **27a** and **27b** (Scheme 10).[15] The synthesis of building block **29a** was then started by coupling the *cis*-5-vinylproline methyl ester **13** with acid **27a** (Scheme 11). The resulting olefin metathesis substrate was then cyclized to afford a 65% yield of the seven-membered ring lactam **24a** along with 24% of the recovered starting material. Hydrogenation of the double bond in **24a** afforded building block **29a**. The synthesis of **29b** proceeded in an identical fashion starting from acid **27b**.

In both cases, the building blocks were readily converted into TRH analogs (Scheme 12). As initial targets, the partially constrained TRH analogs **30a** and **30b** were selected so that the new constraints could be independently evaluated for how they effected the binding and potency of the analog. The synthesis involved cleavage of the *t*-Boc protecting group, coupling of the resulting amine to pyroglutamic acid using standard EDCI conditions, and then conversion of the methyl ester to the primary amide using ammonia in methanol. The final aminolysis step was completed by dissolving the methyl ester in a saturated solution of ammonia in methanol, placing the resulting mixture into a sealed tube, and then heating the reaction to 65°C for two days. In this way, an 77% isolated yield of **30a** was obtained from the corresponding methyl ester. An 85% yield of **30b** was obtained.

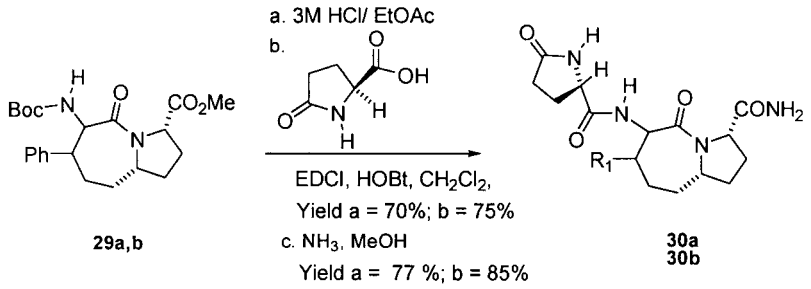
Interestingly, preliminary biological studies on **30a** and **30b** confirmed the suggestion made by molecular modeling.




**Scheme 10.**




**Scheme 11.**



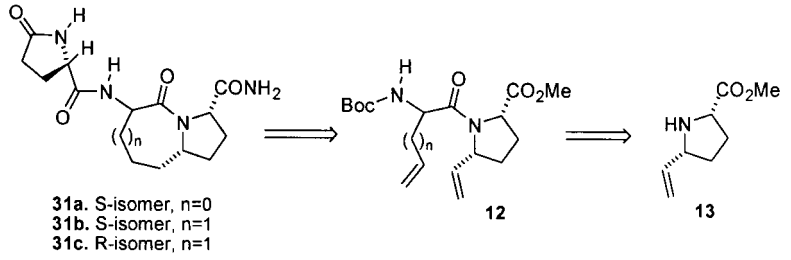

**Scheme 12.**

Analog **30b** had an affinity for TRH-R that was about 35 times greater than that measured for **30a**.[17] In fact, the constraint used in **30b** allowed for binding to TRH-R at a level competitive with the constraint used in the central region of **2a**;[7] an observation that suggested the use of the constraint in **30b** for making a fully constrained TRH analog that is more flexible than **2a**.

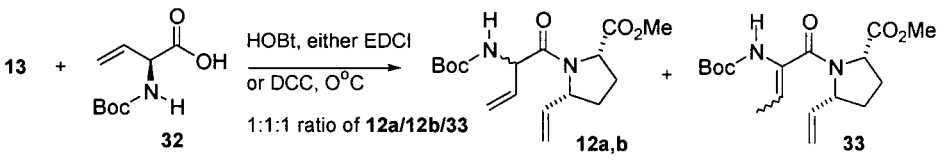
## Analogs without the sidechain on the central amino acid

As mentioned above, we were also interested in synthesizing TRH analogs that did not have the sidechain on the central amino acid. These analogs were desired as probes for determining if the presence of the sidechain was essential for the analog to be a full agonist for TRH-R. Because of the ease with which analogs **30a** and **30b** were made, we hoped that a nearly identical approach would be useful for the synthesis of either analogs like **4** or partially constrained analogs like **31** (Scheme 13). Two concerns immediately arose. First, the route required the coupling of vinylglycine to a secondary amine that was branched on both alpha carbons.[18] The double bond in vinylglycine was known to undergo migration reactions,[19] and it was not clear that the coupling of vinylglycine to a sterically hindered amine could be accomplished without such complications. Second, the yield of olefin metathesis reactions using vinylglycine derived olefins can be dependent on the nature of the surrounding substituents.[20] Would the highly substituted proline derivative needed for the synthesis of analogs like **4** or **31** interfere with the metathesis reaction?

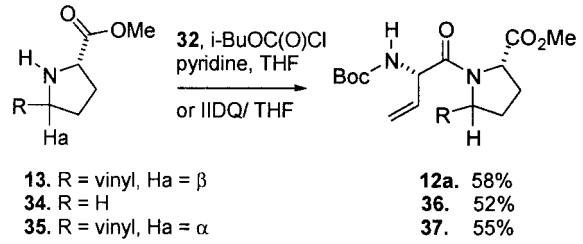
Initially, the coupling of vinylglycine to the vinyl substituted proline derivative was problematic. When the coupling reaction was performed using HOBt conditions with either EDCI or DCC as an activating group three products were obtained in a 1:1:1 ratio (Scheme 14). Only one of the products was the desired **12a**. The other two products resulted from either migration of the double bond or epimerization of the vinylglycine α-carbon. The competitive racemization and olefin migration reactions could not be avoided. Even when short reaction times were used, side reactions dominated these procedures. Fortunately, many of the problems with the coupling reaction could be avoided with the use of a mixed anhydride as the activated ester. When the anhydride derived from the treatment of acid **32** with isobutylchloroformate and pyridine was used to effect the coupling reaction, the desired product was obtained in a 58% isolated yield (Scheme 15). Alternatively, IIDQ (2-isobutoxy-1-isobutoxycarbonyl-1,2-dihyroquinoline) could be used to make the mixed anhydride. While the yield was not excellent using either method, neither the product from migration nor the product from epimerization (**12b**) was observed, and the pure olefin metathesis substrate could be obtained. Interestingly, the yield of the coupling reaction was not dependent on the steric size of the amine. Removing the vinyl group from the proline ring did not improve the yield of the reaction. The coupling of **34** to vinylglycine afforded a 52% yield of product. The use of the more hindered (and normally more difficult to couple) *trans* vinyl proline derivative **35** led to a 55% isolated yield of product. As earlier, no product from




**Scheme 13.**




**Scheme 14.**



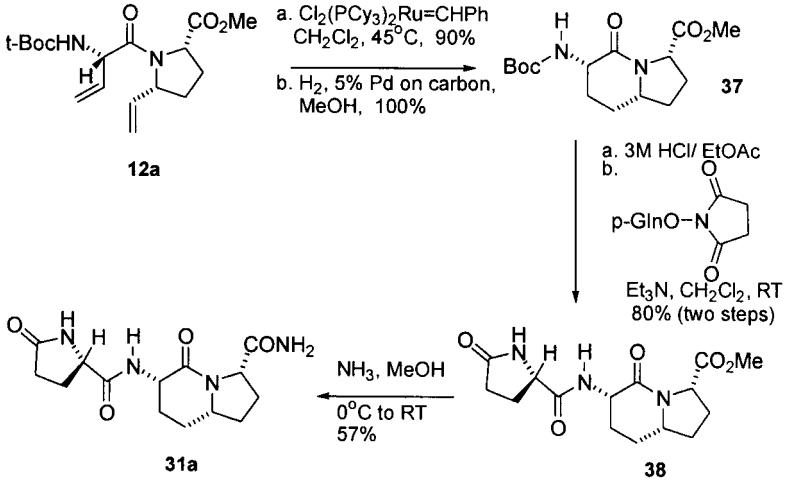

**Scheme 15.**

migration of the double bond or racemization was obtained in either of these reactions.

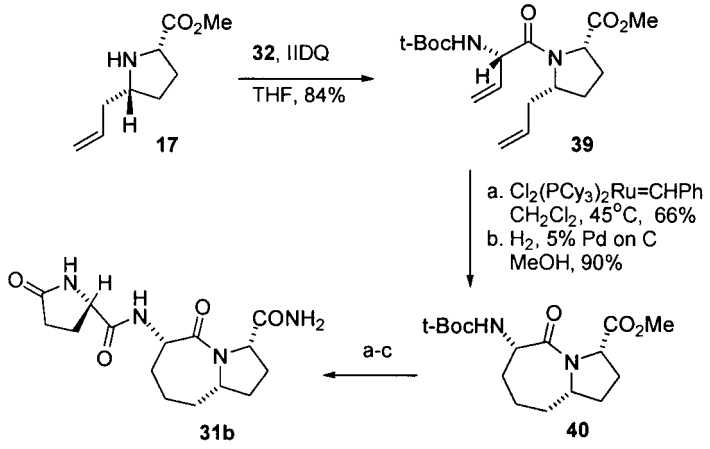
Once the olefin metathesis substrate was in hand, the lactam constraint was readily completed (Scheme 16). Substrate **12a** was cyclized in order to afford an 85% isolated yield of the bicyclic lactam **37**. The double bond in the lactam ring was immediately hydrogenated in order to avoid migration reactions. The N-terminal Boc protecting group on **37** was then removed using HCl in ethyl acetate, and the resulting amine coupled to pyroglutamic acid by using the *N*-hydroxysuccinimide activated ester. The desired TRH analog **31a** was then obtained with the use of ammonia in methanol.

A very similar approach was used to generate the corresponding seven-membered ring analog **31b**. In this case, the synthesis began with the coupling of vinylglycine to the 5-allylproline derivative **17** (Scheme 17).[11b] Olefin metathesis to generate the seven-membered ring lactam, hydrogenation of the double bond, deprotection of the Boc group, coupling to the *N*-hydroxysuccinimide ester of pyroglutamic acid, and conversion of the methyl ester into a primary amide afforded TRH analog **31b**.

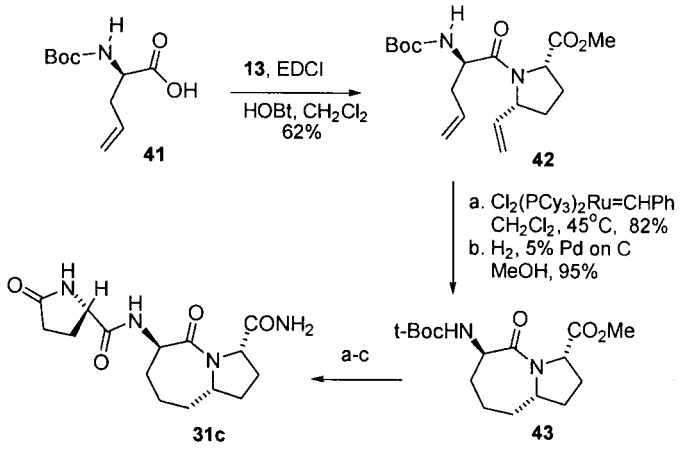
For the synthesis of a seven-membered ring analog, an alternative strategy could be taken that avoided the use of vinylglycine. For example, the synthesis of a TRH analog having the opposite lactam stereochemistry (**31c**) was accomplished by starting the synthesis with a coupling reaction between the vinyl substituted proline derivative **13** and the commercially available vinylalanine derivative **41** (Scheme 18). Following this coupling reaction, the synthesis of the TRH analog proceeded in a fashion directly analogous to the earlier syntheses.




**Scheme 16.**




**Scheme 17.** *Reagents:* (a) 3M HCl, EtOAc. (b) $Et_3N$, pyroglutamate *N*-hydroxysuccinimide ester, $CH_2Cl_2$, RT, 70% (two steps). (c) $NH_3$, MeOH, 0°C–RT, 48 hr, 73%.




**Scheme 18.** *Reagents:* (a) 3 M HCl, EtOAc. (b) $Et_3N$, pyroglutamate *N*-hydroxysuccinimide ester, $CH_2Cl_2$, rt, 71% (two steps). (c) $NH_3$, MeOH, 0°C-rt, 48 h, 40%.

Preliminary biological testing of TRH analogs **31a–c** showed that the analogs did not have a high affinity for TRH-R relative to **2a**.[17] However, both **31a** and **31b** were full agonists of the receptor, an observation that indicated that the presence of the sidechain was not a requirement for full agonist behavior.

## Conclusions

The ability of electrochemical amide oxidations to selectively functionalize amino acid derivatives has made readily available both vinyl- and allyl-substituted proline derivatives. In this work, these building blocks were coupled to vinylalanine and vinylglycine derivatives, and then an olefin metathesis reaction used to complete the synthesis of a family of bicyclic lactam derivatives. In turn, the bicyclic lactams were used to construct a series of previously unavailable analogs for the tripeptidic hormone TRH.

It is clear that the use of a sequential amide oxidation/olefin metathesis strategy can provide a rapid approach to bicyclic lactam peptidomimetics. Because of the availability of chiral, vinyl-substituted amino acid derivatives, the route not only offers rapid access to the desired ring skeletons, but also access to derivatives that vary the stereochemistry of the centers within the lactam constraint. As in the synthesis of analogs **30a** and **30b**, the development of this method allows for the construction of peptidomimetics that fix the pharmacophoric groups of a peptide segment in the same orientation while altering the shape of the scaffold that holds them in place. Such a change can dramatically effect the biological activity of the analog, and therefore the methodology developed here should prove valuable for the synthesis of constrained peptidomimetics in the future.

## Experimental

The synthesis of **13** was conducted as reported in the literature with one exception. The conversion of **14** to **16** was modified as follows: A solution of **14** (3.21 g, 14.8 mmol) and bis(trimethylsilyl)acetylene (5.00 g, 29.4 mmol) in $CH_2Cl_2$ (38 mL) was added 1 M solution of $SnCl_4$ in $CH_2Cl_2$ (19 mL) at −20°C, then $AlCl_3$ (2.7 g) was added. The mixture was warmed to rt and stirred at room temperature for 36 h. Water (10 mL) was added, then neutralized with saturated $Na_2CO_3$ to PH=10, the white solid was filtered out. The filtrate was extracted with ethyl acetate (150 mL), and washed with saturated NaCl, dried over $Na_2SO_4$. After evaporation of the solvent, the crude product was purified with hexane–ether (4:1) to afford 1.57 g (38%) of the *trans* compound and 1.82 g (44%) of the *cis* compound **16** which was converted into **13**.

For the purpose of providing a general synthetic protocols, the synthesis of analog **30b** is detailed below. For the synthesis of analogs **30a** and **31a–c** characterization data are provided along with alternative synthetic procedures where noted. Details concerning the syntheses of building blocks **18**, **22**, and **23** have not been included since they proved ineffective for constructing the desired TRH analogs. However, it should be noted that the synthetic procedures followed for the construction of these building blocks were identical to those reported for the synthesis of **30b**.

***N*-[(2*R*)-*t*-Butoxycarbonylamino-(3*R*)-phenyl-4-pentenoyl]-(5*R*)-vinylproline methyl ester (28b).** A solution of **13** (274 mg, 0.94 mmol) and **27b** (63 mg, 0.47 mmol) in $CH_2Cl_2$ was added HOBt (152 mg, 1.13 mmol), then a 1 M solution of DCC in $CH_2Cl_2$ (1 mL) was added at −20°C. The reaction mixture was warmed to rt and stirred at rt overnight. Ethyl acetate (50 mL) was added to the reaction mixture, washed with 10% citric acid (15 mL×2), 5% $NaHCO_3$ (15 mL×2) and saturated NaCl (20 mL), dried over $Na_2SO_4$. After evaporation of the solvent, the crude product was purified with hexane–ether (1:1) to give **28b** 151 mg (75%) as a colorless oil. $^1H$ NMR (300 MHz/$CDCl_3$) $\delta$: 7.35–7.20 (m, 5H), 6.36–6.24 (m, 1H), 5.82–5.71 (m, 1H), 5.44–5.10 (m, 4H), 4.77–4.72 (m, 1H), 4.26 (t, $J$=8.1 Hz, 1H), 3.83–3.72 (m, 2H), 3.76 (s, 3H), 3.56 (m, 1H), 2.02–1.98 (m, 1H), 1.86–1.57 (m, 3H), 1.37 (s, 9H); $^{13}C$ NMR (75 MHz/$CDCl_3$) $\delta$ 172.2, 169.8, 154.4, 139.8, 136.5, 135.5, 128.5, 128.4, 127.1,

118.2, 117.2, 79.3, 60.2, 59.8, 55.5, 53.7, 52.2, 31.6, 29.7, 28.2, 27.0; IR (neat/NaCl) 3430, 3310, 3060, 2979, 2932, 1750, 1710, 1643, 1498, 1437, 1366, 1265, 1174, 996, 921, 736, 702 $cm^{-1}$; LRMS (FAB) *m/e* (rel. int.) 429 (M+1, 23), 373 (19), 329 (65), 211 (17), 156 (100); HRMS (FAB) *m/e* calcd for $C_{24}H_{32}N_2O_5$ (M+1) 249.2389, found 429.2395.

**(3*R*,4*R*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-4-phenyl-10-carbomethoxybicyclo[5.3.0]dec-5-ene (24b).** A solution of **28b** (118 mg, 0.276 mmol) in $CH_2Cl_2$ (55 mL) was added bis(tricyclohexylphosphine)-benzylidine ruthenium (IV) dichloride (45 mg) and the mixture was heated to reflux for 24 h. After evaporation of the $CH_2Cl_2$ in vacuo, the crude product was purified with hexane–ether (1:2) to afford 68 mg (62%) **24b** as a white solid along with 36 mg (30%) of recovered **28b**. $^1H$ NMR (300 MHz/$CDCl_3$) $\delta$: 7.32–7.21 (m, 5H), 5.83–5.71 (m, 2H), 5.28 (d, *J*=9.9 Hz, 1H), 5.00 (dd, *J*=11.7, 9.0 Hz, 1H), 4.85 (m, 1H), 4.67 (dd, *J*=7.05, 4.2 Hz, 1H), 3.76 (s, 3H), 3.56 (m, 1H), 2.41 (m, 1H), 2.14 (m, 2H), 1.96 (m, 1H), 1.17 (s, 9H); $^{13}C$ NMR (75 MHz/$CDCl_3$) $\delta$: 171.8, 170.0, 154.6, 140.3, 132.6, 129.0, 128.6, 128.0, 126.8, 79.1, 59.8, 55.6, 54.5, 52.4, 48.1, 33.0, 28.1, 27.7; IR (neat/NaCl) 3420, 3057, 2983, 2929, 1745, 1708, 1654, 1507, 1436, 1362, 1265, 1168, 1064, 1023, 862, 735 $cm^{-1}$; LRMS (FAB) *m/e* (rel. int.) 401 (M+1, 8), 345 (11), 301 (100), 282 (60); HRMS (FAB) *m/e* calcd for $C_{22}H_{29}N_2O_5$ (M+1) 401.2076, found 401.2072.

**(3*R*,4*R*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-4-phenyl-10-carbomethoxybicyclo[5.3.0]decane (29b).** A solution of **24b** (124 mg, 0.31 mmol) and 5% Pd/C (62 mg) in methanol (5 mL) was hydrogenated under hydrogen balloon overnight. After removal of the catalyst by filtration and evaporation of the methanol, the residue was purified with hexane–ether (1:2) to afford 115 mg (93%) **5** as a white solid. $^1H$ NMR (300 MHz/$CDCl_3$) $\delta$: 7.29–7.18 (m, 5H), 5.17 (d, *J*=9.3 Hz, 1H), 4.71 (t, *J*=9.9 Hz, 1H), 4.65 (dd, *J*=7.95, 4.2 Hz, 1H), 4.10 (m, 1H), 3.78 (s, 3H), 2.81 (m, 1H), 2.31 (m, 1H), 2.18–2.07 (m, 4H), 1.91 (m, 2H), 1.80 (m, 1H), 1.21 (s, 9H); $^{13}C$ NMR (75 MHz/$CDCl_3$) $\delta$: 172.5, 171.1, 155.0, 142.4, 128.1, 127.8, 126.3, 79.0, 60.3, 58.6, 56.5, 52.3, 47.1, 37.1, 34.5, 32.9, 28.1, 27.8; IR (neat/NaCl) 3424, 2976, 2936, 1746, 1710, 1650, 1500, 1433, 1369, 1249, 1172, 1066, 872, 762, 736 $cm^{-1}$; LRMS (FAB) *m/e* (rel. int.) 409 (M+Li, 90), 359 (10), 309 (100); HRMS (FAB) *m/e* calcd for $C_{22}H_{30}N_2O_5Li$ (M+Li) 409.2315, found 409.2315.

**(3*R*,4*R*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamino-4-phenyl-10-carbomethoxybicyclo[5.3.0]decane.** A solution of **29b** (100 mg, 0.25 mmol) in ethyl acetate–HCl (37%) (3:1) was stirred for 2 h at rt and then the solvent removed in vacuo. Methanol (10 mL) was added and then the solvent again removed in vacuo. The residue was dried under vacuum for 12 h to afford a white solid. To this residue, $CH_2Cl_2$ (5 mL), triethylamine (51 mg, 0.50 mmol) and HOBt (68 mg, 0.50 mmol) were added at 0°C, and then a 1 M solution of DCC in $CH_2Cl_2$ (0.63 mL) was added. The mixture was stirred at rt overnight, ethyl acetate (50 mL) was added, washed with 10% citric acid (25 mL×2), 5% $Na_2CO_3$ (25 mL×2) and saturated NaCl (30 mL), dried over $Na_2SO_4$. After evaporation of the solvent, the crude product was purified with ether–methanol (10:1) to afford 76 mg (75%) **6** as a white solid. $^1H$ NMR (300 MHz/$CDCl_3$) $\delta$: 7.29–7.19 (m, 5H), 7.07 (d, *J*=9.9 Hz, 1H), 6.61 (s, 1H), 5.11 (t, *J*=9.9 Hz, 1H), 4.58 (dd, *J*=8.1, 4.2 Hz, 1H), 4.12 (m, 1H), 3.83 (dd, *J*=9.3, 3.9 Hz, 1H), 3.77 (s, 3H), 2.90 (m, 1H), 2.32 (m, 1H), 2.15–2.04 (m, 6H), 1.93–1.82 (m, 4H), 1.61–1.52 (m, 1H), 1.19–1.14 (m, 2H); $^{13}C$ NMR (75 MHz/$CDCl_3$) $\delta$: 178.8, 172.3, 170.9, 170.5, 142.5, 128.1, 127.9, 126.7, 60.6, 58.8, 56.8, 52.4, 46.7, 37.1, 34.3, 32.9, 28.4, 27.7, 25.3; IR (neat/NaCl) 3282, 3054, 2946, 1742, 1682, 1619, 1538, 1431, 1364, 1267, 1204, 1174, 735, 702 $cm^{-1}$; LRMS (FAB) *m/e* (rel. int.) 420 (M+Li, 100), 303 (8), 160 (22); HRMS (FAB) *m/e* calcd for $C_{22}H_{27}N_3O_5Li$ (M+Li) 420.2111, found 420.2104.

**(3*R*,4*R*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamino-4-phenyl-10-carboxyamidebicyclo[5.3.0]decane (30b).** In a tube, a solution of the methyl ester made above (65 mg, 0.157 mmol) in methanol (5 mL) was saturated with $NH_3$ gas at 0°C. The tube was sealed and heated to 65°C for 2 days. After evaporation of the methanol in vacuo, the crude product was purified with ether–methanol (4:1) to afford 53 mg (85%) **30b** as a white solid along with 8 mg of the recovered starting material. $^1H$ NMR (300 MHz/$CDCl_3$) $\delta$: 7.34 (s, 1H), 7.29–7.15 (m, 6H), 6.94 (d, *J*=9.3 Hz, 1H), 5.94 (s, 1H), 5.10 (t, *J*=9.6 Hz, 1H), 4.46 (dd, *J*=7.2 Hz, *J*=2.7 Hz, 1H), 4.09 (m, 1H), 3.84 (dd, *J*=9.4, 3.3 Hz, 1H), 2.91–2.89 (m, 1H), 2.35–2.23 (m, 3H), 2.19–2.09 (m, 3H), 1.99–1.83 (m, 4H), 1.51–1.25 (m, 2H); $^{13}C$ NMR (75 MHz/$CDCl_3$) $\delta$: 183.4, 179.2, 173.7, 171.3, 171.1, 142.4, 128.3, 127.7, 126.9, 61.7, 59.3, 56.7, 54.8, 46.3, 37.2, 34.3, 33.3, 28.5, 27.2, 25.3; IR (neat/NaCl) 3405, 3291, 3050, 2983, 2930, 1689, 1635, 1445, 1421, 1264, 896, 739 $cm^{-1}$; LRMS (FAB) *m/e* (rel. int.) 399 (M+1, 100), 354 (65), 326 (17), 288 (22), 154 (52); HRMS (FAB) *m/e* calcd for $C_{21}H_{27}N_4O_4$ (M+1) 399.2032, found 399.2025.

***N*-[(2*S*)-*t*-Butoxycarbonylamino-(3*S*)-phenyl-4-pentenoyl]-(5*R*)-vinylproline methyl ester (28a).** The procedure followed was the same as that used for the synthesis of **28b** above except for the substitution of EDCI as the coupling reagent in place of DCC. An 83% yield of the coupled product was obtained. $^1H$ NMR (300 MHz/$CDCl_3$) 7.32–7.18 (m, 5H), 6.06–5.94 (m, 2H), 5.63 (d, *J*=16.8 Hz, 1H), 5.27 (d, *J*=10.2 Hz, 1H),5.10 (d, *J*=10.2 Hz, 1H), 5.01–4.81 (m, 4H), 4.53 (t, *J*=6.9 Hz, 1H), 3.80 (t, *J*=8.1 Hz, 1H), 3.75 (s, 3H), 2.22–2.15 (m, 2H), 2.04–1.99 (m, 1H), 1.89 (m, 1H), 1.24 (s, 9H); $^{13}C$ NMR (75 MHz/$CDCl_3$) 172, 171, 154, 139, 138.8, 137, 130, 128.8, 128.4, 128.2, 126, 117.3, 116.9, 79.5, 61, 60, 53.8, 53.0, 52.8, 52.1, 32, 28, 27; IR (neat/NaCl) 3422, 3300, 3055, 2973, 1742, 1698, 1634, 1494, 1427, 1359, 1260, 1162, 1033, 1009, 914, 731 $cm^{-1}$; LRMS (FAB) *m/e* (rel. int.) 451 (M+Na, 100), 429 (M+1, 20), 373 (30), 329 (96), 297 (12); HRMS (FAB) *m/e* calcd for $C_{24}H_{33}N_2O_5$ (M+1) 429.2389, found 429.2382.

**(3*S*,4*S*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-4-phenyl-10-carbomethoxybicyclo[5.3.0]dec-5-ene (24a).** The olefin metathesis reaction was accomplished using the conditions described above for the synthesis of **24b** in order to form 65% yield of **24a** along with 24% of the recovered starting material. $^1H$ NMR (300 MHz/$CDCl_3$) $\delta$ 7.39 (m, 2H), 7.32–7.20 (m, 3H), 5.94 (d, *J*=12.0 Hz, 1H),

5.75 (b, 1H), 5.21 (d, $J$=5.4 Hz, 1H), 4.71–4.45 (2 bm, 2H), 4.45–4.2 (bm, 1H), 3.87–3.74 (bm, 1H), 3.69 (s, 1H), 2.4–2.29 (bm, 1H), 2.17 (m, 1H), 2.55–1.96 (m, 2H), 1.45 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) $\delta$ 172.3, 167.7, 154.7, 137.4, 129.4, 129.0, 128.2, 127.3, 80.1, 60.8, 55.2, 51.9, 46.9, 33.3, 29.5, 28.1, 27.0; IR (neat/NaCl) 2916, 2822,2747, 1866, 1674, 1643, 1584, 1429, 1329 cm$^{-1}$; LRMS (FAB) *m/e*: 401 (M+1, 28), 359 (20), 345 (35), 301 (M+1−$CO_2C_3H_9$, 100), 282 (35); HRMS (FAB) *m/e* calcd for $C_{22}H_{29}N_2O_5$ (M+1) 401.2076, found 401.2080.

**(3*S*,4*S*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-4-phenyl-10-carbomethoxybicyclo[5.3.0]decane (29a).** The procedure utilized to make **29a** (89%) was identical to the procedure described above for the synthesis of **29b**. $^1$H NMR (300 MHz/$CDCl_3$) $\delta$ 7.32–7.18 (m, 5H), 5.05 (b, 1H), 4.58 (d, $J$=8.4 Hz, with fine splitting, 1H), 4.29 (bm, 2H), 3.74 (s, 1H), 3.50–3.33 (bm, 1H), 2.25–1.76 (m, 9H), 1.32 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$), $\delta$ 172.8, 169.8, 157.7, 142.9, 128.2, 126.5, 79.5, 61.3, 60.7, 57.0, 52.1, 43.6, 32.4, 30.7, 29.9, 28.2, 27.2; IR (neat/NaCl) 2872, 2845, 1669, 1630, 1583 cm$^{-1}$; LRMS (FAB) *m/e*: 403 (M+1, 14), 347 (M−56, 9), 303 (M−$CO_2C_3H_9$, 100), 287(M−115, 13); HRMS (FAB) *m/e* calcd for $C_{22}H_{31}N_2O_5$ (M+1) 403.2233, found 403.2217.

**(3*S*,4*S*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamino-4-phenyl-10-carbomethoxybicyclo[5.3.0]decane.** The deprotection and subsequent coupling to pyroglutamic acid of **29a** was done using the succinimide ester of pyroglutamic as described below for the synthesis of **38**. Using this procedure a 70% yield of the desired product was obtained over the two steps. $^1$H NMR (300 MHz/$CDCl_3$) $\delta$ 7.50 (d, $J$=7.3 Hz, 1H), 7.29–7.14 (m, 5H), 6.98 (s, 1H), 4.55 (dd, $J$=8.0, 3.4 Hz, 1H), 4.41 (bt, $J$=6.8 Hz, 1H), 4.29 (dd, $J$=10.6, 7.7 Hz, 1H), 3.82 (dd, $J_1$=9.4, 3.8 Hz, 1H), 3.71, (s, 3H), 3.71–3.6 (m, 1H), 2.29–1.74 (m, 11H with $H_2O$), 1.51–1.39 (m, 1H); $^{13}$C NMR (75 MHz/$CDCl_3$) $\delta$ 178.9, 172.9, 172.5, 169.7, 143.5, 128.2, 128.1, 126.7, 61.8, 59.1, 57.1, 56.8, 52.2, 42.9, 32.3, 31.6, 30.8, 28.9, 27.2, 25.3; IR (neat/NaCl) 3282, 3063, 2950, 1743,1683, 1626, 1547, 1438, 1368, 1272, 1203, 1177, 737 cm[1]; LRMS (EI) *m/e*: 413 (M, 8), 354 (M−59, 16), 329 (M−84, 33), 287 (37), 269 (37), 257 (M−156, 100); HRMS (FAB) *m/e* calcd for $C_{22}H_{28}N_3O_5$ (M+1) 414.2029, found 414.2025.

**(3*S*,4*S*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamino-4-phenyl-10-carboxyamidebicyclo[5.3.0]decane (30a).** Compound **30a** was made (77%) in a fashion identical to that described for the synthesis of **30b** above. $^1$H NMR (300 MHz/$CD_3OD$) $\delta$ 7.18–7.04 (m, 5H), 4.40 (d, $J$=10.4 Hz, 1H), 4.35 (d, $J$=7.4 Hz, 1H), 4.21 (m, 1H), 3.81–3.78 (m, 1H), 3.36 (t, $J$=10.6 Hz, 1H), 2.87–1.70 (m, 11H); $^{13}$C NMR (75 MHz/$CDCl_3$) $\delta$ 179.9, 175.7, 172.5, 170.6, 143.2, 128.5, 128.1, 126.6, 63.2, 58.5, 57.0, 56.7, 43.4, 32.9, 30.9, 30.2, 29.3, 27.9, 25.1; IR (neat/NaCl) 3280, 2952, 1743, 1688, 1632, 1437 cm$^{-1}$; LRMS (EI) *m/e*: 398(M, 4), 354 (M−HNCO, 79), 314 (M−$C_4$NHO, 22), 269 (65), 226 (81), 84(100); HRMS (FAB) calcd for $C_{21}H_{27}N_4O_4$ (M+1) 399.2032, found 399.2032.

***N*-[(2S)-*t*-Butoxycarbonylamino-3-butenoyl]-(5*R*)-vinylproline methyl ester (12a).** Compound **32** (257 mg/0.128 mmol) was dissolved in 4 mL of THF followed by the addition of pyridine (103 μL/0.128 mmol) at 0°C and treated with 166 μL (0.128 mmol) of isobutylchloroformate. After 15 min, 198 mg (0.128 mmol) of **13** in 1 mL of THF was added, and another 1 mL of THF was used to rinse the glassware. The mixture was stirred and allowed to warm to room temperature over 3 h. The solvent was removed in vacuo and the residue was redissolved in 25 mL of $CH_2Cl_2$. The organic phase was washed with 5% $NaHCO_3$, 5% HCl, and brine, and then dried over $MgSO_4$. After the solvent was removed, the residue was flash chromatographed through silica gel using 20% EtOAc/hexane as eluant to afford 250 mg (58%) of **12a** as clear oil. $^1$H NMR (300 MHz/$CDCl_3$) $\delta$ 5.94–5.70 (m, 2H), 5.45–5.13 (m, 5H), 4.96 (m, 1H), 4.73 (br s, 1H), 4.54 (m, 1H), 3.68 (s, 3H), 2.18–2.07 (m, 2H), 1.99–1.78 (m, 2H), 1.37 (s, 9H); $^{13}$C NMR(75 MHz/$CDCl_3$) 172.1,170.7,155.1, 138.1, 133.4, 117.8,116.8, 79.8,61.2,59.8, 53.4, 52.1, 32.5, 28.2, 27.1; IR (NaCl) 2974, 2931, 1750, 1701, 1651, 1504, 1434, 1356, 1180 cm$^{-1}$; LRMS (FAB) *m/e* (rel. int.) 339 (M+1, 100%); HRMS(FAB) *m/e* calcd for $C_{17}H_{27}N_2O_5$ (M+1) 339.1920; found 339.1915.

**(3*S*,6*R*,9*S*)-1-Aza-3-*t*-butoxycarbonylamino-9-carbomethoxybicyclo[4.3.0]non-4-ene.** Substrate **12a** was cyclized in a fashion identical to the cyclization of **28b** to afford a 90% yield of the bicyclic lactam product. $^1$H NMR (300 MHz/$CDCl_3$) 5.99 (m, 2H) 5.54 (d, $J$=3.9 Hz, 1H), 4.66 (br s, 1H), 4.44 (d, $J$=8.7 Hz, 1H), 4.21 (dt, $J$=11.7 Hz, 5.8 Hz, 1H), 3.71 (s, 3H), 2.32–2.06 (m, 3H), 1.99–1.89 (m, 1H), 1.45 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) 173.4, 167.8, 157.6, 131.2, 127.8, 81.4, 60.2, 59.4, 53.9, 52.7, 30.8, 30.4, 29.8; IR (NaCl/neat) 2976, 2877, 1733, 1717, 1663, 1506, 1436, 1367, 1165 cm$^{-1}$; LRMS (FAB) *m/e* 311(100), 309(76), 307(87), 312(25); HRMS (FAB) *m/e* calcd for $C_{15}H_{23}N_2O_5$ (M+1) 311.1607; found 311.1604.

**(3*S*,6*R*,9*S*)-1-Aza-3-*t*-butoxycarbonylamino-9-carbomethoxybicyclo[4.3.0]nonane (37).** Product **37** was synthesized in a fashion identical to the synthesis of **29b** described above (100%). $^1$H NMR (300 MHz/$CDCl_3$) 5.47 (d, $J$=4.5 Hz, 1H), 4,46 (d, $J$=7.2 Hz, 1H), 4.13–4.06 (m, 1H), 3.69–3.62 (s+m, 4H), 2,45–2.35 (m, 1H), 2.21–1.97 (m, 4H), 1.73–1.57 (m, 3H), 1.39 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) 172.1, 169.1, 155.7, 79.5, 58.1, 56.5, 52.3, 50.0, 32.1, 29.0, 28.3, 27.1, 26.8; IR (NaCl/neat) 3403, 2977, 1739, 1700, 1653, 1506, 1169, 1073 cm$^{-1}$; LRMS (FAB) *m/e* 313.4 (M+1); HRMS (FAB) *m/e* calcd for $C_{15}H_{25}N_2O_5$ (M+1) 313.1763; found 313.1754.

**(3*S*,6*R*,9*S*)-1-Aza-3-pyroglutamoylamine-9-carbomethoxybicyclo[4.3.0]nonane (38).** The *N*-hydroxysuccinimide ester of pyroglutamic acid was prepared by adding 10 mmol of DCC to a slurry solution of 10 mmol pyrogulatmic acid and 10 mmol *N*-hydroxysuccinimide in EtOAc at 0°C. The mixture was stirred at 0°C for 3 h and then placed in a refrigerator overnight. The urea byproduct was then removed by filtration and the solvent evaporated in vacuo. The crude solid was recrystalized from $CH_2Cl_2$ to afford a white solid which was used in the reaction below. $^1$H NMR (300 MHz/$CD_2Cl_2$) 6.19 (s, 1H), 4.60–4.56 (m,

1H), 2.84 (s, 4H), 2.70–2.60 (m, 1H), 2.50–2.30 (m, 3H). mp 133–135°C.

The protected amine **37** (80 mg) was dissolved in 2 mL of 3 M HCl in EtOAc (1:3). The solution was stirred at room temperature for 30 min before the solvent was removed under reduced pressure. The remaining residue was dissolved in 4 mL of $CH_2Cl_2$, and then 89.5 μL (0.64 mmol) of triethylamine was added followed by 145 mg (0.64 mmol) of the active ester made above. The mixture was stirred at room temperature overnight. The solvent was then removed in vacuo, and the residue chromatographed through silica gel to afford 80 mg (80%) of **38**. $^1$H NMR (300 MHz/$CDCl_3$) 7.31(d, $J$=6.3 Hz, 1H), 6.59 (s, 1H), 4.49–4.39 (m,2H), 4.17–4.13 (m, 1H), 3.72 (m+s, 4H), 2.53–2.04 (m, 8H), 1.78–1.62 (m, 4H); $^{13}$C NMR (75 MHz/$CDCl_3$) 178.7, 172.3, 172.0, 169.0, 58.3, 57.0, 56.7, 52.5, 48.7, 32.1, 29.3, 29.0, 27.0, 26.4, 25.9; IR ($CHCl_3$) 3282, 2952, 1735, 1700, 1684, 1652, 1559, 1540, 1436, 1457 cm$^{-1}$; LRMS (FAB) 324(30) 338(50) 307(58) 279(100) 289(70); HRMS (FAB) *m/e* calcd for $C_{15}H_{22}N_3O_5$ (M+1) 324.1559; found 324.1557.

**(3*S*,6*R*,9*S*)-1-Aza-3-pyroglutamoylamine-9-carboxyamidebicyclo[4.3.0]nonane (31a).** Methyl ester **38** (85 mg) was treated with 8 mL of methanolic ammonia solution (saturated) and stirred at room temperature for 4 days. Evaporation of the MeOH and $NH_3$ followed by silica gel chromatography (2:1:1 ether/methanol/dichloromethane) afforded 47 mg (57%) of the desired **31a**. $^1$H NMR (300 MHz/$CDCl_3$) 7.63–7.24 (d+s, $J$=12.6 Hz, 2H), 7.12 (s, 1H), 6.32 (s, 1H), 4.48 (d, $J$=7.5 Hz, 1H), 4.40 (d, $J$=8.1 Hz, 1H), 4.20–4.17 (m, 1H), 3.64–3.61 (m, 1H), 2.50–1.69 (m, 12H); $^{13}$C NMR (75 MHz/$CDCl_3$) 179.3, 174.1, 172.7, 169.5, 59.75, 58.3, 57.2, 48.4, 32.0, 29.6, 28.7, 27.0, 26.2, 25.6; IR (neat/NaCl) 3415(br), 2955, 2879, 1683, 1652, 1559, 1267, 1118 cm$^{-1}$; LRMS (FAB) 309(35), 154(100); HRMS (FAB) *m/e* calcd for $C_{14}H_{21}N_4O_4$ (M+1) 309.1563; found 309.1550.

***N*-[(2*S*)-*t*-Butoxycarbonylamino-3-butenoyl]-(5*R*)-vinylproline methyl ester (39).** Compound **39** was synthesized using the IIDQ coupling method. As in the synthesis of **12a** this route involved the formation of a isobutoxy based mixed anhydride. To this end, 443 mg (2.62 mmol) of the 5*R*-allylproline methyl ester (**17**), 527 mg (2.62 mmol) of vinyl glycine **32**, and 794 mg (2.62 mmol) of IIDQ were dissolved in 10 mL of THF. The reaction mixture was stirred at 23°C for 12 h, at which time the solvent was removed and the crude product was purified by flash chromatography to afford 778 mg of the desired product (84%) as clear oil. The NMR spectra for the amide was complex due to the presence of several rotamers. For this reason, the material was carried on to the next step before complete characterization. HRMS (FAB) *m/e* calcd for $C_{18}H_{29}N_2O_5$ 353.2076, found 353.2072.

**(3*S*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-10-carbomethoxybicyclo[5.3.0]dec-5-ene.** Substrate **39** was cyclized in a fashion identical to that described for the cyclization of **28b** to afford a 66% yield of the desired product. $^1$H NMR (300 MHz/$CDCl_3$) 5.71 (br d, $J$=6.6 Hz, 1H), 5.62–5.56 (m, 1H), 5.40–5.38 (m, 1H), 5.36–5.32 (m, 1H), 4.51 (t, $J$=6.0 Hz, 1H), 4,42–4.35 (m, 1H), 3.71 (s, 3H), 2.48–2.36 (m, 1H), 2.32–2.17 (m, 3H), 2.15–1.98 (m, 1H), 1.79–1.62 (m, 1H), 1.40 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) 172.6, 169.2, 155.7,128.0, 127.7, 79.6, 59.9, 55.5, 52.3, 51.7, 34.8, 31.5, 28.3, 27.9; IR (neat/NaCl) 3259, 1674, 1644, 1583, 1373, 1116 cm$^{-1}$; LRMS (FAB) 325(M+1, 33), 307(100), 289(54), 225(44); HRMS (FAB) *m/e* calcd for $C_{16}H_{25}N_2O_5$ (M+H) 325.1763; found 325.1755.

**(3*S*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-10-carbomethoxybicyclo[5.3.0]decane (40).** The hydrogenation reaction was done in a fashion identical to that described above for the synthesis of **29b** to afford a 90% yield of **40**. $^1$H NMR (300 MHz/$CDCl_3$) 5.84 (br d, $J$=6.3 Hz, 1H), 4.61 (dd, $J$=7.2, 4.5 Hz, 1H), 4.20 (dd, $J$=10.8, 6.3 Hz, 1H), 3.81 (q, $J$=8.1 Hz, 1H), 3.72 (s, 3H), 2.26–2.17 (m, 1H), 2.06–1.95 (m, 4H), 1.82–1.55 (m, 5H), 1.40 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) 172.5, 171.3, 155.2, 79.3, 60.2, 59.1, 54.3, 52.3, 34.2, 32.8, 31.7, 28.3, 27.6, 27.5; IR (neat/NaCl) 3132, 1625, 1674, 1576 cm$^{-1}$; LRMS (FAB) *m/e*: 327(M+1, 45), 227(77), 154(100), 136(67); HRMS (FAB) *m/e* calcd for $C_{16}H_{27}N_2O_5$ (MH+) 327.1920, found 327.1924.

**(3*S*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamine-10-carbomethoxybicyclo[5.3.0]decane.** The synthesis was done in a fashion identical to the preparation of **38** in order to obtain a 70% yield of the desired pyroglutamte coupled product. $^1$H NMR (300 MHz/$CDCl_3$) 7.56 (d, $J$=6.6 Hz, 1H), 7.24 (s, 1H), 4.54 (dd, $J$=9.0, 4.2 Hz, 1H), 4.45 (dd, $J$=10.2, 6.9 Hz, 1H), 4,13 (dd, $J$=8.4, 5.7 Hz, 1H), 3.84 (q, $J$=8.1 Hz, 1H), 3.72 (s, 3H), 2.56–1.54 (m, 14H); $^{13}$C NMR (75 MHz/$CDCl_3$) 179.1, 172.2, 171.1, 170.9, 60.4, 59.2, 57.2, 53.0, 52.4, 34.1, 32.9, 30.9, 29.5, 27.5, 25.8; IR (neat/NaCl) 3502, 1669, 1615, 1584, 1144 cm$^{-1}$; HRMS (FAB) *m/e* calcd for $C_{16}H_{24}N_3O_5$ (M+H) 338.1716, found 338.1722.

**(3*S*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamine-10-carboxyamidebicyclo[5.3.0]decane (31b).** Primary amide **31b** was made using the same procedure used to construct **31a** (73%). $^1$H NMR (300 MHz/$CDCl_3$) 7.64 (d, $J$=6.9 Hz, 1H), 7.51 (s,1H), 6.96 (br s, 1H), 6.00 (br s, 1H), 4.59–4.56 (m, 1H), 4.53–4.50 (m, 1H), 4.17–4.13 (m, 1H), 3.87–3.79 (m, 1H), 2.50–1.52 (m, 14H); $^{13}$C NMR (75 MHz/$CDCl_3$) 179.4, 173.8, 172.3, 171.5, 61.6, 59.7, 57.1, 53.1, 34.3, 33.2, 30.8, 29.4, 27.5, 26.9, 25.5; IR (neat/NaCl) 3191(br), 3086(br), 1613, 1584, 1566, 1393, 1200 cm$^{-1}$; HRMS (FAB) *m/e* calcd for $C_{15}H_{23}N_4O_4$ (M+H) 323.1719, found 323.1709.

***N*-[(2*R*)-*t*-Butoxycarbonylamino-4-pentenoyl]-(5*R*)-vinylproline methyl ester (42).** Compound **42** was obtained (62%) from the coupling of 5*R*-vinyl proline methyl ester **13** with D-*N*-Boc-allylglycine (**41**) using EDCI and HOBt as coupling reagents. The procedure followed was the same as that used for the synthesis of **28b** above except for the substitution of EDCI as the coupling reagent in place of DCC. Due to the number of rotomers produced, compound **42** was converted into the cyclic derivative before full characterization. LRMS (FAB) *m/e* (rel. int.) 359 (M+Li, 100), 303 (20), 259 (54), 156 (18); HRMS (FAB) *m/e* calcd for $C_{18}H_{28}N_2O_5Li$ (M+Li) 359.2158, found 359.2165.

**(3*R*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-10-carbomethoxybicyclo[5.3.0]dec-5-ene.** The olefin metathesis originating from **42** was accomplished using the same procedure used for the cyclization of **28b** (82%). $^1$H NMR (300 MHz/$CDCl_3$) 5.73–5.68 (m, 2H), 5.28 (br s, 1H), 4.60–4.50 (m, 2H), 4.27 (m, 1H), 3.68 (s, 3H), 2.79–2.74 (m, 1H), 2.43–2.37 (m, 1H), 2.29–2.23 (m, 1H), 1.99–1.90 (m, 3H), 1.42 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) 172.2, 170.2, 155.0, 129.8, 124.4, 79.9, 60.7, 60.2, 55.3, 52.0, 32.9, 28.6, 28.1, 26.6; IR (neat/NaCl) 3293, 2976, 1741, 1704, 1643, 1505, 1435, 1167 cm$^{-1}$; LRMS (FAB) *m/e* (rel. int.) 331 (M+Li, 100), 275 (40), 231 (80); HRMS (FAB) *m/e* calcd for $C_{16}H_{25}N_2O_5$ (M+H) 325.1764, found 325.1752.

**(3*R*,7*R*,10*S*)-1-Aza-3-*t*-butoxycarbonylamino-10-carbomethoxybicyclo[5.3.0]decane (43).** The hydrogenation reaction was done in a fashion identical to that described above for the synthesis of **29b** to afford a 95% yield of **43**. $^1$H NMR 5.32 (br s, 1H), 4.50 (d, *J*=7.8 Hz, 1H), 4.24 (q, *J*=4.8 Hz, 1H), 3.76 (m, 1H), 3.69 (s, 3H), 2.08–1.65 (m, 10H), 1.40 (s, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) 172.6, 170.6, 155.2, 79.5, 61.0, 58.3, 54.7, 51.9, 32.8, 32.1, 28.1, 27.4, 27.1, 22.3; IR (neat/NaCl) 3302, 2967, 1708, 1741, 1636, 1514, 1436, 1169 cm$^{-1}$; LRMS (FAB) *m/e* (rel. int.) 333 (M+Li, 100), 277 (26), 233 (62); HRMS (FAB) *m/e* calcd for $C_{16}H_{27}N_2O_5$ (M+H) 327.1921, found 327.1929.

**(3*R*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamine-10-carbomethoxybicyclo[5.3.0]decane.** The synthesis was done in a fashion identical to the preparation of **38** in order to obtain a 71% yield of the desired pyroglutamte coupled product. $^1$H NMR 7.37 (d, *J*=5.1 Hz, 1H), 7.10 (s, 1H), 4.47–4.44 (m, 1H), 4.37–4.32 (m, 1H), 4.15 (dd, *J*=8.1, 5.1 Hz, 1H), 3.81–3.69 (m, 1H), 3.68 (s, 3H), 2.45–2.24 (m, 3H), 2.18–1.70 (m, 11H); $^{13}$C NMR (75 MHz/$CDCl_3$) 179.0, 172.4, 171.7, 170.1, 61.4, 58.9, 57.0, 53.6, 52.3, 32.9, 31.2, 29.6, 27.4, 27.2, 25.7, 22.6; IR (neat/NaCl) 3279, 2944, 1744, 1689, 1626, 1441, 1207, 1178 cm$^{-1}$; LRMS (FAB) *m/e* (rel. int.) 344 (M+Li, 18), 313 (34); HRMS (FAB) *m/e* calcd for $C_{16}H_{23}N_3O_5Li$ (M+Li) 344.1798, found 344.1794.

**(3*R*,7*R*,10*S*)-1-Aza-3-pyroglutamoylamine-10-carboxyamidebicyclo[5.3.0]decane (31c).** Primary amide **31c** was made using the same procedure used to construct **31a** (40%). $^1$H NMR (300 MHz/$CDCl_3$) 8.56 (d, *J*=6.9 Hz, 1H), 7.52 (br s, 1H), 7.08 (br s, 1H), 6.17 (br s, 1H), 4.53 (t, *J*=8.1 Hz, 1H), 4.40 (d, *J*=6.3 Hz, 1H), 4.19–4.18 (m, 1H), 3.80–3.78 (m, 1H), 2.39–2.27 (m, 3H), 2.15–2.02 (m, 2H), 1.96–1.74 (m, 9H); $^{13}$C NMR (75 MHz/$CDCl_3$) 179.4, 175.5,172.9, 170.5, 62.6, 59.0, 56.9, 53.0, 33.1, 31.3, 30.0, 27.9, 27.7, 25.0, 22.6; IR (neat/NaCl) 3293(br), 2927, 1678, 1622, 1540, 1439, 1260 cm$^{-1}$; HRMS (FAB) *m/e* calcd for $C_{15}H_{27}N_4O_4Li$ (M+Li) 329.1801, found 329.1809.

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