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Solid Phase Synthesis of Fused Bicyclic Amino Acid Derivatives via Intramolecular Pauson-Khand Cyclization: Versatile Scaffolds for Combinatorial Chemistry.

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Abstract: Solution and solid phase synthetic methods leading to the rapid, stereocontrolled construction of highly functionalized fused bicyclic amino acid derivatives have been developed. The key step involves a unique application of the intramolecular Pauson-Khand cyclization for the construction of hexahydro-1H-[2]pyrindinone ring systems. Further modifications which demonstrate the potential for combinatorial library generation are also disclosed. © 1997 Published by Elsevier Science Ltd.

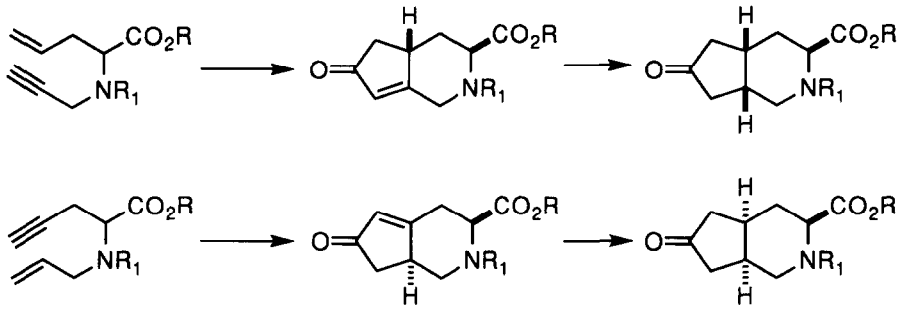
Introduction

The combinatorial generation and screening of libraries of small organic molecules has recently gained increased recognition as a promising approach for the discovery of new compounds with biological activity. Solid phase synthesis techniques have been the primary method for the rapid and efficient preparation of a majority of these large numbers of compounds, and has been the subject of a number of recent reviews.[1] The rapid development of solid phase organic synthesis (SPOS) is currently being driven by numerous recent reports involving the adaptation of various well-established solution phase synthetic transformations to a solid-supported format.

The design of rigid scaffolds which allow the incorporation of a variety of substituents is an attractive approach for the preparation of combinatorial libraries.[2] Indeed, this strategy has been successfully utilized in the solid phase syntheses of a number of diversely functionalized heterocycles.[1] Other analogs with biological activity have been designed from glucose[3a] or steroid scaffolds[3b] in a non-combinatorial fashion. Many of these compounds contain a well recognized pharmacophore as their core structure such as benzodiazepines[4a,b] and hydantoins.[4b,c] We were interested in avoiding such known pharmacophores and have focused instead on the development of libraries of more novel, yet still drug-like compounds. In particular, we directed our efforts toward synthetic routes which allow variation of both the shape of the scaffold and its appended functionalities in order to maximize the molecular diversity within the library while maintaining a common synthetic theme. As such, highly saturated fused bicyclic ring systems are appealing core structures, provided one has stereochemical control of the ring junction during the synthesis and the ability to introduce subsequent functionality with a high level of regio- and stereoselectivity. A final objective, inherent in this approach, was to develop new synthetic methodology for SPOS, with particular emphasis on the formation of carbon-carbon bonds.

With these goals in mind, a route was devised to the 1H-[2]pyrindinone ring system via Pauson-Khand cyclization of an appropriately substituted amino acid derivative as shown in Scheme 1.[5] This strategy offers a uniquely flexible diversity element, in that two topographically distinct scaffolds can be obtained in a straightforward manner, depending on the allyl or propargyl glycine derivative chosen as starting material. The potential for regio- and stereoselective functionalization at multiple positions about the bicyclic system, through the use of substituted alkene and alkyne components or 1,2- and 1,4-addition to the enone system, further extends the family of scaffolds while permitting the introduction of a variety of functional groups. In addition,

Scheme 1



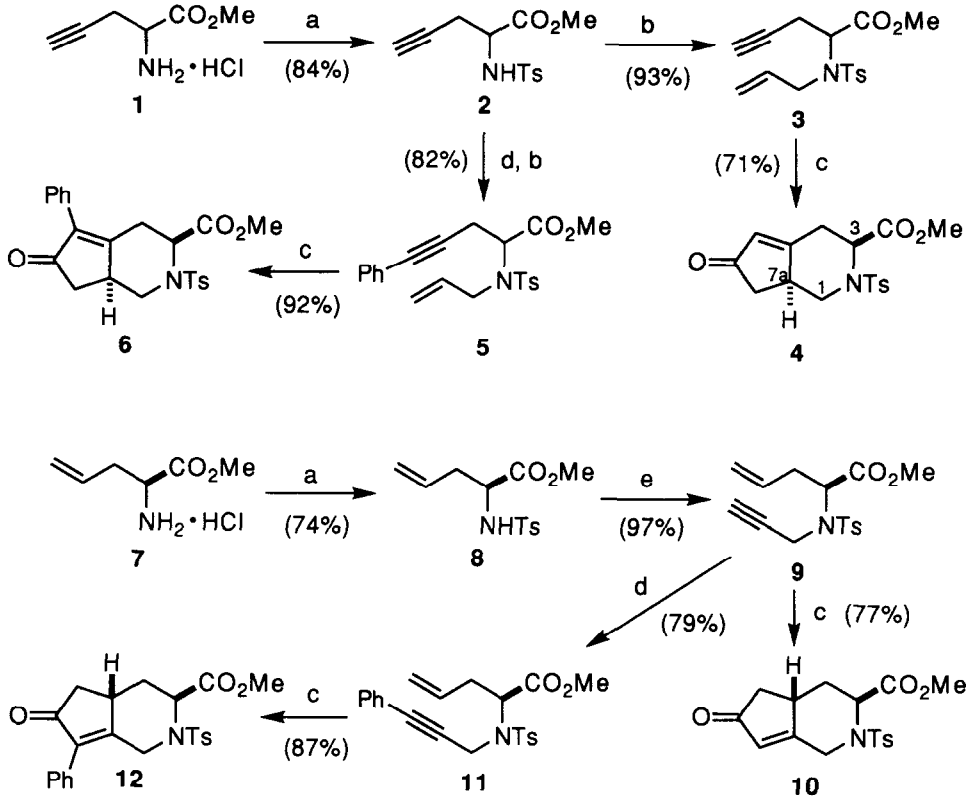
adaptation of this process to the solid phase and subsequent modifications of the resin-bound template allowed a range of previously unexamined synthetic transformations to be investigated during the course of this work.

The cyclization of acetylenes with olefins and carbon monoxide mediated by dicobalt octacarbonyl (Pauson-Khand reaction) is a highly efficient method for the construction of cyclopentenone derivatives.[6] Both the inter- and intramolecular version of the reaction have been used in the synthesis of a number of natural products.[7] A number of recent improvements, including amine oxide promotion, have increased the synthetic utility of the process.[8] Although most success has been realized with stoichiometric quantities of the cobalt reagent, recent reports have demonstrated the feasibility of a catalytic procedure.[9] The use of this methodology in the preparation of 1H-[2]pyrindinones has seen minimal investigation,[8a,10a-d] although the formation of other heterocyclic ring systems by incorporation of a heteroatom within the alkyne-olefin tether has been more extensively examined.[10e-g] The likelihood of adapting the intramolecular process shown in Scheme 1 to the solid phase seemed promising. Organometallic reactions which employ soluble catalysts or reagents would seem to be particularly well suited for combinatorial library generation via solid phase synthesis. A number of palladium catalyzed solid phase coupling reactions have been recently disclosed.[1] Most notably, a dry-state silica gel supported variant of the Pauson-Khand reaction has been shown to proceed efficiently,[11a,10e] and the advantages of a solid-supported alkyne component in the intermolecular Pauson-Khand reaction have been previously reported.[11b] Described herein are details concerning the solution and solid phase reactions which demonstrate the chemical versatility of the 1H-[2]pyrindinone ring system, and its potential for the combinatorial generation of libraries of functionally and topologically diverse compounds.[12]

Results and Discussion

Solution Studies. The commercial availability of allyl or propargylglycine permitted the viability of the proposed ring system to be quickly examined. The acid offered a convenient attachment point to a number of available resins, obviating the need to develop a specialized linker strategy or modified resin. The key cyclization precursors **3** and **9** were prepared in straightforward fashion as shown in Scheme 2. Tosylation of the respective amino acid methyl ester hydrochloride salts proceeded efficiently to provide sulfonamides **2** and **8**. The sulfonamide was initially chosen to facilitate subsequent N-alkylation, and this was found to be the case. Rapid and efficient alkylation with allyl bromide or propargyl bromide in the presence of cesium carbonate afforded esters **3** and **9**, respectively. Treatment of these intermediates with $Co_2(CO)_8$ in CH_2Cl_2 for two to three hours led to clean formation of the intermediate cobalt complexes. Subsequent addition of excess N-methylmorpholine-N-oxide (NMO) at 0°C resulted in vigorous gas evolution and rapid formation of a new product as observed by thin-layer chromatography. Addition of a second portion of NMO was found to be

Scheme 2



a) TsCl, Et_3N, CH_2Cl_2 ; b) allyl bromide, Cs_2CO_3, DMF ; c) $Co_2(CO)_8$, NMO, CH_2Cl_2 ;
d) $(PPh_3)_2PdCl_2$, CuI, iodobenzene, Et_3N, CH_2Cl_2 ; e) propargyl bromide, Cs_2CO_3, DMF

necessary to drive the reaction to completion. Filtration and flash chromatography provided the bicyclic products **4** and **10** in good yields. Enone **4** was obtained as a single diastereomer whose relative stereochemical assignment was supported by ^1H NMR analysis.[13] Enone **10** was obtained as a single enantiomer starting from chiral **7**, and the absolute configuration was established by an X-ray crystal structure determination (Figure 1).[14] The piperidine ring assumes a chair conformation, with the carbomethoxy substituent in an axial position, presumably due to $A_{1,3}$ strain with the sulfonamide moiety. The ring junction stereochemistry in both **4** and **10** could result from a chairlike transition state, although the exact nature is unknown.

Further diversification can easily be incorporated into the sequence (Scheme 2). Palladium catalyzed coupling of iodobenzene with either terminal alkyne **2** or **9** proceeded smoothly at room temperature in the presence of triethylamine and catalytic copper iodide to afford **5** (after alkylation with allyl bromide) and **11**, respectively.[15] In the case of **11**, the mildness of the coupling procedure eliminates any interference arising from a potential competing palladium catalyzed cyclization process.[16] Pauson-Khand cyclization of these

intermediates proceeded in excellent yields to provide enones **6** and **12**, as approximately 5:1 mixtures of diastereomers. The major isomers could be obtained by chromatography, and the relative stereochemical assignment of **6**, expected to be analogous with **4**, was confirmed by an X-ray crystal structure determination (Figure 1). The absolute stereochemistry of **12** was assigned by analogy with **10**.

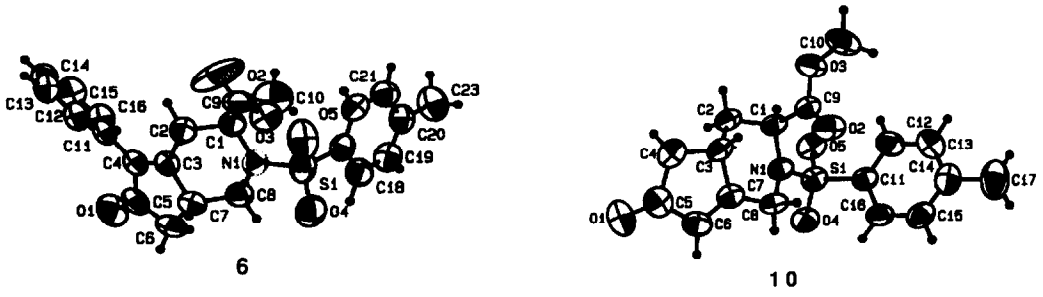
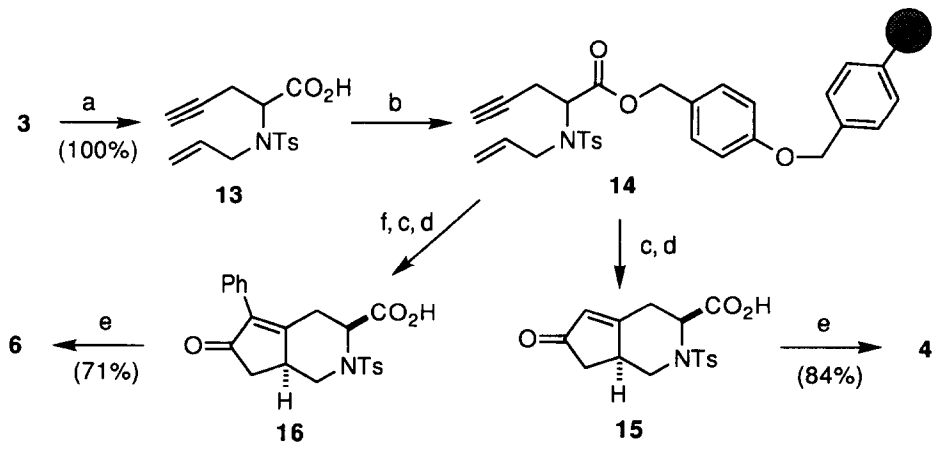


Figure 1. ORTEP Plots of Compounds 6 and 10.

Solid Phase Studies. As shown in Scheme 3, initial solid phase studies began with hydrolysis of **3** to acid **13**, which was loaded onto commercial Wang resin[17] via the mixed anhydride.[18] The loading of resin **14** was found to be 0.6 mmol/g based on cleavage of a sample with 50% TFA/CH_2Cl_2. Subjection of **14** to cyclization conditions similar to the above solution conditions gave nearly a quantitative yield of acid **15** after cleavage and aqueous workup. Esterification and flash chromatography provided **4** in high yield. Inclusion of the palladium coupling step in the sequence prior to cyclization also provided the desired enone **16** in high yield.

Scheme 3



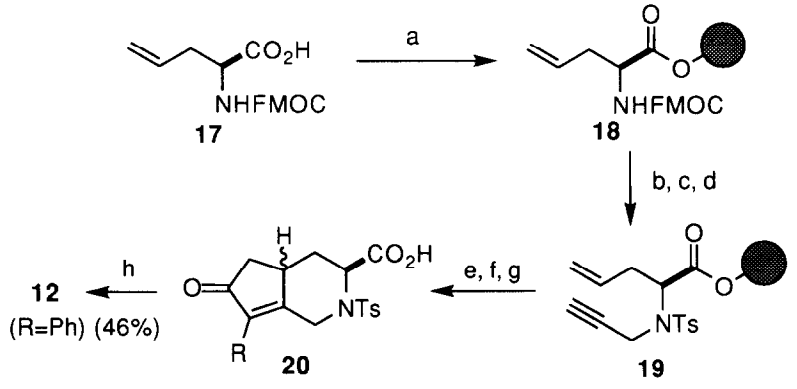
a) LiOH, THF, H_2O ; b) 2,6-dichlorobenzoyl chloride, pyridine, Wang resin, DMF ; c) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; d) TFA/CH_2Cl_2 (1:1) ; e) CH_2N_2 ; f) $(PPh_3)_2PdCl_2$, CuI, iodobenzene, Et_3N, CH_2Cl_2

Subsequent esterification afforded **6** in 74% yield after chromatography. Thus, this tandem organometallic reaction sequence also proceeds cleanly and efficiently on solid phase. Although several examples of palladium catalyzed coupling of solid supported aryl halides with alkynes have been reported, the reverse process involving a solid supported alkyne component has rarely been used.[1] The wider selection of commercially available aryl halides makes this a more desirable strategy for combinatorial library generation.

Some general comments regarding the isolation of the products from solid phase are in order. The use of freshly opened bottles of $Co_2(CO)_8$ generally gave the best results. The solid phase process allows clean isolation of the resin-bound intermediate cobalt complex by simple filtration. Use of aged $Co_2(CO)_8$ leaves some insoluble cobalt species behind at this point which can contaminate the final product upon cleavage from the resin. Some additional insoluble material is produced following treatment with NMO. This material can easily be removed after cleavage from the resin by washing the crude acid product with dilute aqueous HCl, or by esterification of the crude residue and filtration through a small pad of silica gel. We have also found that washing the resin with acetic acid prior to cleavage will remove nearly all of the inorganic material. Nevertheless, this solid phase procedure offers advantages over the solution phase by simplifying product isolation and purification.

With confidence that the two key reactions in the sequence proceeded smoothly on solid phase, it was attempted to carry out the entire sequence on solid phase starting from **17** as shown in Scheme 4. The protected amino acid **17** was loaded onto Wang resin as before, and carried through the sequence of deprotection, tosylation, and alkylation to provide resin **19**. However, treatment of this resin in the same fashion as **14** resulted in a different outcome. Following cleavage and esterification, two other products in addition to the desired **12** were obtained. These products, identified as **8** and **10**, are the result of both incomplete N-alkylation and coupling of iodobenzene. These steps proceed to completion within two hours in solution, but require both longer reaction times and larger excesses of reagents to achieve complete reaction on solid phase.

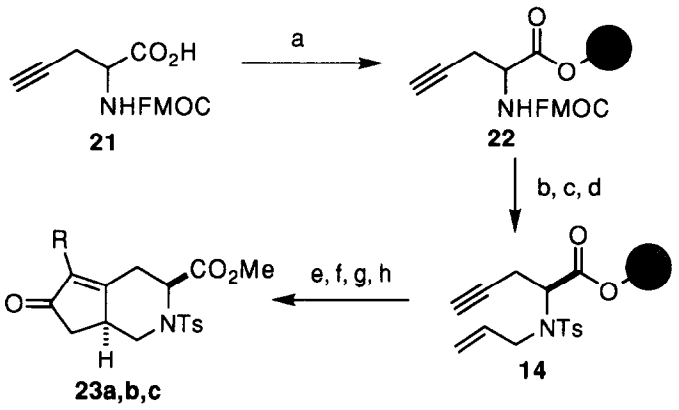
Scheme 4



a) 2, 6-dichlorobenzoyl chloride, pyridine, Wang resin, DMF ; b) 20% piperidine, CH_2Cl_2, DMF ; c) TsCl, Et_3N, CH_2Cl_2 ; d) propargyl bromide, Cs_2CO_3, DMF ; e) $(PPh_3)_2PdCl_2$, CuI, aryl iodide, Et_3N, CH_2Cl_2; f) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; g) TFA/CH_2Cl_2 (1:1) ; h) CH_2N_2

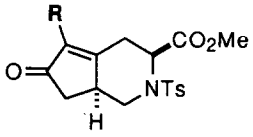
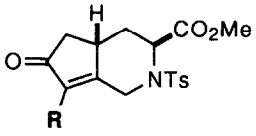
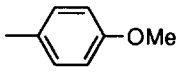
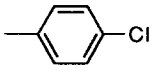
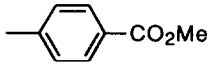
When both of these reactions were allowed to proceed overnight, **12** was isolated in 46% yield for this eight-step sequence which required only a single chromatography after cleavage to provide material of analytical purity. Assuming quantitative yields for loading and final esterification, the average yield for the remaining six

Scheme 5



a) 2, 6-dichlorobenzoyl chloride, pyridine, Wang resin, DMF ; b) 20% piperidine, CH_2Cl_2, DMF ; c) TsCl, Et_3N, CH_2Cl_2 ; d) allyl bromide, Cs_2CO_3, DMF ; e) $(PPh_3)_2PdCl_2$, CuI, aryl iodide, Et_3N, CH_2Cl_2; f) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; g) TFA/CH_2Cl_2 (1:1) ; h) CH_2N_2

Table 1

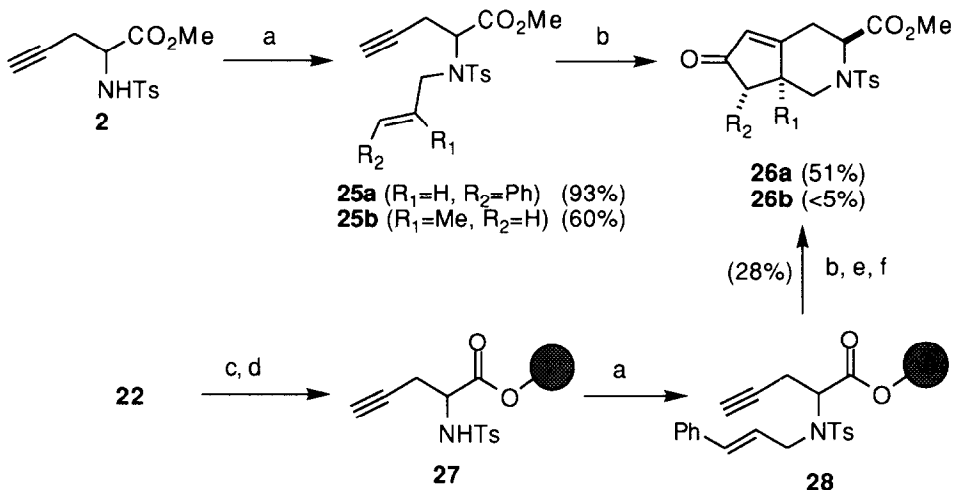
R		
H	**4** (84%)[a]	**10** (74%)[c]
Ph	**6** (71%)[a]	**12** (46%)[d]
	**23a** (38%)[b]	**24a** (50%)[d]
	**23b** (86%)[a]	**24b** (54%)[d]
	**23c** (53%)[b]	**24c** (88%)[c]

Yield determined from: [a] resin **14**; [b] resin **22**; [c] resin **19**; [d] resin **18**

steps is nearly 90%. As shown in Scheme 5, the entire sequence could also be carried out starting with protected amino acid **21**, leading to good yields of esters **23**. A series of substituted aryl iodides were employed in both sequences, leading to good yields of the products shown in Table 1. As indicated, the best yields correspond to the shortest solid phase sequences. The electronic nature of the aromatic substituent has little effect on the efficiency of the process. A single attempt to effect coupling of 3-iodothiophene failed under these conditions. Nonetheless, the large number of commercially available aromatic halides offers the potential for the preparation of a range of substituted analogs in both sequences. Modifications of the coupling step to allow the inclusion of heteroaromatic halides are in progress.

Alkene substitution was briefly examined in solution and solid phase as shown in Scheme 6. Alkylation of **2** with cinnamyl bromide gave **25a** and subsequent Pauson-Khand cyclization afforded **26a** in a more modest yield. The lower efficiency of the cyclization was also reflected upon extension to solid phase, providing **26a** in only 28% yield. Interestingly, when monitoring this process by cleavage of a resin sample after each step, it was discovered that the cinnamyl sidechain in **28** (or **25a**) was cleanly removed upon treatment with TFA/CH_2Cl_2 (1:1) to provide **2**. Only a trace amount of **26b** was obtained upon attempted cyclization of the methallyl derivative **25b**. Thus, alkene substitution will not be a significant source of diversification of this template.

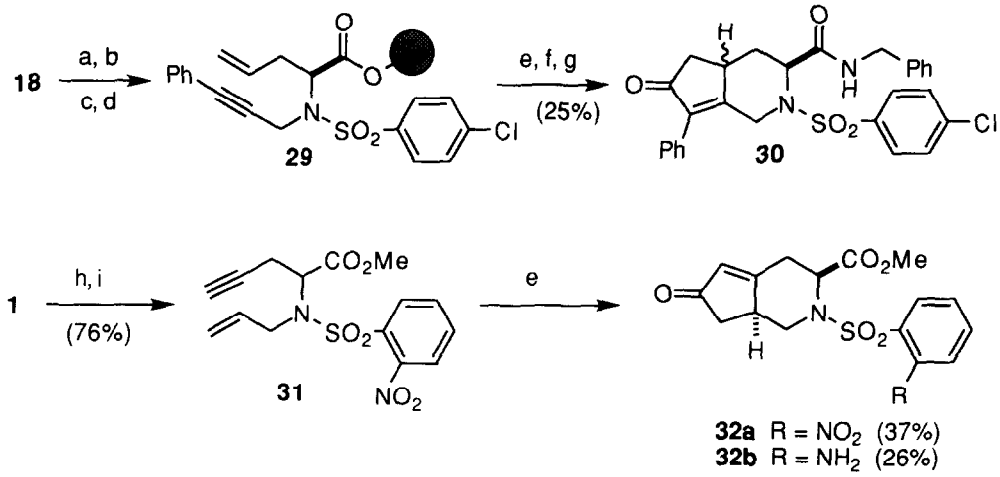
Scheme 6



a) methallyl chloride or cinnamyl bromide, Cs_2CO_3, DMF; b) $Co_2(CO)_8$, NMO, CH_2Cl_2 ;
c) 20% piperidine, CH_2Cl_2, DMF ; d) TsCl, Et_3N, CH_2Cl_2 ; e) TFA/CH_2Cl_2 (1:1) ; f) CH_2N_2

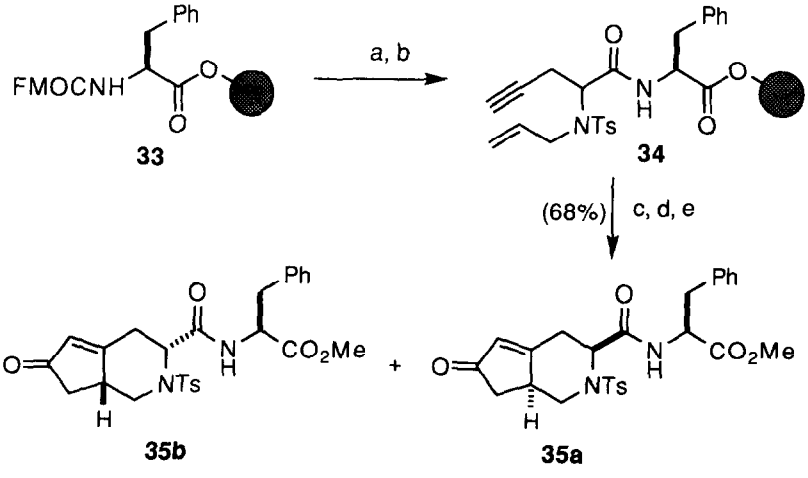
Other sulfonyl chlorides can be utilized to extend the range of N-substitution as shown in Scheme 7. 4-Chlorobenzenesulfonyl chloride was inserted in the sequence to provide resin bound **29** after alkylation and coupling. Pauson-Khand reaction followed by cleavage gave a crude acid which was converted to amide **30** in solution to illustrate that other functionalization of the liberated acid can be readily accomplished. A more efficient solution to N-functionalization would be to employ a group which would facilitate N-alkylation yet be readily removed after cyclization and replaced with a variety of other substituents. A recent report suggested that the 2-nitrobenzenesulfonyl moiety, which can be removed under mild conditions, would be useful in this regard.[19] Sulfonamide **31** was readily prepared in solution, however, Pauson-Khand cyclization of this

Scheme 7



a) 20% piperidine, CH_2Cl_2, DMF ; b) 4-chlorobenzenesulfonyl chloride, Et_3N, CH_2Cl_2 ;
c) propargyl bromide, Cs_2CO_3, DMF ; d) $(PPh_3)_2PdCl_2$, CuI, iodobenzene, Et_3N, CH_2Cl_2;
e) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; f) TFA/CH_2Cl_2 (1:1) ; g) DCC, HOBT, $BnNH_2$, DMF ;
h) 2-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2 : i) Cs_2CO_3, allyl bromide, DMF

Scheme 8



a) 20% piperidine, DMF ; b) EDAC, HOBT, **13**, DMF; c) $Co_2(CO)_8$, NMO, CH_2Cl_2 ;
d) TFA/CH_2Cl_2 (1:1) ; e) CH_2N_2

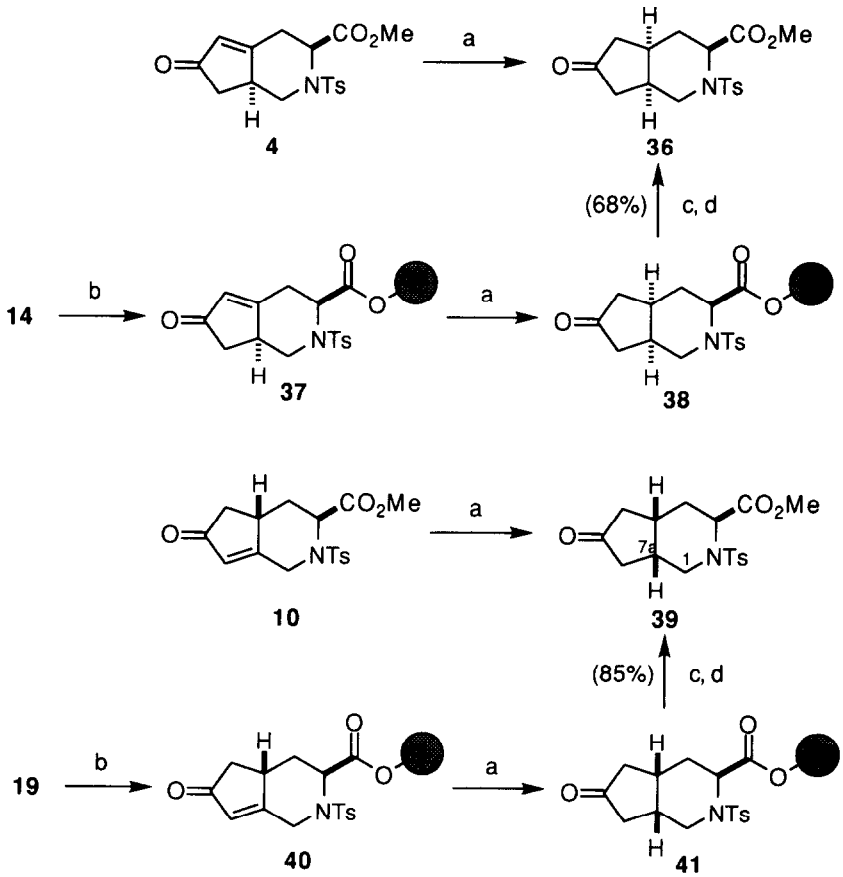
substrate gave a mixture of the desired product **32a** and a significant amount of aniline **32b**. Similar results were obtained on solid phase. Although it is known that under certain conditions, cyclopentenone reduction can occur during the Pauson-Khand reaction,[10a,b] this appears to be the first example of in situ reduction of an aromatic nitro group to an aniline during this process. Since the nitro group is critical for removal of this sulfonyl moiety under mild conditions, these results are disappointing. Presumably, the nitrosulfonyl group could be removed and replaced prior to cyclization, but this option has yet to be explored.

Insertion of an amino acid linker prior to attachment of the Pauson-Khand substrate can be utilized to create dipeptide derivatives as shown in Scheme 8. Deprotection of phenylalanine Wang resin followed by acylation with racemic **13** gave resin **34**. Cyclization of this substrate followed by cleavage and esterification afforded dipeptides **35a,b** as a 2:1 mixture of diastereomers. Incorporation of the the palladium coupling step and the commercial availability of many resin bound amino acids offers potential access to a variety of unusual dipeptide derivatives.

Further functionalization of the ketone can also be accomplished as shown in Scheme 9. Various attempts at 1,2-functionalization of the enone in solution led to sluggish reactivity and/or mixtures of products. Thus, to simplify this process, various approaches for selective 1,4-reduction were investigated. Although a number of methods exist for this type of transformation, a high yielding, selective, and experimentally compatible procedure was desired for extension to solid phase. Catalytic asymmetric hydrogenation of dehydropeptides has been carried out on solid phase, but we were interested in a more convenient procedure.[20] A survey of the literature revealed two promising methods. The first, a palladium catalyzed silane reduction,[21] appeared to be well suited for solid phase. However, no reduction of either enone template was observed under these conditions in solution. We then turned to a procedure employing a soluble copper hydride reagent which is commercially available.[22] Very promising results were observed in solution for both enones **4** and **10** as shown in Scheme 9. Excellent results were also obtained upon adaptation of this method to solid phase. Thus, cobalt-mediated cyclization of resin **14** gave enone **37**, which was treated with 50 mol % of $[(PPh_3)CuH]_6$ (3 hydride equiv.) in toluene for 24 hours. After cleavage and esterification, an excellent yield of ketone **36** was obtained. The cis ring fusion is the expected consequence of hydride addition from the least hindered face of **37** (or **4**) and was unambiguously established by an X-ray crystal structure determination (Figure 2). Similar results were obtained with a racemic version of resin **19**, providing the other cis-fused ketone **39** after cyclization, reduction, cleavage, and esterification. The cis ring fusion was assigned by analogy with **36**, and the equatorial disposition of the newly installed bridgehead proton was clearly evident by ^1H NMR.[23] The copper reagent is extremely sensitive to air, and freshly opened bottles gave the most reproducible results. In cases where aged reagent was used, the reduction did not proceed to completion, but the material may be resubjected to the reaction conditions with no appreciable loss in yield or purity of products. It should be noted that treatment of **6** (containing a tetrasubstituted double bond) with this reagent in solution failed to provide any reduced product.

As shown in Figure 2, the conformation of **36** is indicative that selective additions to the ketone moiety from the convex face should be possible. We first examined a simple reductive amination-acylation protocol as shown in Scheme 10. Treatment of resin **38** with excess benzylamine and sodium triacetoxyborohydride[24] gave an intermediate secondary amine which was acylated with acetic anhydride. Following cleavage and esterification, acetamide **42** was obtained in 52% yield (overall from **14**) as primarily a single diastereomer. Analysis of the crude mixture by NMR was complicated by line broadening and doubling due to the presence of amide rotomers. High temperature NMR or HPLC analysis also did not allow an exact determination of stereochemical purity, although the it is estimated to be >90%. The relative configuration of the major diastereomer has not been determined, but is presumably that obtained by reduction of the intermediate imine from the least hindered face. Reductive amination with methylamine followed by acylation with an isocyanate also proceeded smoothly to provide urea **43** as a 7:1 mixture of diastereomers (estimated by high temperature

Scheme 9



a) $[(PPh_3)CuH]_6$, PhMe ; b) $Co_2(CO)_8$, NMO, CH_2Cl_2 ; c) TFA/CH_2Cl_2 (1:1) ; d) CH_2N_2

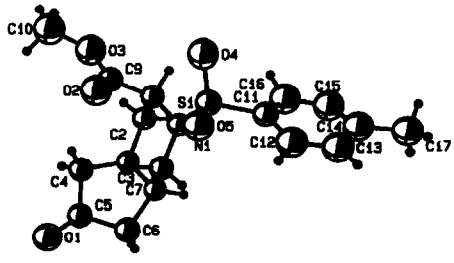
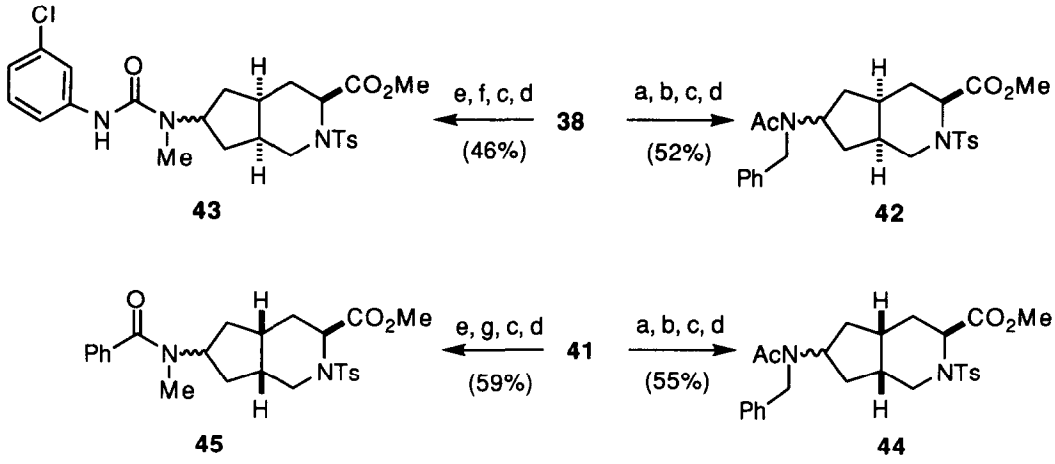


Figure 2. ORTEP Plot of Ketone 36.

Scheme 10



a) $BnNH_2$, $NaBH(OAc)_3$, HOAc, CH_2Cl_2 ; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2 ; c) TFA/CH_2Cl_2 (1:1) ; d) CH_2N_2 ; e) $MeNH_2$, $NaBH(OAc)_3$, HOAc, CH_2Cl_2 ; f) 3-chlorophenylisocyanate, Et_3N, DMAP, CH_2Cl_2 ; g) benzoyl chloride, Et_3N, DMAP, CH_2Cl_2

NMR). Application of this protocol to resin **41** provided acetamide **44** in good yield as a single diastereomer after chromatography. It is again presumed that hydride delivery from the less hindered face of the imine would be favored, resulting in predominant formation of the isomer with the opposite configuration at this center (vs. **42**) in this case. Benzamide **45** was also obtained as a single diastereomer in 59% overall yield from **19** following reductive amination of **41** with methylamine and acylation with benzoyl chloride. In this case, another component was also isolated in 5% yield, whose high temperature proton NMR spectrum was consistent with its assignment as the other possible diastereomer. Thus, highly diastereoselective functionalization of the ketone in this fashion has the potential to provide a wide range of novel bicyclic compounds. Examination of the products derived from this process reveals that, in effect, reductive amination of these ketone diastereomers produces two unique conformationally constrained bicyclic lysine analogs, which may find utility as components in various peptides.[25]

In conclusion, we have demonstrated the preparation of novel, bicyclic amino acids that can be readily extended to a solid supported format. Adaptation of a number of reactions employing soluble organometallic reagents to the solid phase were investigated during the course of this work. The key step involved a solid phase application of a novel variant of the Pauson-Khand reaction. Palladium catalyzed coupling of aryl iodides with a solid supported alkyne intermediate provided a further site of diversity. Insertion of an amino acid resin linker led to unusual dipeptide analogs. Chemoselective 1,4-reduction of the cyclopentenone ring system with a soluble copper hydride reagent has been achieved on solid phase. Subsequent reductive amination and acylation resulted in the formation of novel bicyclic conformationally constrained lysine analogs. The methods described allow for the efficient synthesis of a library of compounds wherein both the scaffold shape and functional groups are sources of molecular diversity. Investigation of additional modifications of these highly functionalized bicyclic systems that would further extend the range of drug-like molecules available to the library are in progress.

Experimental Section

General.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Wang resin was obtained from Novabiochem. Dicobalt octacarbonyl was obtained from Strem Chemical Co. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bio-Rad FTS-45 TGA/FTIR spectrophotometer. Proton NMR spectra were recorded on either a Varian Gemini 2000 (300 MHz) or Varian Unity (400 MHz) spectrometer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on a VG Trio-2 mass spectrometer. Elemental analyses were determined on a Lehman Laboratories 440 elemental analyzer or by Robertson Laboratories. Optical rotations were determined at 23°C using a Perkin-Elmer 241 polarimeter.

2-(Toluene-4-sulfonylamino)-pent-4-ynoic acid methyl ester (2).

To a suspension of 2-amino-pent-4-ynoic acid methyl ester hydrochloride salt (**1**) (2.12 g, 12.96 mmol) in CH_2Cl_2 (100 mL) at 0°C was added Et_3N (5.4 mL, 38.9 mmol) followed by tosyl chloride (2.96 g, 15.55 mmol). The mixture was stirred at 0°C for 3 h, then allowed to warm to room temperature and stirred an additional 2 h. Most of the solvent was removed by rotary evaporation, and the residue was partitioned between EtOAc and water. The aqueous layer was extracted three times with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (35% EtOAc/hexanes) gave 3.07 g (84%) of **2** as a white solid, mp 83-85°C; IR(KBr) 3280, 1734, 1347, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J=8Hz, 2H), 7.30 (d, J=8Hz, 2H), 5.41 (d, J=9Hz, 1H), 4.12 (ddd, J=9, 5, and 4Hz, 1H), 3.62 (s, 3H), 2.69 (m, 2H), 2.43 (s, 3H), 2.03 (t, J=3Hz, 1H); MS(CI) 282 (M+1); Anal. calcd. for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98; Found: C, 55.27; H, 5.33; N, 4.90.

2-[N-(Toluene-4-sulfonyl)-N-(prop-2-enyl)amino]-pent-4-ynoic acid methyl ester (3)

To a solution of ester **2** (1.90 g, 6.75 mmol) in DMF (20 mL) was added cesium carbonate (2.86 g, 8.78 mmol). The suspension was cooled to 0°C and allyl bromide (1.16 mL, 13.51 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2 h. Most of the DMF was removed by concentration and the residue was partitioned between EtOAc and aqueous NH_4Cl. The aqueous layer was extracted three times with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (30% EtOAc/hexanes) gave 2.01 g (93%) of **3** as a light yellow oil. IR(KBr) 1743, 1344, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J=8Hz, 2H), 7.29 (d, J=8Hz, 2H), 5.80 (m, 1H), 5.18 (dt, J=17 and 1Hz, 1H), 5.12 (dt, J=10 and 1Hz, 1H), 4.73 (dd, J=9 and 6Hz, 1H), 3.93 (dd, J=16 and 6Hz, 1H), 3.87 (dd, J=16 and 6Hz, 1H), 3.63 (s, 3H), 2.88 (ddd, J=17, 6, and 3Hz, 1H), 2.20 (ddd, J=17, 9, and 3Hz, 1H), 2.43 (s, 3H), 1.97 (t, J=3Hz, 1H); MS(CI) 322 (M+1); Anal. calcd. for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.35; Found: C, 59.78; H, 5.90; N, 4.24.

General Procedure for Solution Pauson-Khand Reactions. The procedure for **4** is typical.

trans-6-Oxo-2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (4).

To a solution of the ester **3** (0.61 g, 1.90 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (0.71 g, 2.09 mmol)

and the solution was stirred until complete disappearance of the starting material was indicated by thin-layer chromatography (2 h). The solution was cooled to 0°C, and NMO (0.67 g, 5.69 mmol) was added in one portion. The mixture was allowed to warm to room temperature and stirred for 1 h. After recooling to 0°C, another portion of NMO (0.67 g, 5.69 mmol) was added, and the mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was filtered through a pad of silica gel, washing with EtOAc, and the filtrate was concentrated. Flash chromatography of the residue (50-60% EtOAc/hexanes) afforded 0.47 g (71%) of **4** as a sticky oil. IR(film) 1743, 1710, 1630, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8Hz, 2H), 7.31 (d, J=8Hz, 2H), 5.97 (s, 1H), 5.11 (d, J=7Hz, 1H), 4.18 (dd, J=11 and 5Hz, 1H)3.54 (s, 3H), 3.26 (d, J=14Hz, 1H), 2.91 (m, 2H), 2.89 (dd, J=14 and 7Hz, 1H), 2.51 (dd, J=19 and 6Hz, 1H), 2.43 (s, 3H), 1.92 (dd, J=19 and 2Hz, 1H); MS(CI) 350 (M+1); Anal. calcd. for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01; Found: C, 58.18; H, 5.16; N, 3.98.

2-[N-(Toluene-4-sulfonyl)-N-(prop-2-enyl)amino]-5-phenylpent-4-ynoic acid methyl ester (5).

To a solution of ester **2** (0.51 g, 1.81 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (1 mL) followed by CuI (9 mg, 0.045 mmol) and iodobenzene (0.20 mL, 1.81 mmol). $(PPh_3)_2PdCl_2$ (32 mg, 0.045 mmol) was added and the mixture was stirred for 2 h. The mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (35% EtOAc/hexanes) gave 0.57 g (88%) of 2-amino-5-phenylpent-4-ynoic acid methyl ester as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J=8Hz, 2H), 7.29 (m, 7H), 5.44 (d, J=9Hz, 1H), 4.18 (m, 1H), 3.63 (s, 3H), 2.93 (dd, J=17 and 5Hz, 1H), 2.85 (dd, J=17 and 5Hz, 1H), 2.40 (s, 3H). Alkylation of this material according to the procedure for **3** gave **5** as a light yellow oil (93%). IR(film) 1744, 1345, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J=8Hz, 2H), 7.29 (m, 5H), 7.17 (d, J=8Hz, 2H), 5.85 (m, 1H), 5.24 (dd, J=17 and 1Hz, 1H), 5.13 (dd, J=9 and 1 Hz, 1H), 4.80 (dd, J=9 and 6Hz, 1H), 4.00 (dd, J=16 and 7Hz, 1H), 3.91 (dd, J=16 and 6Hz, 1H), 3.67 (s, 3H), 3.09 (dd, J=17 and 6Hz, 1H), 2.97 (dd, J=17 and 9Hz, 1H), 2.34 (s, 3H); MS(CI) 398 (M+1); Anal. calcd. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52; Found: C, 66.08; H, 5.90; N, 3.30.

trans-6-Oxo-5-phenyl-2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (6).

Cyclization of **5** according to the general procedure above, afforded **6** (92%) as a 5:1 mixture of diastereomers. Flash chromatography (40% EtOAc/hexanes) afforded a partial separation. Major diastereomer: mp 149-150°C; IR(KBr) 1741, 1700, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8Hz, 2H), 7.35 (m, 5H), 7.19 (d, J=8Hz, 2H), 5.05 (d, J=7Hz, 1H), 4.24 (dd, J=18 and 12Hz, 1H), 3.41 (dd, J=14 and 1Hz, 1H), 3.37 (s, 3H), 3.05 (d, J=18Hz, 1H), 3.00 (d, J=18Hz, 1H), 2.79 (dd, J=14 and 7Hz, 1H), 2.67 (dd, J=19 and 6Hz, 1H), 2.43 (s, 3H), 2.07 (d, J=19 Hz, 1H); MS(CI) 426 (M+1); Anal. calcd. for $C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29; Found: C, 64.78; H, 5.51; N, 3.27. Minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J=8Hz, 2H), 7.35 (m, 5H), 7.24 (d, J=8Hz, 2H), 4.08 (m, 2H), 3.79 (s, 3H), 3.23 (m, 3H), 2.72 (dd, J=19 and 7Hz, 1H), 2.62 (t, J=11Hz, 1H), 2.43 (s, 3H), 2.10 (dd, J=19 and 3Hz, 1H).

S-2-(Toluene-4-sulfonylamino)-pent-4-enoic acid methyl ester (8).

According to the procedure for **2** above, starting with (S)-2-aminopent-4-enoic acid methyl ester hydrochloride (**7**), **8** was obtained (74%) as a white solid, mp 65-67°C; $[\alpha]_D$=+13 (c=1.000, $CHCl_3$); IR(KBr) 3289, 1746,

1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J=8Hz, 2H), 7.29 (d, J=8Hz, 2H), 5.62 (m, 1H), 5.11 (m, 3H), 4.03 (dt, J=9 and 6Hz, 1H), 3.52 (s, 3H), 2.47 (t, J=6Hz, 2H), 2.42 (s, 3H); MS(CI) 284 (M+1); Anal. calcd. for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; Found: C, 55.07; H, 6.02; N, 4.92.

S-2-[N-(Toluene-4-sulfonyl)-N-(prop-2-ynyl)amino]-pent-4-enoic acid methyl ester (9).
To a solution of **8** (5.0 g, 17.6 mmol) in DMF (40 mL) was added cesium carbonate (6.9 g, 21.2 mmol). The suspension was stirred for 20 min., then cooled to 0°C, and propargyl bromide (3.9 mL, 80% in toluene, 35.3 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. Most of the DMF was removed by concentration, and the residue was partitioned between EtOAc and aqueous NH_4Cl. The aqueous layer was extracted three times with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (30% EtOAc/hexanes) gave 5.5 g (97%) of **9** as a light yellow liquid. IR(KBr) 1742, 1344, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J=8Hz, 2H); 7.28 (d, J=8Hz, 2H), 5.73 (m, 1H), 5.13 (dd, J=17 and 1Hz, 1H), 5.06 (dd, J=10 and 1Hz, 1H), 4.58 (dd, J=9 and 7Hz, 1H), 4.20 (t, J=3Hz, 2H), 3.56 (s, 3H), 2.69 (m, 1H), 2.58 (m, 1H), 2.43 (s, 3H), 2.18 (t, J=3Hz, 1H); MS(CI) 322 (M+1); Anal. calcd. for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36; Found: C, 60.08; H, 5.94; N, 4.24.

[3S-(3α,4aα)]-6-Oxo-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (10).
Cyclization of **9** according to the general procedure for **4** above, gave **10** (77%) as a white solid, mp 140-141°C; $[\alpha]_D$= -167 (c=1.275, $CHCl_3$); IR(KBr) 1741, 1713, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=8Hz, 2H), 7.30 (d, J=8Hz, 2H), 5.98 (s, 1H), 4.88 (dd, J=5 and 2Hz, 1H), 4.76 (d, J=14Hz, 1H), 4.20 (d, J=14Hz, 1H), 3.61 9s, 3H), 2.76 (m, 1H), 2.58 (dd, J=19 and 6Hz, 1H), 2.49 (ddd, J=13, 5, and 2Hz, 1H), 2.43 (s, 3H), 1.95 (dd, J=19 and 2Hz, 1H), 1.59 (dt, J=13 and 5Hz, 1H); MS(CI) 351 (M+1); Anal. calcd. for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01; Found: C, 58.60; H, 5.53; N, 3.97.

S-2-[N-(Toluene-4-sulfonyl)-N-(3-phenylprop-2-ynyl)amino]-pent-4-enoic acid methyl ester (11).
Coupling of **9** according to the procedure for **5** above provided **11** as a yellow oil (79%). IR(film) 1741, 1349, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J=8Hz, 2H), 7.26 (m, 7H), 5.76 (m, 1H), 5.15 (dd, J=17 and 1Hz, 1H), 5.07 (d, J=10Hz, 1H), 4.67 (dd, J=9 and 7Hz, 1H), 4.42 (s, 2H), 3.55 (s, 3H), 2.75 (m, 1H), 2.63 (m, 1H), 2.38 (s, 3H); MS(CI) 398 (M+1); Anal. calcd. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52; Found: C, 66.09; H, 5.80; N, 3.36.

[3S-(3α,4aα)]-6-Oxo-7-phenyl-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (12).
Cyclization of **11** according to the general procedure for **4** above, gave **12** as a white solid. Major diastereomer: $[\alpha]_D$= -80 (c=1.055, $CHCl_3$); IR(KBr) 1741, 1706, 1348, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J=8Hz, 2H), 7.43 (m, 3H), 7.20 (m, 4H), 4.97 (br d, J=4Hz, 1H), 4.92 (d, J=15Hz, 1H), 4.30 (d, J=15Hz, 1H), 3.68 (s, 3H), 2.86 (m, 1H), 2.75 (dd, J=19 and 7Hz, 1H), 2.55 (ddd, J=13, 5, and 2Hz, 1H), 2.42 (s, 3H), 2.07 (dd, J=19 and 3Hz, 1H), 1.60 (dt, J=13 and 6Hz, 1H); MS(CI) 426 (M+1); Anal. calcd. for

$C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29; Found: C, 64.72; H, 5.54; N, 3.15.

2-[N-(Toluene-4-sulfonyl)-N-(prop-2-enyl)amino]-pent-4-ynoic acid (13).
To a solution of **3** (1.49 g, 4.64 mmol) in THF (25 mL) and water (8 mL) was added lithium hydroxide hydrate (0.29 g, 6.95 mmol). The mixture was stirred 3 h at room temperature and then concentrated, taken up in water, acidified to pH 2 with 5% HCl, and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 1.42 g (100%) of **13** as a light yellow oil which slowly solidified, mp 84-86°C; IR(KBr) 3264, 1716, 1318, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J=8Hz, 2H), 7.30 (d, J=8Hz, 2H), 5.83 (m, 1H), 5.24 (dd, J=17 and 1Hz, 1H), 5.15 (dd, J=10 and 1Hz, 1H), 4.67 (dd, J=9and 6Hz, 1H), 3.93 (dt, J=16 and 6Hz, 2H), 2.90 (ddd, J=17, 6, and 3Hz, 1H), 2.76 (ddd, J=17, 9, and 3Hz, 1H), 2.43 (s, 3H), 1.91 (t, J=3Hz, 1H); MS(CI) 308 (M+1); Anal. calcd. for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.57; N, 4.56; Found: C, 58.54; H, 5.41; N, 4.41.

General Procedure for Amino Acid Loading onto Wang Resin.
According to the method of Sieber,[18] the procedure for **14** is typical. To a suspension of Wang resin (3.12 g, 0.71 mmol/g, 2.21 mmol) in DMF (20 mL) in a peptide shaker flask was added **13** (1.36 g, 4.42 mmol) followed by pyridine (0.54 mL, 6.64 mmol) and 2,6-dichlorobenzoyl chloride (0.63 mL, 4.42 mmol). The mixture was shaken for 22 h, filtered, washed with DMF (4x), CH_2Cl_2 (4x), and dried in vacuo to give 3.70 g of **14**; Anal. Found: C, 84.20; H, 7.16; N, 1.02; S, 1.98. The loading was determined by shaking a small sample of **14** (0.208 g) with 50% TFA/CH_2Cl_2 (5 mL) for 1 h. The resin was filtered, washed with CH_2Cl_2 (3x), and the combined filtrates were concentrated. The residue was taken up in CH_2Cl_2 and reconcentrated (2x) and dried in vacuo to give **13** (41 mg, 0.133 mmol) which corresponds to a loading of 0.64 mmol/g. The theoretical loading of the the commercial resin is 0.59 mmol/g. Resins **18**, **19**, and **22** were prepared in similar fashion from the acid derived from **17**, **9**, and **21**, respectively. Loadings were found to be quantitative as determined by cleavage as above.

trans-6-Oxo-2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid (15).
To a suspension of resin **14** (0.53 g, 0.34 mmol, 0.64 mmol/g) in CH_2Cl_2 (10mL) in a peptide shaker flask was added $Co_2(CO)_8$ (0.17 g, 0.51mmol). The suspension was shaken under N_2 for 2 hr. with periodic venting. The solvent was filtered off and the resin was washed with CH_2Cl_2 (3x10ml). The resin was suspended in CH_2Cl_2 (10mL) and N-methylmorpholine-N-oxide (0.13 g, 1.11 mmol) was added. The mixture was shaken under N_2 with periodic venting for 1 hr, and a second portion of NMO (0.13 g) was added. After shaking another 1 hr, the solvent was filtered off, and the resin was washed with CH_2Cl_2 (3x10mL), HOAc/CH_2Cl_2 (1:3, 3x10mL), and CH_2Cl_2 (3x10mL). The resin was then shaken with TFA/CH_2Cl_2 (1:1, 15mL) for 1 hr, filtered, and washed with CH_2Cl_2 (3x10mL). The combined filtrates were concentrated, taken up in CH_2Cl_2 and reconcentrated (2x), and dried in vacuo to give 0.11g of **15** as a tan solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J=8Hz, 2H), 7.30 (d, J=8Hz, 2H), 6.03 (s, 1H), 5.16 (d, J=7Hz, 1H), 4.15 (m, 1H), 3.32 (d, J=14Hz, 1H), 2.91 (m, 2H), 2.81 (dd, J=14 and 8Hz, 1H), 2.54 (dd, J=20 and 6Hz, 1H), 2.42 (s, 3H), 2.02 (d, J=20Hz, 1H). The residue was taken up in Et_2O (5 mL) and EtOH (1 mL), cooled to 0°C, and treated with an excess of ethereal diazomethane. After 15 min, the mixture was concentrated, taken up in EtOAc and filtered through a small pad of silica gel, eluting with 50% EtOAc/hexanes. The filtrate was

concentrated to provide material identical with **4** above.

Resin 18.
Treatment of 2-(9H-fluoren-9-ylmethoxycarbonylamino)-pent-4-enoic acid according to the procedure for **14** above provided resin **18**. IR(KBr) 1726, 1675 cm^{-1}; Anal. Found: C, 84.32; H, 7.11; N, 1.22.

Resin 19.
Treatment of **9** according to the procedure for **13** above gave S-2-[N-(Toluene-4-sulfonyl)-N-(prop-2-ynyl)amino]-pent-4-enoic acid as a thick oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J=8Hz, 2H), 7.29 (d, J=8Hz, 2H), 5.66 (m, 1H), 5.12 (ddd, J=17, 3, and 1Hz, 1H), 5.03 (dd, J=10 and 1Hz, 1H), 4.55 (dd, J=9 and 6 Hz, 1H), 4.29 (dd, J=19 and 3Hz, 1H), 4.09 (dd, J=19 and 3Hz, 1H), 2.78-2.52 (m, 2H) , 2.43 (s, 3H), 2.21 (t, J=3Hz, 1H). Treatment of this acid according to the procedure for **14** above gave resin **19**. IR(KBr) 1734 cm^{-1}; Anal. Found: C, 84.56; H, 7.29; N, 0.98.

General Procedure for the Preparation of Compounds 12, 24a, and 24b from Resin 18.
The procedure for **24a** is typical.

[3S-(3α,4aα)]-7-(4-Methoxy-phenyl)-6-oxo-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (24a).
To a suspension of resin **18** (2.01 g, 0.57 mmol/g, 1.15 mmol) in CH_2Cl_2 (8 mL) and DMF (8 mL) in a peptide shaker flask was added piperidine (4 mL) and the mixture was shaken for 20 min. After filtration, this process was repeated and the resin was washed with CH_2Cl_2 (4x). The resin was resuspended in CH_2Cl_2 (15 mL) and Et_3N (0.48 ml, 3.44 mmol) was added followed by tosyl chloride (0.44 g, 2.29 mmol) and the mixture was shaken for 7 h. After filtration, the resin was washed with CH_2Cl_2 (5x) and dried in vacuo. To a supension of this resin (1.12 g, 0.75 mmol) in DMF (15 mL) was added Cs_2CO_3 (0.49 g, 1.50 mmol) followed by propargyl bromide (0.33 mL, 80% in toluene, 3.00 mmol) and this mixture was shaken for 20 h. After filtration, the resin was washed with DMF (2x), DMF/H_2O (1:1, 2x), DMF (3x), CH_2Cl_2 (4x), and dried in vacuo. The resin was suspended in CH_2Cl_2 (12 mL) and Et_3N (2 mL) was added followed by 4-methoxyiodobenzene (0.26 g, 1.13 mmol), CuI (7 mg, 0.0375 mmol) and $(PPh_3)_2PdCl_2$ (26 mg, 0.0375 mmol) and the mixture was shaken for 18 h. After filtration, the resin was washed with CH_2Cl_2 (5x) and dried in vacuo. The resin was suspended in CH_2Cl_2 (15 mL) and $Co_2(CO)_8$ (0.38 g, 1.13 mmol) was added and the mixture was shaken for 3 h with periodic venting. After filtration and washing with CH_2Cl_2 (3x), the resin was resuspended in CH_2Cl_2 (15 mL) and NMO (0.26 g, 2.25 mmol) was added. Shaken with periodic venting for 1 h. Another portion of NMO (0.26 g) was added and the mixture was shaken for another hour. After filtration, the resin was washed with CH_2Cl_2 (3x), HOAc/CH_2Cl_2 (1:3, 3x), and CH_2Cl_2 (5x). The resin was shaken with 50% TFA/CH_2Cl_2 (20 mL) for 1 h. After filtration, the resin was washed with CH_2Cl_2 (3x) and the combined filtrates were concentrated. The residue was taken up in CH_2Cl_2 and reconcentrated (3x) to afford 0.35 g of a brown foam. This material was taken up in Et_2O (5 mL) and EtOH (1 mL) and cooled to 0°C. Excess CH_2N_2 was added and the mixture was stirred for 15 min and then concentrated. Flash chromatography (50% EtOAc/hexanes) gave 0.17 g (50%) of **24a** as a white foam. Major diastereomer: IR(KBr) 1741, 1705, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J=8Hz, 2H), 7.23 (d, J=8Hz, 2H), 7.16 (d, J=9Hz, 2H), 6.96 (d, J=9Hz, 2H), 4.95

(br d, J=4Hz, 1H), 4.94 (d, J=15Hz, 1H), 4.31 (d, J=15 Hz, 1H), 3.86 (s, 3H), 3.68 (s, 3H), 2.82 (m, 1H), 2.72 (dd, J=9 and 7Hz, 1H), 2.53 (ddd, J=13, 5, and 2Hz, 1H), 2.41 (s, 3H), 2.05 (dd, J=19 and 3Hz, 1H), 1.55 (dt, J=13 and 6Hz, 1H); MS(CI) 456 (M+1); Anal. calcd. for $C_{24}H_{25}NO_6S$: C, 63.28; H, 5.53; N, 3.07; Found: C, 63.21; H, 5.70; N, 2.96.

[3S-(3α,4aα)]-7-(4-Chloro-phenyl)-6-oxo-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (24b).

Major diastereomer: IR(KBr) 1729, 1700, 1150, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J=8Hz, 2H), 7.41 (d, J=9Hz, 2H), 7.24 (d, J=9Hz, 2H), 7.16 (d, J=8Hz, 2H), 4.96 (br d, J=4Hz, 1H), 4.85 (d, J=15Hz, 1H), 4.28 (d, J=15Hz, 1H), 3.67 (s, 3H), 2.85 (m, 1H), 2.75 (dd, J=19 and 7Hz, 1H), 2.57 (ddd, J=13, 5, and 2Hz, 1H), 2.42 (s, 3H), 2.08 (dd, J=19 and 2Hz, 1H), 1.64 (dt, J=13 and 6Hz, 1H); MS(CI) 463, 461 (M+1); Anal. calcd. for $C_{23}H_{22}ClNO_5S$: C, 60.06; H, 4.82; N, 3.05; Found: C, 59.76; H, 4.69; N, 2.91.

[3S-(3α,4aα)]-7-(4-Methoxycarbonyl-phenyl)-6-oxo-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (24c).

Starting with resin **19** (0.66 mmol/g, 0.53 mmol), by coupling with 4-iodo-methylbenzoate and cyclization according to the general procedure for **24a**, **24c** (0.225 g, 88%) was obtained as a white foam. Major diastereomer: IR(KBr) 1716, 1279, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J=8Hz, 2H), 7.53 (d, J=8Hz, 2H), 7.29 (d, J=8Hz, 2H), 7.23 (d, J=8Hz, 2H), 4.98 (br d, J=4Hz, 1H), 4.85 (d, J=15Hz, 1H), 4.30 (d, J=15Hz, 1H), 3.96 (s, 3H), 3.68 (s, 3H), 2.90 (m, 1H), 2.77 (dd, J=19 and 7 Hz, 1H), 2.58 (ddd, J=13, 5, and 2Hz, 1H), 2.42 (s, 3H), 2.11 (dd, J=19 and 3Hz, 1H), 1.64 (dt, J=13 and 6Hz, 1H); MS(CI) 484 (M+1); Anal. calcd. for $C_{25}H_{25}NO_7S$: C, 62.10; H, 5.21; N, 2.90; Found: C, 62.08; H, 5.37; N, 2.67.

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-pent-4-ynoic acid (21).

To a suspension of 2-aminopent-4-ynoic acid (2.5 g, 22.1 mmol) in dioxane (90 mL) was added 10% Na_2CO_3 (90 mL). A solution of FMOC-OSu (7.46 g, 22.1 mmol) in dioxane (40 mL) was added over 15 min. The mixture was stirred at room temperature for 3 h. Most of the dioxane was removed by rotary evaporation. Water was added and the mixture was cooled to 0°C and carefully acidified to pH 3 with 10% HCl. The mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 7.5 g of a white solid which was recrystallized (EtOAc/hexanes) to give 6.64 g (90%) of **21** as a white solid, mp 188-190°C; IR(KBr) 1752, 1725, 1682, 1544 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 12.92 (br s, 1H), 7.90 (d, J=7Hz, 2H), 7.79 (d, J=8Hz, 1H), 7.74 (d, J=7Hz, 2H), 7.42 (t, J=7Hz, 2H), 7.33 (t, J=7Hz, 2H), 4.29 (m, 3H), 4.13 (m, 1H), 2.90 (t, J=2Hz, 1H), 2.60 (m, 2H); MS(CI) 336 (M+1); Anal. calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18; Found: C, 71.64; H, 5.20; N, 4.04.

Resin 22.

Treatment of acid **21** according to the procedure for **14** above gave resin **22** (loading 0.60 mmol/g).

Preparation of Compounds 6 and 23b (from resin 18) and 23a,c (from resin 22).

Compounds **23a,c** were obtained from resin **22** according to the general procedure described above, by

substitution of allyl bromide for propargyl bromide in the alkylation step. Compounds **6** and **23b** were obtained from resin **18** by coupling with the appropriate aryl iodide and cyclization as described above.

trans-5-(4-Methoxy-phenyl)-6-oxo-2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (23a).
Major diastereomer: mp 143-144°C; IR(KBr) 1740, 1702, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8Hz, 2H), 7.31 (d, J=8Hz, 2H), 7.15 (d, J=9Hz, 2H), 6.92 (d, J=9Hz, 2H), 5.06 (d, J=7Hz, 1H), 4.25 (dd, J=18 and 12Hz, 1H), 3.81 (s, 3H), 3.44 (dd, J=14 and 1Hz, 1H), 3.39 (s, 3H), 3.02 (d, J=11Hz, 1H), 2.98 (d, J=11Hz, 1H0, 2.79 (dd, J=14 and 7Hz, 1H), 2.66 (dd, J=19 and 6Hz, 1H), 2.43 (s, 3H), 2.06 (d, J=19Hz, 1H); MS(CI) 456 (M+1); Anal. calcd. for $C_{24}H_{25}NO_6S \cdot 0.25\ CHCl_3$: C, 60.00; H, 5.24; N, 2.89; Found: 60.00; H, 5.00; N, 2.92.

trans-5-(4-Chloro-phenyl)-6-oxo-2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (23b).
Major diastereomer: IR(KBr) 1744, 1706, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8Hz, 2H), 7.37 (d, J=8Hz, 2H), 7.32 (d, J=8Hz, 2H), 7.16 (d, J=8Hz, 2H),5.07 (d, J=7Hz, 1H), 4.24 (dd, J=11 and 5Hz, 1H), 3.40 (s, 3H), 3.37 (dd, J=14 and 1Hz, 1H), 3.00 (m, 2H), 2.80 (dd, J=14 and 7Hz, 1H), 2.67 (dd, J=19 and 6Hz, 1H), 2.44 (s, 3H), 2.07 (dd, J=19 and 2Hz, 1H); MS(CI) 462, 460 (M+1); Anal. calcd. for $C_{23}H_{22}ClNO_5S$: C, 60.06; H, 4.82; N, 3.05; Found: C, 60.08; H, 4.69; N, 2.97.

trans-5-(4-Methoxycarbonyl-phenyl)-6-oxo-2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (23c).
Major diastereomer: mp 153-155°C; IR(KBr) 1723, 1704, 1280, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J=8Hz, 2H), 7.71 (d, J=8Hz, 2H), 7.31 (d, J=8Hz, 2H), 7.28 (d, J=8Hz, 2H), 5.06 (d, J=7Hz, 1H), 4.25 (m, 1H), 3.92 (s, 3H), 3.38 9d, J=12Hz, 1H), 3.37 (s, 3H), 3.00 (m, 2H), 2.81 (dd, J=14 and 7Hz, 1H), 2.69 (dd, J=19 and 7Hz, 1H), 2.43 (s, 3H), 2.09 (dd, J=19 and 2Hz, 1H); MS(CI) 484 (M+1); Anal. calcd. for $C_{25}H_{25}NO_7S$: C, 62.10; H, 5.21; N, 2.90; Found: C, 62.14; H, 4.92; N, 2.85.

2-[N-Toluene-4-sulfonyl)-N-(3-phenylprop-2-enyl)]-pent-4-ynoic acid methyl ester (25a).
Treatment of **2** (0.76 g, 2.70 mmol) with cinnamyl bromide (0.48 mL, 3.24 mmol) according to the procedure given for **3** provided 1.00 g (93%) of **25a** as a light yellow oil after flash chromatography (25% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=8Hz, 2H), 7.28 (m, 7H), 6.47 (dd, J=16 and 1Hz, 1H), 6.11 (dt, J=16 and 7Hz, 1H), 4.79 (dd, J=9 and 6Hz, 1H), 4.06 (tdd, J=16, 7, and 1Hz, 2H), 3.61 (s, 3H), 2.90 (ddd, J=17, 6, and 3Hz, 1H), 2.75 (ddd, J=17, 9, and 3Hz, 1H), 2.41 (s, 3H), 1.99 (t, J=3Hz, 1H).

(3α,7β,7aβ)-6-Oxo-7-phenyl-2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (26a).
Treatment of **25a** (0.99 g, 2.49 mmol) according to the general procedure given for **4** gave 0.54 g (51%) of **26a** as a white solid, mp 174-176°C; IR(KBr) 1733, 1704, 1350, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=8Hz, 2H), 7.30 (m, 5H), 7.07 (d, J=8Hz, 2H), 6.06 (s, 1H), 5.11 (d, J=7Hz, 1H), 4.28 (dd, J=11

and 5Hz, 1H), 3.55 (s, 3H), 3.31 (dd, J=14 and 1Hz, 1H), 3.08 (m, 3H), 2.90 (dd, J=13 and 7Hz, 1H), 2.43 (s, 3H); MS(CI) 426 (M+1); Anal. calcd. for $C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29; Found: C, 64.48; H, 5.46; N, 3.15.

[3S-(3α,4aα)]-2-(4-Chloro-benzenesulfonyl)-6-oxo-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-[2]pyrindine-3-carboxylic acid benzylamide (30).

Treatment of resin **18** (1.64 g, 0.57 mmol/g, 0.93 mmol) according to the general procedure given for **24a**, but substituting 4-chlorobenzenesulfonyl chloride (0.39 g, 1.87 mmol) for tosyl chloride, gave resin **29** after alkylation with propargyl bromide. Coupling and cyclization of a sample of this resin (0.75 g, 0.46 mmol) provided 0.17 g of the crude acid after cleavage. This acid (0.16 g, 0.37 mmol) was taken up in EtOAc (3 mL) and HOBT (60 mg, 0.44 mmol) and DCC (92 mg, 0.44 mmol) were added, followed by benzylamine (0.045 mL, 0.41 mmol). The mixture was stirred overnight at room temperature and then filtered. The filtrate was washed with 5% HCl, sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (50% EtOAc/hexanes) provided a semisolid which was suspended in 50% EtOAc/hexanes and filtered. The filtrate was concentrated to give 60 mg (25% overall from **18**) as a white foam. IR(KBr) 1704, 1683, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.24 (m, 12H), 7.17 (dd, J=8 and 1Hz, 2H), 6.98 (br t, J=6Hz, 1H), 5.03 (d, J=16Hz, 1H), 4.73 (d, J=5Hz, 1H), 4.59 (dd, J=15 and 6Hz, 1H), 4.47 (dd, J=15 and 6Hz, 1H), 4.07 (d, J=16Hz, 1H), 3.08 (m, 1H), 2.75 (m, 1H), 2.71 (dd, J=19 and 6Hz, 1H), 1.91 (dd, J=19 and 2Hz, 1H), 0.92 (dt, J=13 and 5Hz, 1H); MS(CI) 523, 521 (M+1); Anal. calcd. for $C_{28}H_{25}ClN_2O_4S$: C, 64.55; H, 4.84; N, 5.38; Found: C, 64.72; H, 5.19; N, 5.44.

2-[Allyl-(2-nitro-benzenesulfonyl)-amino]-pent-4-ynoic acid methyl ester (31).

Treatment of **1** (1.43 g, 8.74 mmol) with 2-nitrobenzenesulfonyl chloride (2.32 g, 10.49 mmol) according to the procedure for **2** gave 2.25 g (82%) of 2-(2-nitrobenzenesulfonylamino)-pent-4-ynoic acid methyl ester as a white solid, mp 112-113°C; IR(KBr) 3277, 1733, 1543, 1366, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 1H), 7.96 (m, 1H), 7.75 (m, 2H), 4.40 (dt, J=9 and 5Hz, 1H), 3.60 (s, 3H), 2.83 (ddd, J=17, 5, and 3Hz, 1H), 2.77 (ddd, J=17, 5, and 3Hz, 1H), 2.06 (t, J=3Hz, 1H); MS(CI) 313 (M+1); Anal. calcd. for $C_{12}H_{12}N_2O_6S$: C, 46.15; H, 3.87; N, 8.97; Found: C, 46.14; H, 3.60; N, 8.93. Alkylation of this ester (2.03 g, 6.50 mmol) with allyl bromide (1.13 mL, 13.00 mmol) according to the procedure for **3** provided 2.10 g (92%) of **31** as a tan powder, mp 118-119°C; IR(KBr) 3276, 1743, 1544, 1366, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 1H), 7.69 (m, 2H), 7.63 (m, 1H), 5.90 (m, 1H), 5.25 (dd, J=17 and 1Hz, 1H), 5.14 (dd, J=10 and 1Hz, 1H), 4.88 (dd, J=9 and 6Hz, 1H), 4.14 (dd, J=16 and 6Hz, 1H), 4.05 (dd, J=16 and 6Hz, 1H), 3.67 (s, 3H), 2.92 (dd, J=17, 6, and 3Hz, 1H), 2.79 (ddd, 17, 9, and 3Hz, 1H), 1.99 (t, J=3Hz, 1H); MS(CI) 353 (M+1); Anal. calcd. for $C_{15}H_{16}N_2O_6S$: C, 51.13; H, 4.58; N, 7.95; Found: C, 50.92; H, 4.50; N, 7.76.

trans-2-(2-Nitro-benzenesulfonyl)-6-oxo-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (32a) and trans-2-(2-amino-benzenesulfonyl)-6-oxo-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (32b).

Cyclization of **31** (1.64 g, 4.65 mmol) according to the general procedure given for **4** gave a mixture of 0.65 g of **32a** (37%) as a white foam and 0.42 g of **32b** (26%) as a white solid after flash chromatography (75%

EtOAc/hexanes). **32a**: IR(KBr) 1745, 1710, 1544, 1372, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 1H), 7.74 (m, 3H), 6.00 (s, 1H), 5.10 (d, J=7Hz, 1H), 4.21 (dd, J=12 and 6Hz, 1H), 3.63 (s, 3H), 3.37 (d, J=13Hz, 1H), 3.08 (dd, J=13 and 12Hz, 1H), 2.95 (m, 2H), 2.53 (dd, J=19 and 6Hz, 1H), 1.95 (dd, J=19 and 2Hz, 1H); MS(CI) 381 (M+1); Anal. calcd. for $C_{16}H_{16}N_2O_7S$: C, 50.52; H, 4.24; N, 7.36; Found: C, 50.71; H, 4.39; N, 7.04. (**32b**): Mp 160-162°C; IR(KBr) 3477, 3375, 1730, 1705, 1671, 1616, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, J=8 and 1Hz, 1H), 7.32 (dt, J=8 and 1Hz, 1H), 6.79 (dt, J=8 and 1Hz, 1H), 6.73 (d, J=8Hz, 1H), 5.96 (s, 1H), 5.08 (d, J=7Hz, 1H), 4.96 (s, 2H), 4.16 (dd, J=13 and 6Hz, 1H), 3.60 (s, 3H), 3.25 (d, J=13Hz, 1H), 2.98 (dd, J=13 and 12Hz, 1H), 2.89 (m, 1H), 2.77 (dd, J=14 and 7Hz, 1H), 2.47 (dd, J=19 and 6Hz, 1H), 1.90 (dd, J=19 and 2Hz, 1H); MS(CI) 351 (M+1); Anal. calcd. for $C_{16}H_{18}N_2O_5S$: C, 54.85; H, 5.18; 7.99; Found: 55.13; H, 5.32; N, 7.98.

3S-[3α(R*), 7aβ] and 3R-[3α(S*), 7aβ]-2-{[6-Oxo-[2-(toluene-4-sulfonyl)-2,3,4,6,7,7a-hexahydro-1H-[2]pyrindine-3-carbonyl]-amino}-3-phenyl propionic acid methyl ester (35a,b).

To a suspension of resin **33** (1.25g, 0.54 mmol/g, 0.68 mmol) in DMF (9 mL) in a peptide shaker tube was added piperidine (3 mL) and the mixture was shaken for 15 min. After filtration, the deprotection was repeated and the resin was washed with DMF (5x). The resin was resuspended in DMF (10 mL) and **13** (0.42 g, 1.36 mmol) was added followed by HOBT (0.18 g, 1.35 mmol) and EDAC (0.26 g, 1.35 mmol). The mixture was shaken overnight, filtered, washed with DMF (3x), MeOH (2x), CH_2Cl_2 (5x), and dried in vacuo. Cyclization of this resin according to the procedure for **15** gave 0.41 g of a crude residue after cleavage (1:1 TFA/CH_2Cl_2) and esterification with CH_2N_2. This material was taken up in EtOAc, washed with 5% HCl, brine, dried over $MgSO_4$, and concentrated to give 0.36 g of a tan solid. Flash chromatography (60% EtOAc/hexanes) gave 0.22 g (68%) of a mixture of **35a,b** as a light yellow solid. The ratio of diastereomers was estimated to be 2:1 by ^1H NMR analysis. IR(KBr) 1739, 1703, 1673, 1633, 1519, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) Major diastereomer: δ 7.73 (d, J=8Hz, 2H), 7.33 (m, 5H), 7.09 (d, J=8Hz, 2H), 6.74 (d, J=8Hz, 1H), 5.93 (s, 1H), 4.77 (m, 2H), 4.12 (dd, J=14 and 7Hz, 1H), 3.70 (s, 3H), 3.39 (d, J=14 Hz, 1H), 3.12 (dd, J=14 and 9Hz, 1H), 3.01 (dd, J=14 and 7Hz, 1H), 2.73 (d, J=14Hz, 1H), 2.59 (m, 1H), 2.44 (s, 3H), 2.38 (dd, J=19 and 7Hz, 1H), 2.10 (m, 1H), 1.80 (d, J=19Hz, 1H); Minor diastereomer: δ 5.91 (s, 1H), 3.78 (s, 3H), 2.45 (s, 3H); MS(CI) 497 (M+1); Anal. calcd. for $C_{26}H_{28}N_2O_6S$: C, 62.89; H, 5.68; N, 5.64; Found: C, 62.51; H, 5.78; N, 5.37.

[3α, 4aβ, 7aβ]-6-Oxo-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindine-3-carboxylic acid methyl ester (36).

Cyclization of resin **14** according to the procedure given for **15** provided resin **37**. Resin **37** (0.73 g, 0.6 mmol/g, 0.44 mmol) was suspended in degassed toluene (15 mL) in a peptide shaker flask. Degassed water (0.025 mL) was added followed by $[(PPh_3)CuH]_6$ (0.43 g, 0.22 mmol) and the mixture was shaken for 24 h. After filtration, the resin was washed with toluene (3x), MeOH (2x), CH_2Cl_2 (2x), HOAc/CH_2Cl_2 (1:3, 3x), and CH_2Cl_2 (4x) to afford resin **38**. The resin was shaken with 50% TFA/CH_2Cl_2 (15 mL) for 30 min. After filtration, the resin was washed with CH_2Cl_2 (3x) and the combined filtrates were concentrated. The residue was taken up in CH_2Cl_2 and reconcentrated (2x). The residue was taken up in EtOAc, washed with 5% HCl, brine, dried over $MgSO_4$, and concentrated. The residue was taken up in Et_2O (5 mL) and EtOH (1 mL), cooled to 0°C, and esterified with excess CH_2N_2. After 15 min, the mixture was concentrated. Flash chromatography (50% EtOAc/hexanes) gave 105 mg (68%) of **36** as a white powder, mp 108-110°C; IR(KBr) 1739, 1330,

1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J=8Hz, 2H), 7.29 (d, J=8Hz, 2H), 4.66 (ddd, J=7, 4, and 1Hz, 1H), 3.72 (dd, J=14 and 6Hz, 1H), 3.57 (s, 3H), 2.98 (dd, J=14 and 12Hz, 1H), 2.52 (m, 1H), 2.42 (s, 3H), 2.39-2.12 (m, 5H), 1.96 (m, 2H); MS(CI) 352(M+1); Anal. calcd. for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; Found: C, 58.00; H, 6.07; N, 3.87.

[3α, 4aα, 7aα]-6-Oxo-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindine-3-carboxylic acid methyl ester (39).

Cyclization of resin **19** according to the procedure given for **15** provided resin **40**. Reduction according to the procedure given for **36** gave resin **41**. A sample of this resin (0.80 g, 0.48 mmol) was cleaved with 50% TFA/CH_2Cl_2 and esterified as described above. Flash chromatography (50% EtOAc/hexanes) provided 143 mg (85%) of **39** as a white foam. IR(KBr) 1742, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J=8Hz, 2H), 7.30 (d, J=8Hz, 2H), 4.80 (br d, J=5Hz, 1H), 3.76 (d, J=13Hz, 1H), 3.56 (s, 3H), 3.48 (dd, J=13 and 3Hz, 1H), 2.43 (s, 3H), 2.43-2.10 (m, 6H), 2.05 (d, J=18Hz, 1H), 1.58 (m, 1H); MS(CI) 352 (M+1); Anal. calcd. for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; Found: C, 58.16; H, 5.81; N, 3.88.

[3α, 4aβ, 6(α and β), 7aβ]-6-(Acetylbenzylamino)-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindine-3-carboxylic acid methyl ester (42).

To a suspension of resin **38** (0.74 g, 0.44 mmol) in CH_2Cl_2 (10 mL) in a peptide shaker flask was added benzylamine (0.15 mL, 1.33 mmol) followed by $NaBH(OAc)_3$ (0.47 g, 2.22 mmol) and HOAc (0.076 mL, 1.33 mmol). The mixture was shaken for 24 h, with periodic venting. After filtration, the resin was washed with CH_2Cl_2, MeOH (3x), CH_2Cl_2 (2x), CH_2Cl_2/Et_3N (1:1, 2x), and CH_2Cl_2 (3x). This resin was resuspended in CH_2Cl_2 (10 mL) and Et_3N (0.37 mL, 2.64 mmol) was added followed by acetic anhydride (0.21 mL, 2.20 mmol) and DMAP (5 mg). The mixture was shaken for 4 h. After filtration, the resin was washed with CH_2Cl_2 (3x), then shaken with 50% TFA/CH_2Cl_2 (15 mL) for 30 min. After filtration, the resin was washed with CH_2Cl_2 (3x) and the combined filtrates were concentrated. The residue was taken up in CH_2Cl_2 and reconcentrated (2x). The residue was taken up in Et_2O (5 mL) and EtOH (1 mL), cooled to 0°C, and esterified with excess CH_2N_2. After concentration, flash chromatography (75% EtOAc/hexanes) of the residue provided 110 mg (52%) of **42** as a white foam. IR(KBr) 1747, 1645, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) Approximately a 4:1 mixture of rotomers; major rotomer: δ 7.70 (d, J=8Hz, 2H), 7.29 (m, 5H), 7.12 (d, J=7Hz, 2H), 4.79 (m, 1H), 4.40 (br s, 2H), 4.26 (dd, J=9 and 6Hz, 1H), 3.66 (dd, J=14 and 7Hz, 1H), 3.57 (s, 3H), 2.97 (dd, J=14 and 12Hz, 1H), 2.43 (s, 3H), 2.03 (m, 1H), 1.99 (s, 3H), 1.84 (m, 3H), 1.66 (m, 1H), 1.08 (m, 2H); minor rotomer: δ 3.61 (s), 2.41 (s), 2.13 (s); MS(CI) 485 (M+1); Anal. calcd. for $C_{26}H_{32}N_2O_5S$: C, 64.44; H,7.66; N, 5.78; Found: C,64.29; H, 6.56; N, 5:61.

[3α, 4aβ, 6(α or β), 7aβ]-6-[3-(3-Chlorophenyl)-1-methyl-ureido]-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindine-3-carboxylic acid methyl ester (43).

Reductive amination of **38** (0.78 g, 0.47 mmol) with methylamine (3 eq., 2.0M solution in THF), and subsequent acylation with 3-chlorophenyl isocyanate (3 eq.) in the presence of Et_3N and DMAP according to the procedure for **42** afforded 112 mg (46%) of **43** as a white powder. IR(KBr) 1744, 1658, 1648, 1590, 1526, 1482, 1342, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) Approximately a 9:1 mixture of rotomers; major rotomer: δ 7.74 (d, J=8Hz, 2H), 7.48 (t, J=2Hz, 1H), 7.30 (d, J=8Hz, 2H), 7.20 (m, 2H), 6.99 (dt, J=7 and 2Hz, 1H), 6.32 (s, 1H), 4.59 (M, 1H), 4.32 (dd, J=10 and 6Hz, 1H), 3.76 (dd, J=14 and 7Hz, 1H), 3.71 (s, 3H),

3.07 (dd, J=14 and 12Hz, 1H), 2.81 (s, 3H), 2.44 (s, 3H), 2.10 (m, 2H), 1.95-1.73 (m, 4H), 1.20 (m, 2H); minor rotomer: δ 3.62 (s), 2.83 (s), 2.43 (s); MS(CI) 522, 520 (M+1); Anal. calcd. for $C_{25}H_{30}ClN_3O_5S$: C, 57.74; H, 5.81; N, 8.08; Found: C, 58.00; H, 5.74; N, 7.70.

[3α, 4aα, 6(α or β), 7aα]-6-(Acetylbenzylamino)-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindine-3-carboxylic acid methyl ester (44).
Reductive amination and acylation of resin **41** (0.99 g, 0.6 mmol) according to the procedure for **42** provided 0.16 g (55%) of **44** as a white foam. IR(KBr) 1747, 1645, 1164 cm^{-1}; ^1H NMR (400 MHz, DMSO, 100°C) δ 7.63 (d, J=8Hz, 2H), 7.35 (d, J=8Hz, 2H), 7.29 (m, 2H), 7.20 (m, 1H), 7.14 (d, J=7Hz, 2H), 4.49-4.30 (m, 4H), 3.55 (s, 3H), 3.33 (dd, J=12 and 7Hz, 1H), 2.48 (s, 3H), 2.38 (s, 3H), 2.18 (m, 1H), 2.05-1.80 (m, 4H), 1.65 (m, 2H), 1.37 (m, 1H), 1.17 (m, 1H); MS(CI) 485 (M+1); Anal. calcd. for $C_{26}H_{32}N_2O_5S$: C, 64.44; H, 6.66; N, 5.78; Found: C, 64.12; H, 6.51; N, 5.73.

[3α, 4aα, 6(α and β), 7aα]-6-(Benzoylmethylamino)-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindine-3-carboxylic acid methyl ester (45).
Reductive amination of resin **41** (0.80 g, 0.48 mmol) with methylamine and acylation with benzoyl chloride as described for **42** provided 134 mg (59%) of **45** as a white foam after flash chromatography (70% EtOAc/hexanes). Major diastereomer: IR(KBr) 1742, 1633, 1161 cm^{-1}; ^1H NMR (400 MHz, DMSO, 100°C) δ 7.67 (d, J=8Hz, 2H), 7.40 (m, 5H), 7.30 (m, 2H), 4.48 (br t, J=5Hz, 1H), 4.25 (m, 1H), 3.56 (s, 3H), 3.38 (dd, J=13 and 5Hz, 1H), 3.16 (dd, J=13 and 6 Hz, 1H), 2.72 (s, 3H), 2.39 (s, 3H), 2.10 (m, 1H), 2.01-1.82 (m, 3H), 1.65 (m, 2H), 1.45 (m, 1H), 1.33 (m, 1H); MS(CI) 471 (M+1) Anal. calcd. for $C_{25}H_{30}N_2O_5S$: C, 63.81; H, 6.43; N, 5.95; Found: C, 63.53; H, 6.19; N, 5.79. Minor diastereomer: ^1H NMR (400 MHz, DMSO, 100°C) δ 7.61 (d, J=8Hz, 2H), 7.40 (m, 5H), 7.28 (m, 2H), 4.51 (br d, J=4Hz, 2H), 3.51 (s, 3H), 3.33 (dd, J=13 and 4Hz, 1H), 3.28 (dd, J=13 and 4Hz, 1H), 2.78 (s, 3H), 2.40 (s, 3H), 2.31 (m, 1H), 2.02 (m, 1H), 1.87 (m, 2H), 1.75-1.50 (m, 3H), 1.30 (m, 1H).

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