Synthesis and Further Reactivity of Functionalized Lactam-Derived Enol Triflates

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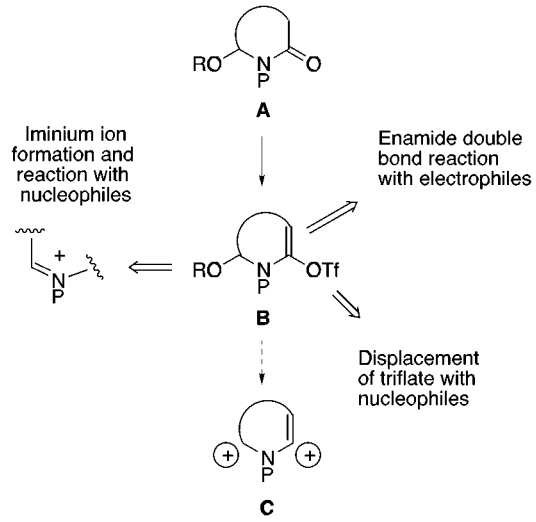
Pyrrolidinone- and piperidinone-derived enol triflates **2** were prepared in high yield (60−97%) from the corresponding lactams **1** using KHMDS and *N*-(5-chloro-2-pyridyl)triflimide. A structure−stability study on the less stable pyrrolidinone-derived triflates revealed that an *N*-tosyl group is essential, and an α-ethoxy substituent enhances thermal stability. Substituents at the 3- and 4-position are tolerated. Substitution of the triflate moiety by a wide variety of functional groups was achieved under mild conditions *via* metal-mediated reactions. Although cuprate couplings proceeded in only moderate yields, several palladium-catalyzed reactions gave good yields of interesting molecules for further synthetic operations (for example, Stille coupling with vinylstannanes, cross-coupling with arylzincs, and carbonylation processes). Preparation of the first enantiopure lactam-derived enol triflate **15** (from (*S*)-pyroglutamic acid) is described. Enamide hydrogenation of derivative **17** allowed the synthesis of a proline analogue **18** in excellent yield and diastereoselectivity (86% de).

Introduction

Enol triflates are now widely regarded as powerful intermediates for organic synthesis.[1] Lactam-derived variants, however, have only become accessible during the last three years. Since the pioneering efforts of Isobe[2a,b] and Comins,[2c] and our first publication,[3a] we have undertaken a research program directed toward expanding the range of such lactam-derived triflates available to the organic chemist, and developing useful further elaboration reactions of the triflate moiety. A preliminary account of this work has been disclosed.[3b] It was hoped that such methodology would allow entry to novel classes of compound and also find use in natural product synthesis.[2c] Our efforts were recently rewarded when we accomplished an efficient total synthesis of the alkaloid desoxoprosophylline *via* a piperidinone-derived enol triflate intermediate.[3c] Scheme 1 indicates how the synthesis of enol triflates such as **B** from α-alkoxy lactams **A** gives rise to a useful building block containing three reactive sites for further functionalization: the enol triflate moiety, the enamide double bond, and the α-alkoxy-amide/amine (a well-known precursor for iminium ions[4]). Thus, triflates **B** can be conceptually represented as synthons **C** containing formally two cationic sites. Shono has previously shown synthons similar to **C** (but lacking the double bond) to be useful for the rapid construction of alkaloid skeletons.[4d,e]

Herein we give a full account of our investigations, focusing primarily on the range of triflates available and the further coupling reactions developed. As the majority of these couplings take place under mild conditions, our procedures should also be useful to chemists working with other enol triflate derivatives of limited stability.

Scheme 1



Results and Discussion

In view of the previous successes in preparing six-membered lactam-derived triflates, we initially turned our attention to the more problematic five-membered analogues which had been documented as rapidly decomposing.[2] The first target selected was triflate **2a** derived from the corresponding *N*-protected lactam, *N*-tosyl-5-ethoxy-2-pyrrolidinone **1a**.[3,5] Scheme 2 shows the dramatic effects of different base/triflating agent

[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1997.

(1) Review: Ritter, K. *Synthesis* **1993**, 735.

(2) (a) Okita, T.; Isobe, M. *Synlett* **1994**, 589. (b) Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737. (c) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656.

(3) (a) Bernabé, P.; Rutjes, F. P. J. T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 3561. (b) Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 8257. (c) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592.

(4) (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Åhman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537. (c) Weinreb, S. M. *J. Heterocycl. Chem.* **1996**, *33*, 1437. (d) Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243. (e) Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Chem. Lett.* **1987**, 919.

(5) Precursors to triflates **2a**−**e**, *N*-tosyl lactams **1a**−**e**, were prepared from the known *N*-H lactams: Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179. Lactam **1d** was prepared by a different route: Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Tetrahedron Lett.* **1986**, *27*, 1411. Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3801. For full details see Experimental Section.

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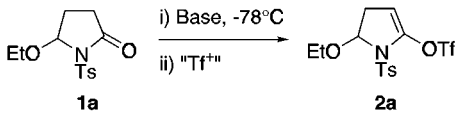
Scheme 2



1a **2a**

Table 1. Synthesis of Triflate 2a

M[a]	Tf+[b]	yield[d] %
K	1	ca. 35 [lit[3a] 60)
Li	2	0
K	2	60
K	2[c]	97

[a] MHMDS (1.25 equiv). [b] 1 = Tf_2O, 2 = *N*-(5-chloro-2-pyridyl)triflimide (both 1.25 equiv). [c] Kugelrohr distilled before use. [d] Isolated.

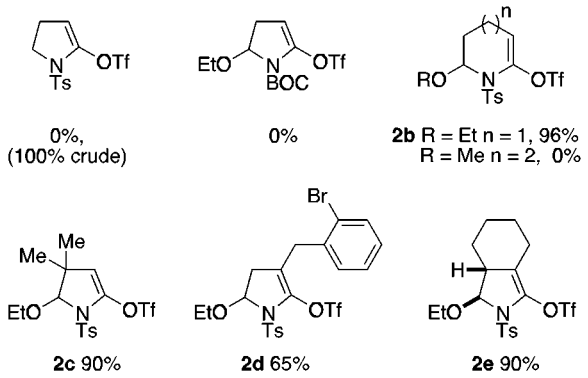
combinations on the efficiency of the desired transformation. Our previous route[3a] to triflate **2a** (KHMDS, Tf_2O) was found to be somewhat erratic with yields varying and product decomposition (elimination of ethanol yielding a pyrrole) a problem. It was felt that these problems could be attributed to the triflic anhydride, its decomposition product being the strong triflic acid which would certainly catalyze the unwanted ethanol elimination step. Comins's crystalline triflating agent, *N*-(5-chloro-2-pyridyl)triflimide,[6] combines high reactivity with good stability and so seemed the reagent of choice. Surprisingly, the lithium enolate of **1a** (LiHMDS) failed to react with Comins's reagent, in stark contrast to previous reports on similar six-membered lactam enolates.[2] Gratifyingly, switching to the potassium enolate of **1a** (KHMDS) circumvented this problem, affording the pyrrolidinone-derived triflate **2a** in an acceptable 60% yield. Finally, the reaction was dramatically improved by purification of the commercially obtained triflating agent (Kugelrohr distilled material is stable for periods >3 months at 0 °C). Using these optimized conditions, a pyrrolidinone-derived triflate **2a** was accessible for the first time in a reproducible 97% yield on scales ranging from 20 mg to 2 g. This triflate was thermally stable in neat form for short periods (ca. 10 min) at rt and for extended periods (months) when stored in a freezer. It was conveniently handled as a CH_2Cl_2 solution at rt.

With an efficient protocol in hand we sought to elucidate both the full scope of this reaction and which structural features present in the lactam precursors were essential for reasonable triflate thermal stability. Scheme 3 shows the results of our survey. The triflate derived from *N*-tosyl-2-pyrrolidinone (*i.e.* no ethoxy substituent) could be isolated in crude form. However, it was of lower stability than **2a** and could not be satisfactorily purified. Thus, a small stabilizing influence from the α-ethoxy substituent was inferred. When the *N*-tosyl group of **1a** was replaced with a BOC group we were unable to detect any of the desired triflate, indicating the need for a highly electron-withdrawing *N*-substituent. This is in accord with previous reports documenting *N*-benzoyl analogues as unstable.[2]

Increasing ring size also dramatically affected the course of the reaction. Whereas the analogous six-membered piperidinone-derived triflate **2b**[3c] was formed in excellent yield (a fairly stable crystalline solid) under

(6) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

Scheme 3



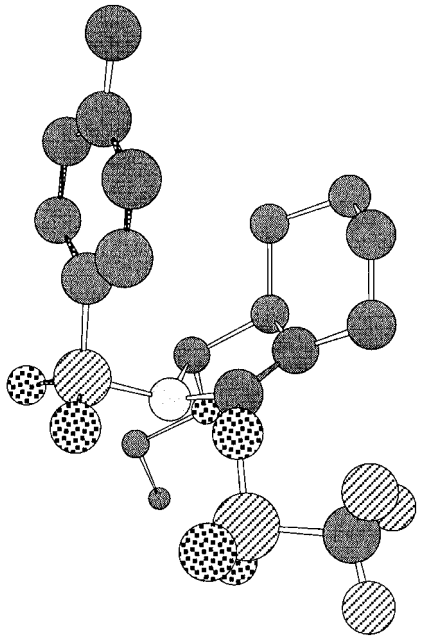


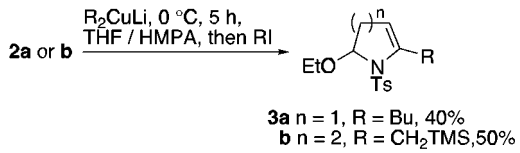
Figure 1. ORTEP diagram of **2e** (H atoms omitted for clarity).

our standard conditions, the seven-membered analogue, despite numerous attempts, remains elusive. It was pleasing to find that increasing steric congestion on the pyrrolidinone ring did not have a deleterious effect on the efficiency of triflate formation. Triflates **2c**−**e** were all isolated in excellent yields from a minor modification of our standard procedure (the enolates of the corresponding lactams **1c**−**e** were best formed in inverse manner, adding the lactam to the KHMDS). Surprisingly, **2c** was of similar stability to **2a** despite the fact that ethanol elimination was now an impossibility. Triflates **2d** and **2e** were somewhat more stable. Triflate **2e** gave colorless needles after recrystallization, allowing an X-ray crystal structure to be determined. This unambiguously proved the relative stereochemistry between the ethoxy substituent and the cyclohexane ring. The structure (showing the *trans* relationship between these substituents) is shown in Figure 1.

From this series of experiments it became apparent that for a five- or six-membered lactam-derived enol triflate to be of useful thermal stability, a highly electron-withdrawing *N*-substituent was essential. In the less stable five-membered series, an α-ethoxy group gave useful additional stability, as did ring substitution at the 3-position of the pyrrolidinone ring.

We next focused on developing productive methodology for the replacement of the triflate moiety with alternative

Scheme 4



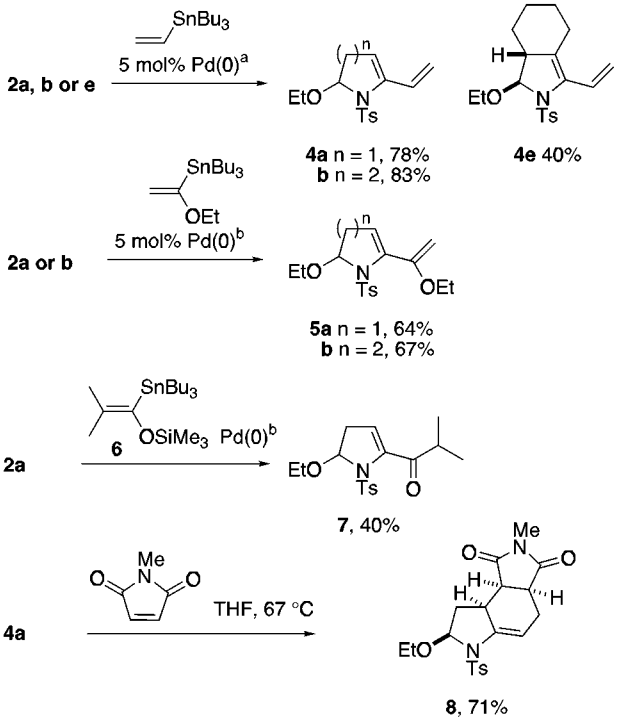
3a n = 1, R = Bu, 40%
b n = 2, R = CH_2TMS,50%

functional groups. In view of the sometimes limited thermal stability of these enol triflates, such transformations needed to occur under mild conditions. First we examined reaction of triflates **2a** and **2b** with lithium diorganocuprates (Scheme 4).[2c,7a] Unfortunately the desired couplings proved surprisingly difficult. Cuprates such as Bu_2CuLi and $Bu_2Cu(CN)Li_2$, previously successful with other enol triflate classes,[1] gave mainly protonation products (ROTf → RH) with **2a** in THF, even when BuI was added to quench any vinyl cuprate intermediates.[2c] Eventually it was found that the addition of HMPA as a cosolvent was necessary. Best results were achieved with an excess of Bu_2CuLi at 0 °C in THF/HMPA, followed by quenching with BuI, allowing a moderate yield of **3a** to be obtained. Reaction of **2b** with $(Me_3SiCH_2)_2CuLi$ allowed the useful synthesis of allylsilane **3b**, a transformation previously only achieved in reasonable yield by the use of aluminum reagents.[7b] Silane **3b** is expected to have interesting further reactivity as it contains both a nucleophilic (the allylsilane) and an electrophilic (the α-ethoxysulfonamide) site in the same molecule.

Palladium-catalyzed reactions of ketone-derived enol triflates with nucleophiles are now well established.[1] Relatively little is known regarding similar transformations of lactam-derived examples.[2c] For example, Comins reported the efficient Stille coupling[8] of a piperidinone derived triflate with vinyltributylstannane.[2c] Unfortunately the elevated temperatures used (refluxing THF) made this method unsuitable for our systems. We were heartened by an elegant mechanistic investigation reported by Farina which showed that the use of tetrakis(triphenylarsine)palladium (formed *in situ* from Pd_2dba_3/Ph_3As) in NMP accelerated similar reactions sufficiently for them to take place at rt.[8c] Scheme 5 shows the excellent yields obtained by employing this procedure for the couplings of lactam-derived triflates **2a** and **2b** with vinyltributyltin. Since our original disclosure of this reaction (with **2a**),[3a] we have found that $Pd(MeCN)_2Cl_2$ is a better precursor for the required $Pd(AsPh_3)_4$ catalyst than Pd_2dba_3.[9] Aside from cost advantages, the yields remained constant, and the difficult chromatographic separation of dba from the products **4a**,**b** (both have similar R_f's on TLC) was now avoided. Triflate **2e** proved surprisingly reluctant to undergo the same cross-coupling reaction. Raising the reaction temperature to 50 °C gave the optimum yield of **4e**. It was suspected that the increased steric congestion around the triflate moiety was inhibiting the desired transformation.

Couplings with (α-ethoxyvinyl)tributyltin[10] are also shown in Scheme 5. Previously the enol ether product

Scheme 5[a]



[a] Conditions: (a) $Pd(MeCN)_2Cl_2$ / Ph_3As, NMP, rt (50 °C for **2e**). (b) $Pd(PPh_3)_2Cl_2$, DMF, 40 °C.

5a was directly hydrolyzed to the corresponding ketone.[3a] However, the sensitive 1,3-dienes could be isolated in good yields. The reaction was also extended to include the more hindered stannane **6**.[11] Cross coupling, the first with an enol triflate, occurred in reasonable yield allowing the one pot incorporation of the isobutanone unit affording **7**. Unfortunately, **2a**, **6**, and **7** were all of similar polarity making isolation of the product difficult and hence lowering the overall yield. One obvious use of such 1,3-dienes is as substrates in Diels−Alder reactions. Indeed, diene **4a** reacted smoothly with *N*-methylmaleimide, to afford the expected endo-cycloadduct **8** in excellent yield as a single diastereomer. Assignment of the relative stereochemistry in **8** proved difficult. Eventually 2D NOESY NMR experiments revealed strong correlations between each of the three adjacent ring-junction protons, showing them to be on the same face of the molecule. The pseudo-equatorial ethoxy group was tentatively assigned from a much weaker correlation between the axial proton on the same carbon with the ring-junction proton three carbon atoms away.

The palladium-catalyzed methoxycarbonylation of enol triflates using CO and MeOH is a very mild elaboration method.[2c,3,12] Replacement of the *in situ* formed $Pd(PPh_3)_4$ catalyst, described in the original publication by Cacchi,[12] with *in situ* formed $Pd(AsPh_3)_4$ offered similar advantages in rate and efficiency with our lactam-derived triflates (**2a**,**b**) as was found for the aforementioned Stille couplings (Scheme 6). Full details of this transformation (to **9b**) have been previously disclosed.[3c] Herein we show, in common with ketone-derived triflates,[1] that phenols and anilines also successfully took part in the reaction,

(7) (a) McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313, see also ref 1. (b) Saulnier, M. G.; Kadow, J. F.; Tun, M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320.

(8) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (c) Farina, V.; Krishman, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

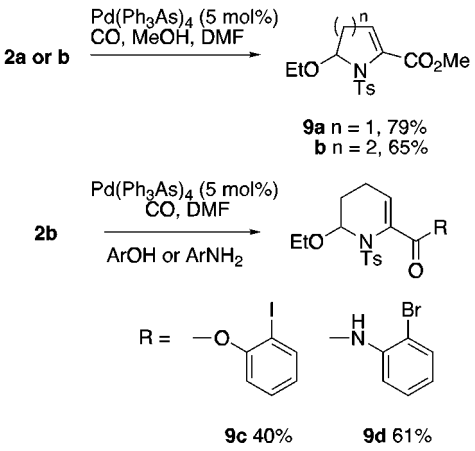
(9) For use of $Pd(PhCN)_2Cl_2$ as a precursor to $Pd(AsPh_3)_4$ see: Phillips, D.; O'Neill, B. T. *Tetrahedron Lett.* **1990**, *31*, 3291.

(10) Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114.

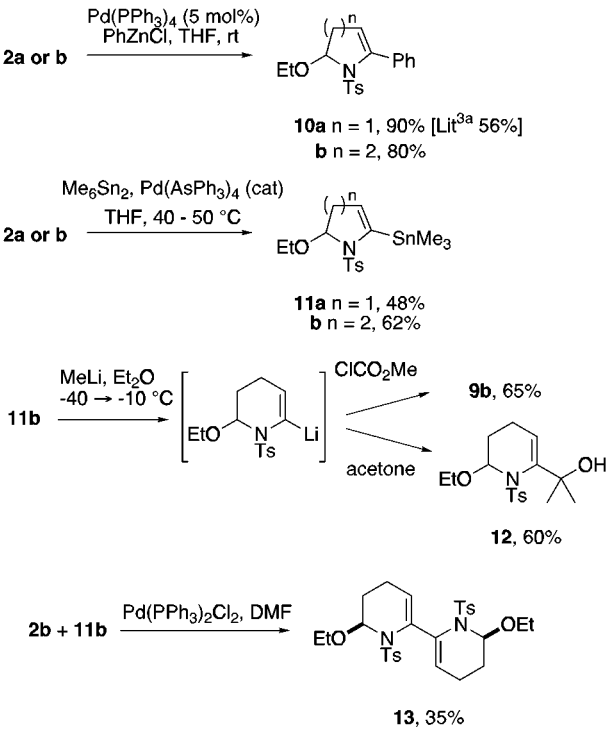
(11) Velhac, J.-B.; Pereyre, M.; Shin, H. *Organometallics* **1991**, *10*, 3007.

(12) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

Scheme 6



Scheme 7



allowing aromatic esters and amides **9c** and **9d** to be prepared. Aromatic halides were tolerated in the reaction, illustrating the known higher reactivity of enol triflates toward oxidative addition to Pd(0) catalysts than aryl bromides.[1] Remarkably, the reaction was also successful in the presence of an aryl iodide, allowing isolation of **9c** in reasonable yield.

We have previously been able to arylate triflate **2a** by palladium-catalyzed coupling with phenyltributyltin.[3a] Unfortunately the reaction was sluggish and did not reach completion even after 2 days. We have since found analogous palladium-catalyzed coupling with phenylzinc chloride (prepared *in situ* from PhLi and $ZnCl_2$)[13] to be far superior (Scheme 7). The reactions of triflates **2a** and **2b** were complete in only 30−90 min at rt and afforded the desired arylated products **10** in excellent yields. Efforts to include alkylzinc halides as coupling partners were unsuccessful, the reactions affording only protonation products (ROTf → RH). Others have reported such problems which are consistent with a β-hydride elimination step in the catalytic cycle.[14]

Whereas vinyl triflates are (usually) formally considered as electrophiles, conversion to the corresponding vinylstannanes results in an umpolung. Such stannanes are easily converted to vinyllithiums *via* transmetalation, and either species now formally reacts as a nucleophile. Palladium-catalyzed coupling with Me_6Sn_2 has been shown to be an effective protocol for the conversion of both ketone-[15a] and lactone-[15b] derived vinyl triflates to the corresponding stannanes. As expected, elevated temperatures were required to effect this transformation (refluxing THF, 12 h), and so we sought milder conditions for use with our more sensitive triflates **2a** and **2b**. Scheme 7 shows the successful preparation of vinylstannanes **11a** and **11b**. The strict use of $Pd(AsPh_3)_4$ in THF at 40 °C (**2a**) or 50 °C (**2b**) followed by workup as soon as TLC indicated complete reaction (3−5 h) allowed reasonable yields to be obtained. Surprisingly, all other catalyst/additive/solvent combinations effected the preferential replacement of the triflate moiety with a methyl rather than the desired trimethylstannyl group, independent of the purity of the Me_6Sn_2 used. Indeed, stannanes **11** were slowly converted to the unwanted methylated product under our optimized conditions if longer reaction times were used. Scheme 7 also shows some recent results obtained using stannane **11b**. Transmetalation to the corresponding lithium derivative using MeLi followed by further reaction with electrophiles was investigated. Initial experiments used methyl chloroformate as the electrophile. This afforded the known ester **9b** (more directly obtained from Pd-catalyzed methoxycarbonylation, Scheme 6) and hence gave a rapid indication of the efficiency of Sn → Li transmetalation. The use of THF gave poor results (no transmetalation at −78 and only protonation at 0 °C). However, upon changing to Et_2O a good yield of the desired ester was obtained. Reaction with acetone was also successful, and we hope that further variation of the electrophile component will allow access to a wide range of other novel enamides. The direct metalation of enamides has previously been used to prepare similar vinyllithiums,[15c,d] although the efficiency of this process can be limited.[15d] As structurally more complex lactam-derived enol triflates become available, we predict our methodology to offer chemoselectivity advantages in the preparation of such vinyllithiums as has been shown with lactone-derived systems.[15b]

With both stannane **11b** and the corresponding triflate **2b** in hand, we were in a position to attempt a dimerization of the enamide nucleus *via* a new Stille coupling, to hopefully form an interesting new 2,3-diamino-1,3-diene derivative **13** (Scheme 7). Ley has shown the 2,3-oxygen analogues to be powerful desymmetrization reagents.[16a,b] The nitrogen variants have so far received little attention. Recently, a similar reaction sequence

(13) McCague, R. *Tetrahedron Lett.* **1987**, *28*, 701.

(14) Orsini, F.; Pelizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375.

(15) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277. (b) Barber, C.; Jarowicki, K.; Kocienski, P. *Synlett* **1991**, 197. (c) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109 and references therein. (d) Paquette, L. A.; Tae, J. *Tetrahedron Lett.* **1997**, *38*, 3151.

(16) (a) Boons, G.-J.; Entwhistle, D. A.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1990**, *31*, 3291. (b) Genicot, C.; Ley, S. V. *Synthesis* **1994**, 1275. (c) Beddoes, R. L.; Cheeseright, T.; Wang, J.; Quayle, P. *Tetrahedron Lett.* **1995**, *36*, 283.

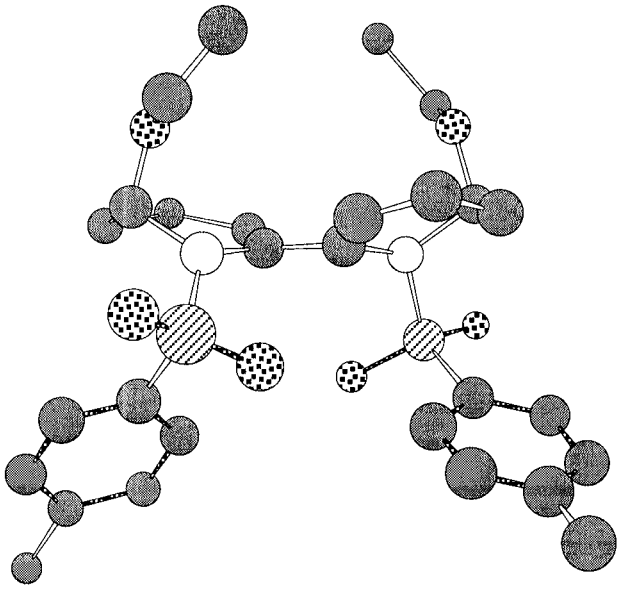
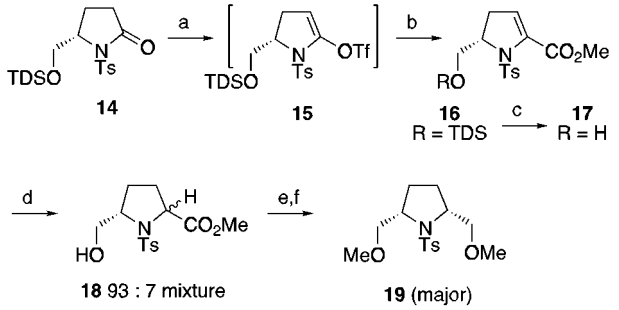


Figure 2. ORTEP diagram of **13** (H atoms omitted for clarity).

was reported using indole "monomers",[17a] and the dimer product was shown to have interesting further reactivity for natural product synthesis.[17b] The Stille coupling indeed proceeded in moderate (unoptimized) yield affording **13** as beautiful white crystals. Attempts to dimerize the stannane itself using alternative copper-mediated protocols[16] gave inferior results. As both **11b** and **2b** contain a stereocenter, dimer **13** was expected to be a mixture of diastereomers. Analysis of the ^{1}H NMR spectrum gave no insight as peaks were broadened due to restricted rotation. The ^{13}C NMR spectrum, to our great surprise, showed **13** to be a single diastereomer. We tentatively suggest this to be a self-organization effect taking place on the palladium catalyst, but in view of the moderate reaction yield, it is not yet possible to state this with certainty. Fortuitously, the crystals obtained were of sufficient quality for an X-ray structure determination. Figure 2 shows **13** to be the centro-symmetric dimer (2*R**2′*R**) with both ethoxy groups on the same face of the molecule. Work is in progress to increase the yield and expand the range of such dimer compounds to enable a study of their further reactivity.

All of the results disclosed above used racemic substrates, and we were keen to broaden the scope of our procedures to include enantiopure variants. To this end we prepared **14** (Scheme 8) by tosylation of the known *N*-H analogue, itself derived from (*S*)-pyroglutamic acid.[18] As expected, enol triflate formation proceeded in almost quantitative yield under our standard conditions. The triflate **15** was of limited thermal stability and so, in view of the more valuable starting material, was immediately subjected to palladium-catalyzed methoxycarbonylation without full characterization. The pleasing isolation of enantiopure ester **16** in 53% overall yield confirmed that these reactions had occurred with similarly high efficiency as found for the racemic analogues previously discussed.

Scheme 8[a]



[a] (TDS = (Me_2CHMe_2C)Me_2Si) Conditions: (a) KHMDS (1.25 equiv), -78 °C, THF; then *N*-(5-chloro- 2-pyridyl)triflimide (1.25 equiv). (b) $Pd(AsPh_3)_4$ (cat), CO, MeOH, DMF 53% (2 steps). (c) TBAF, THF 76%. (d) H_2, Pd / C, MeOH 96%. (e) DIBAL, THF 63%. (f) NaH, THF, 0 °C then MeI 90%.

With quantities of **16** available, we decided to investigate hydrogenation of the enamide double bond with a view to synthesizing an enantiopure analogue of the amino acid proline. It was hoped that the pendent hydroxymethyl group would direct reduction of the double bond, either by purely sterics, or by direct complexation of the hydrogenation catalyst. Deprotection of the silyl protecting group under standard conditions gave **17**, the desired precursor for our key step. After stirring **17** under an atmosphere of H_2 (1 atm) with a Pd/C catalyst, we isolated the reduced product **18** in virtually quantitative yield as a 93:7 mixture of inseparable diastereomers, indicating the hydrogenation was occurring with excellent levels of facial selectivity. Conversion to the 2,5-bis(methoxymethyl)-derivative seemed to be the easiest way to prove the major stereochemical pathway for this hydrogenation, as Somfai had reported full data for the *trans* isomer, prepared by a different route.[4b] Attempted reduction of ester **18** using $LiAlH_4$ resulted in decomposition. The use of DIBAL-H circumvented these problems, affording a diol product. Methylation of the two hydroxyl groups gave the desired derivative **19** as a separable 93:7 mixture of diastereomers, indicating no racemization had taken place during the hydride reduction step. The minor diastereomer of our mixture **19** had identical ^{1}H NMR data to that reported by Somfai, with the spectrum of the major isomer being markedly different. Thus, the major isomer was of 2,5-*cis* stereochemistry resulting from a hydrogenation reaction directed not by Pd-complexation to the OH, but merely by sterics. Lack of optical activity confirmed the structure of the major meso-isomer. At this time we became aware of the work of Baldwin et al. describing the hydroxyl-directed heterogeneous hydrogenation of a conceptually similar pyrrolidine-derived trisubstituted enamide.[19] The reason for their reversal in selectivity (sterics vs complexation) is not understood. We note that Baldwin does not report results with a protected OH derivative to confirm the hydrogenation in his system is indeed directed by the hydroxyl group rather than by other ring substituents. Nevertheless, the high selectivity's make our method

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(18) Dijkink, J.; Eriksen, K.; Goubitz, K.; van Zanden, M. N. A.; Hiemstra, H. *Tetrahedron: Asymmetry* **1996**, *7*, 515 and references therein.

(19) (a) Baldwin, J. E.; Fryer, A. M.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1996**, *37*, 6923. (b) Baldwin, J. E.; Fryer, A. M.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5273.

useful for the preparation of unnatural proline derivatives. These results compliment those of Comins,[2c] who has previously used chiral Ru-catalysts to control enantioselective hydrogenations of similar (achiral) enamides obtained from lactam-derived enol triflates.

In conclusion, since the original work on lactam-derived enol triflates was disclosed we have significantly broadened both the range of these compounds available to the organic chemist and the understanding of the factors affecting their stability. The variety of successful palladium-catalyzed couplings occurring under mild conditions have proved invaluable for converting these sometimes sensitive triflates into novel enamide products, almost all of which contain functionality useful for further applications. Finally, our protocols now include enantiopure analogues for the first time.

Experimental Section

General. As previously described.[3c]

General Procedure 1: Preparation of Starting Lactams 1 *via* *N*-Tosylation. To a stirred solution of the *N*-H lactam[5] (7.0 mmol) in THF (50 mL) at −78 °C was added dropwise ^{n}BuLi (5.5 mL of a 1.6 M solution in hexanes, 8.75 mmol, 1.25 equiv), and the solution was stirred for 1 h. A solution of recrystallized *p*-toluenesulfonyl chloride (1.67 g, 8.75 mmol, 1.25 equiv) in the minimum amount of THF was added dropwise, and the reaction mixture was slowly warmed to rt. When TLC indicated no further progress (3−18 h), the solvent was removed *in vacuo*, and the residue was subjected to column chromatography and/or recrystallization to afford the pure *N*-tosyl lactam **1**.

5-Ethoxy-1-*p*-toluenesulfonyl-2-pyrrolidinone (1a). Column chromatography (1:2 ethyl acetate/light petroleum ether, on SiO_2) followed by recrystallization gave **1a** (80%) as white crystals, mp 152−153 °C from ethyl acetate: IR 1740 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.96 (2 H, d, J = 8.6), 7.32 (2 H, d, J = 8.6), 5.63 (1 H, t, J = 5.7), 3.76 (1 H, dq, J = 9.0, 7.0), 3.60 (1 H, dq, J = 9.0, 7.0), 2.64 (1 H, ddd, J = 17.7, 11.0, 8.7), 2.42 (3 H, s), 2.35 (1 H, dd, J = 17.7, 9.9), 2.15 (1 H, m), 2.04 (1 H, m), 1.22 (3 H, t, J = 7.0); ^{13}C NMR (50 MHz) δ 173.1 (s), 145.0 (s), 135.7 (s), 129.3 (2d), 128.7 (2d), 89.3 (d), 64.3 (t), 29.9 (t), 26.6 (t), 21.7 (q), 15.1 (q); MS (FAB) 284 $(MH)^+$ (69); HRMS calcd for $C_{13}H_{18}NO_4S$ 284.0947, found 284.0967. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 55.10; H, 6.09; N, 4.90.

6-Ethoxy-1-*p*-toluenesulfonyl-2-piperidinone (1b). Column chromatography (1:5 → 1:3 ethyl acetate/light petroleum ether, on SiO_2) followed by recrystallization gave **1b** (48%) as white crystals, mp 123−125 °C from ethyl acetate/light petroleum ether: IR 1703 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.95 (2 H, d, J = 8.4), 7.30 (2 H, d, J = 8.2), 5.74 (1 H, t, J = 2.7), 3.78 (1 H, dq, J = 9.0, 7.0), 3.63 (1 H, dq, J = 9.0, 7.0), 2.55 (1 H, dddd, J = 17.4, 6.6, 3.0, 1.2), 2.42 (3 H, s), 2.35 (1 H, ddd, J = 17.2, 10.0, 7.2), 2.20 (1 H, m), 2.05 (1 H, m), 1.73 (2 H, m), 1.27 (3 H, t, J = 7.0); ^{13}C NMR (50 MHz) δ 170.4 (s), 144.7 (s), 136.6 (s), 129.2 (4d), 84.7 (d), 64.3 (t), 33.6 (t), 28.0 (t), 21.8 (q), 15.3 (q), 15.1 (t); MS 252 $(M - OEt)^+$ (35); HRMS calcd for $C_{12}H_{14}NO_3S$ 252.0694, found 252.0689. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.55; H, 6.39; N, 4.59.

4,4-Dimethyl-5-ethoxy-1-*p*-toluenesulfonyl-2-pyrrolidinone (1c). Starting *N*-H lactam was a 3:1 mixture of 5- and 2-ethoxy regioisomers.[5] Column chromatography (1:5 → 1:3 ethyl acetate/light petroleum ether, on SiO_2) (combined yield 78%) followed by slow fractional recrystallization (−30 °C) gave the desired single regioisomer **1c** (ca. 40%) as white crystals, mp 80−82 °C from ethyl acetate/light petroleum ether: IR 1748 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.95 (2 H, d, J = 8.3), 7.33 (2 H, d, J = 8.3), 5.05 (1 H, s), 3.99 (1 H, dq, J = 9.0, 7.1), 3.72 (1 H, dq, J = 9.0, 7.1), 2.55 (1 H, d, J = 16.9), 2.44 (3 H, s), 2.01 (1 H, d, J = 16.9), 1.25 (3 H, t, J = 7.0), 1.15 (3 H, s), 1.03 (3 H, s); ^{13}C NMR (100 MHz) δ 172.7 (s), 144.9 (s), 135.4 (s), 129.3 (2d), 128.4 (2d), 96.9 (d), 66.5 (t), 44.1 (s), 38.8 (t), 26.2 (q), 21.7 (q), 21.52 (q), 15.01 (q); MS (FAB) 334 $(MNa)^+$ (65), 312 $(MH)^+$ (10); HRMS calcd for $C_{15}H_{22}NO_4S$ 312.1270, found 312.1247. Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 58.00; H, 6.92; N, 4.56.

2-*p*-Toluenesulfonyl-3*β*-ethoxy-3α,3a*β*,4,5,6,7,7a*β*-hexahydroisoindol-1-one (1e). Recrystallization gave **1e** (70%) as white crystals, mp 98−102 °C from diethyl ether: IR 1700 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.94 (2 H, d, J = 8.2), 7.30 (2 H, d, J = 8.2), 5.07 (1 H, s), 3.77 (1 H, dq, J = 9.2, 7.1), 3.63 (1 H, dq, J = 9.2, 7.1), 2.87 (1 H, t, J = 6.0), 2.41 (3 H, s), 2.30 (1 H, m), 2.00 (1 H, brd, J = 14.0), 1.81 (1 H, m), 1.52 (1 H, brd, J = 13.1), 1.44 (1 H, brd, J = 13.3), 1.32 (1 H, m), 1.19 (3 H, t, J = 7.0), 1.10 (1 H, m), 0.83 (2 H, m); ^{13}C NMR (100 MHz) δ 174.7 (s), 144.9 (s), 135.6 (s), 129.3 (2d), 128.5 (2d), 92.8 (d), 64.8 (t), 40.1 (d), 39.9 (d), 25.9 (t), 23.1 (t), 22.4 (t), 22.1 (t), 21.6 (q), 15.1 (q); MS (FAB) 338 $(MH)^+$ (22); HRMS calcd for $C_{17}H_{24}NO_4S$ 338.1426, found 338.1430. Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15. Found: C, 60.05; H, 6.85; N, 4.09.

3-(2-Bromobenzyl)-5-ethoxy-1-*p*-toluenesulfonyl-2-pyrrolidinone (1d). To a stirred solution of 5-ethoxy-1-(*tert*-butyldimethylsilyl)-2-pyrrolidinone[5] (0.500 g, 2.06 mmol) in THF (5 mL) at −78 °C was added dropwise LiHMDS (2.6 mL of a 1 M solution in THF, 2.58 mmol, 1.25 equiv), and the solution was stirred for 1 h. A solution of 2-bromobenzyl bromide (0.644 g, 2.58 mmol, 1.25 equiv) in the minimum amount of THF (1.5 mL) was added dropwise, and the reaction was stirred at −78 °C for 4 h and then slowly warmed to rt. The solvent was removed *in vacuo*, the residue dissolved in MeOH (3 mL), and KF (2 mL of a 2 M solution in MeOH) added. After stirring for 15 h, the MeOH was removed *in vacuo*, and the residue was dissolved in ethyl acetate and filtered through Celite. Solvent removal *in vacuo* gave a dark red oil. Column chromatography (1:5 → 1:3 ethyl acetate/light petroleum ether (to remove byproducts) → 1:1 (for product), on SiO_2) gave the *N*-H analogue of the title compound as a yellow oil (0.316 g, 51%). This was tosylated using the general procedure 1, to afford, after chromatography (1:5 → 1:3 ethyl acetate/light petroleum ether, on SiO_2), **1d** as a pale yellow oil which partially crystallized on standing for a period of weeks (0.347 g, 73%) (3:1 inseparable mixture of diastereomers by ^{1}H NMR): IR 1738 cm^{-1}; ^{1}H NMR (400 MHz) δ (major only) 7.96 (2 H, d, J = 8.3), 7.51 (1 H, dd, J = 7.9, 1.4), 7.32 (2 H, d, J = 8.4), 7.16 (2 H, m), 7.07 (1 H, td, J = 8.0, 1.9), 5.54 (1 H, d, J = 5.2), 3.73 (1 H, dq, J = 9.2, 7.0), 3.58 (1 H, dq, J = 9.1, 7.0), 3.34 (1 H, dd, J = 14.0, 4.8), 3.14 (1 H, m), 2.72 (1 H, dd, J = 14.0, 9.2), 2.44 (3 H, s), 2.06 (1 H, dd, J = 13.0, 7.7), 1.89 (1 H, ddd, J = 13.0, 11.4, 5.2), 1.20 (3 H, t, J = 7.0); ^{13}C NMR (100 MHz) δ 173.8 (s), 144.8 (s), 137.4 (s), 135.3 (s), 132.6 (d), 130.8 (d), 129.0 (2d), 128.3 (2d), 128.1 (d), 127.4 (d), 124.2 (s), 87.1 (d), 64.2 (t), 40.7 (d), 35.3 (t), 32.6 (t), 21.3 (q), 14.7 (q); MS (FAB) 454 $(MH^{81}Br)^+$ (100), 452 $(MH^{79}Br)^+$ (100); HRMS calcd for $C_{20}H_{23}NO_4SBr$ 454.0512 (^{81}Br) and 452.0531 (^{79}Br), found 454.0502 and 452.0541, respectively.

5-Ethoxy-1-*p*-toluenesulfonyl-2-((trifluoromethanesulfonyl)oxy)-2,3-dihydropyrrole (2a). Prepared (from **1a**) by an identical route to that previously described for **2b**.[3c] Column chromatography (1:4 → 1:1 CH_2Cl_2/light petroleum ether, on SiO_2), afforded **2a** as a colorless oil (97%). Data as previously reported.[3a]

6-Ethoxy-1-*p*-toluenesulfonyl-2-((trifluoromethanesulfonyl)oxy)-1,4,5,6-tetrahydropyridine {2b}. Full details of the preparation and characterization of **2b** (96%, white crystals, mp 67−70 °C) (from **1b**) have been previously reported.[3c]

General Procedure 2: Preparation of Ring Substituted Triflates 2c−e by Inverse Addition. To a stirred solution of KHMDS (2.5 mL of a 0.5 M solution in toluene, 1.25 mmol, 1.25 equiv) in THF (6 mL) at −78 °C was added the *N*-tosyl lactam **1** (1.0 mmol) in THF (2 mL), and the pale yellow solution was stirred for 1.5 h. A solution of *N*-(5-chloro-2-pyridyl)triflimide (0.491 g, 1.25 mmol, 1.25 equiv) in THF (1 mL) was added rapidly in one portion. After stirring for 1 h, the reaction was warmed to ca. 0 °C. Saturated ammonium chloride solution (4 mL) followed by CH_2Cl_2 (10 mL) and water (4 mL) were added, and the organic layer was separated. The

aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL), the combined organic solutions were dried, and the solvent was removed *in vacuo*. Column chromatography (1:5 → 1:1 CH_2Cl_2/light petroleum ether, on SiO_2) afforded the triflate **2**.

4,4-Dimethyl-5-ethoxy-1-*p*-toluenesulfonyl-2-((trifluoromethanesulfonyl)oxy)-2,3-dihydropyrrole (2c). General procedure 2 afforded **2c** as a white solid (90%). This triflate proved fairly sensitive at rt in neat form, and so the final 5 mL of solvents remaining after chromatography were routinely removed at 0 °C: IR 1661 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.78 (2 H, d, J = 8.3), 7.35 (2 H, d, J = 8.2), 5.00 (1 H, s), 4.89 (1 H, s), 3.93 (1 H, dq, J = 9.3, 7.1), 3.61 (1 H, dq, J = 9.4, 7.1), 2.45 (3 H, s), 1.22 (3 H, t, J = 7.0), 1.10 (3 H, s), 0.65 (3 H, s); ^{13}C NMR (50 MHz, C_6D_6) δ 144.6 (s), 138.9 (s), 135.0 (s), 129.6 (2d), 127.6 (2d), 118.2 (s; q J = 322), 110.8 (d), 97.8 (d), 64.1 (t), 43.7 (s), 26.3 (q), 21.3 (q), 20.2 (q), 14.4 (q); MS 443 M^+ (36); HRMS calcd for $C_{16}H_{20}NO_6F_3S_2$ 443.0684, found 443.0704.

3-(2-Bromobenzyl)-5-ethoxy-1-*p*-toluenesulfonyl-2-((trifluoromethanesulfonyl)oxy)-2,3-dihydropyrrole (2d). General procedure 2 afforded **2d** as a colorless oil (65%): IR 1617 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.51 (2 H, d, J = 8.3), 7.12 (1 H, dd, J = 8.0, 1.2), 6.64 (1 H, td, J = 7.5, 1.2), 6.55 (2 H, d, J = 8.3), 6.51 (1 H, td, J = 7.6, 1.6), 6.43 (1 H, dd, J = 7.6, 1.6), 5.02 (1 H, d, J = 5.8), 4.15 (1 H, dq, J = 9.6, 7.1), 3.62 (1 H, dq, J = 9.6, 7.1), 3.60 (1 H, d, J = 14.6), 3.17 (1 H, d, J = 15.4), 1.82 (1 H, d, J = 17.2), 1.79 (3 H, s), 1.49 (1 H, dd, J = 17.1, 6.0), 1.17 (3 H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 144.9 (s), 136.8 (s), 135.0 (s), 133.5 (d), 131.6 (d), 130.6 (2d), 129.1 (2d), 129.0 (s), 128.5 (d), 128.1 (d), 125.3 (s), 119.9 (s; q, J = 319), 119.8 (s), 91.4 (d), 64.1 (t), 37.4 (t), 33.4 (t), 21.8 (q), 15.5 (q); MS (FAB) 585 $(M^{81}Br)^+$ (39), 583 $(M^{79}Br)^+$ (34); HRMS calcd for $C_{21}H_{21}NO_6BrF_3S_2$ 584.9927 (^{81}Br) and 582.9946 (^{79}Br), found 584.9935 and 582.9929, respectively.

Trifluoromethanesulfonic Acid 2-*p*-Toluenesulfonyl-3β-ethoxy-3α,3aβ,4,5,6,7-hexahydroisoindol-1-yl Ester (2e). General procedure 2 afforded **2e** as colorless needles (90%), mp 81−84 °C from pentane: IR 2940, 1430 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.62 (2 H, d, J = 8.3), 6.66 (2 H, d, J = 8.0), 4.86 (1 H, s), 4.22 (1 H, dq, J = 9.7, 7.0), 3.74 (1 H, dq, J = 9.7, 7.1), 2.26 (1 H, d, J = 13.4), 2.15 (1 H, dd, J = 12.9, 5.1), 1.77 (3 H, s), 1.56 (1 H, dt, J = 13.0, 4.9), 1.19 (3 H, t, J = 7.0), 1.14 (2 H, m), 0.96 (1 H, d, J = 13.7), 0.61 (1 H, qt, J = 13.3, 3.3), 0.41 (1 H, m), −0.56 (1 H, qd, J = 12.4, 3.5); ^{13}C NMR (100 MHz, C_6D_6) δ 145.3 (s), 134.6 (s), 131.8 (s), 130.4 (2d), 129.4 (2d), 123.0 (s), 119.9 (s; q J = 320), 95.2 (d), 64.3 (t), 50.3 (d), 30.3 (t), 27.1 (t), 25.4 (t), 24.9 (t), 21.7 (q), 15.7 (q); MS (FAB) 469 M^+ (72); HRMS calcd for $C_{18}H_{23}NO_6F_3S_2$ 470.0919, found 470.0956. Anal. Calcd for $C_{18}H_{22}NO_6S_2F_3$: C, 46.05; H, 4.72; N, 2.98. Found: C, 46.26; H, 5.06; N, 3.06. An X-ray crystal structure was obtained: monoclinic, $P2_1/n$, a = 9.1540(8), b = 13.2138(9), c = 18.493(10) Å, β = 103.35(1) °, v = 2176(1) Å,[3] Z = 4, D_x = 1.43 g cm^{-1}, λ (Cu Kα) = 1.5418 Å, μ (Cu Kα) = 27.23 cm^{-1}, F(000) = 976, −25 °C. Final R = 0.047 for 3500 observed reflections. Full details are given in Supporting Information.

2-Butyl-5-ethoxy-1-*p*-toluenesulfonyl-2,3-dihydropyrrole (3a). To a suspension of CuI (0.044 g, 0.253 mmol, 2.7 equiv) in THF (1.5 mL) at −78 °C was added ^{n}BuLi (0.29 mL of a 1.6 M solution in hexanes, 0.47 mmol), and the solution was stirred and slowly warmed until dissolution of the copper salt (ca. 5 min). After recooling to −78 °C, HMPA (150 μL, 2.16 mmol) was added. After 5 min, a solution of triflate **2a** (0.039 g, 0.093 mmol) in THF (0.5 mL) was added, and after 5 min the solution was warmed to 0 °C. After 5 h, butyl iodide (37 μL, 0.322 mmol) was added and the solution warmed to rt over 2 h. Saturated aqueous ammonium chloride (2 mL) was added, and the solution was stirred until dissolution of the copper salts (ca. 10 min). The aqueous layer was extracted with ethyl acetate (3 × 6 mL), the combined organics were washed with water (2 × 3 mL) and brine (3 mL) and dried, and the solvent was removed *in vacuo*. Column chromatography (1:10 ethyl acetate/light petroleum ether, on SiO_2) gave **3a** as a colorless oil (0.012 g, 40%): ^1H NMR (400 MHz) δ 7.62 (2 H, d, J = 8.3), 7.28 (2 H, d, J = 8.3), 5.37 (1 H, d, J = 4.6), 5.04 (1 H, brs), 3.96 (1 H, dq, J = 9.6, 7.1), 3.64 (1 H, dq, J = 9.6, 7.1), 2.45 (1 H, m), 2.41 (3 H, s), 2.37 (1 H, m), 2.06 (2 H, m), 1.60−1.24 (4 H, m), 1.21 (3 H, t, J = 7.1), 0.91 (3 H, t, J = 7.2).

6-Ethoxy-1-*p*-toluenesulfonyl-2-((trimethylsilyl)methyl)-1,4,5,6-tetrahydropyridine (3b). To a suspension of CuI (0.044 g, 0.253 mmol, 2.7 equiv) in THF (1.5 mL) at −78 °C was added ((trimethylsilyl)methyl)lithium (0.47 mL of a 1 M solution in pentane, 0.47 mmol), and the solution was stirred and slowly warmed until dissolution of the copper salt (ca. 5 min). After recooling to −78 °C, HMPA (150 μL, 2.16 mmol) was added. After 5 min, a solution of triflate **2b** (0.040 g, 0.093 mmol) in THF (0.5 mL) was added, and after 5 min the solution was warmed to 0 °C. After 5 h, (iodomethyl)trimethylsilane (50 μL, 0.322 mmol) was added and the solution warmed to rt over 12 h. Saturated aqueous ammonium chloride (2 mL) was added, and the solution stirred until dissolution of the copper salts (ca. 10 min). The aqueous layer was extracted with ethyl acetate (3 × 6 mL), the combined organics were washed with water (2 × 3 mL) and brine (3 mL) and dried, and the solvent removed *in vacuo*. Column chromatography (1:10 ethyl acetate/light petroleum ether, on SiO_2) gave **3b** as a colorless oil (0.016 g, 50%): IR 3016 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.63 (2 H, d, J = 8.3), 6.74 (2 H, d, J = 8.0), 5.52 (1 H, t, J = 3.0), 4.80 (1 H, t, J = 3.7), 4.07 (1 H, dq, J = 9.7, 7.1), 3.68 (1 H, dq, J = 9.7, 7.0), 3.13 (1 H, dt, J = 14.4, 1.8), 2.12 (1 H, m), 1.84 (3 H, s), 1.63 (1 H, d, J = 14.2), 1.54 (1 H, m), 1.46 (1 H, m), 1.16 (3 H, t, J = 7.0), 0.91 (1 H, m), 0.28 (9 H, s); ^{13}C NMR (100 MHz) δ 143.3 (s), 136.3 (s), 132.7 (s), 129.5 (2d), 127.1 (2d), 112.5 (d), 84.5 (d), 63.6 (t), 26.4 (t), 25.3 (t), 21.5 (q), 18.2 (t), 14.7 (q), −1.2 (3q); MS (FAB) 390 $(MNa)^+$ (50), 368 $(MH)^+$ (68); HRMS calcd for $C_{18}H_{30}NO_3SSi$ 368.1716, found 368.1704.

6-Ethoxy-1-*p*-toluenesulfonyl-2-vinyl-1,4,5,6-tetrahydropyridine (4b). A solution of triflate **2b** (0.100 g, 0.233 mmol), $Pd(MeCN)_2Cl_2$ (3 mg, 11.7 μmol, 0.05 equiv), and triphenylarsine (14 mg, 46.7 μmol, 0.2 equiv) in dry NMP (*N*-methylpyrrolidinone) (2 mL) was stirred at rt for 10 min, and then vinyl tributylstannane (88.5 μL, 0.303 mmol) was added and the solution stirred for 2 h. Saturated aqueous KF (1 mL) was added and the solution stirred for 1 h. Ethyl acetate (5 mL) was added and the solution filtered through Celite to remove the precipitated tin salts (which were washed with further ethyl acetate). The combined organic filtrate was washed with water (5 × 5 mL) and brine (5 mL) and then dried and solvent removed *in vacuo*. Column chromatography (1:20 and then 1:7 ethyl acetate/light petroleum ether, on SiO_2) gave **4b** as a colorless oil (0.059 g, 83%): IR 1597 cm^{-1}; ^1H NMR (400 MHz) δ 7.59 (2 H, d, J = 8.3), 7.27 (2 H, d, J = 8.3), 6.52 (1 H, ddt, J = 17.0, 10.6, 1.0), 5.51 (1 H, t, J = 4.1), 5.37 (1 H, dd, J = 17.0, 1.3), 5.36 (1 H, t, J = 2.8), 5.03 (1 H, dd, J = 10.6, 1.2), 3.82 (1 H, dq, J = 9.9, 7.1), 3.64 (1 H, dq, J = 9.9, 7.0), 2.41 (3 H, s), 2.16 (1 H, m), 1.69 (2 H, m), 1.19 (3 H, t, J = 7.0), 0.96 (1 H, m); ^{13}C NMR (100 MHz) δ 143.5 (s), 136.9 (d), 136.0 (s), 133.9 (s), 129.5 (2d), 127.3 (2d), 116.5 (d), 112.7 (t), 83.3 (d), 63.1 (t), 25.4 (t), 21.5 (q), 18.7 (t), 14.9 (q); MS (FAB) 330 $(MNa)^+$ (70); HRMS calcd for $C_{16}H_{21}NO_3SNa$ 330.1140, found 330.1150. The known[3a] homologue **4a** was also prepared by this route in 78% yield (details not given here). Data as previously reported.

1β-Ethoxy-2-*p*-toluenesulfonyl-3-vinyl-2,4,5,6,7,7aβ-hexahydro-1*H*-isoindole (4e). Using a similar procedure to that described for **4b**, triflate **2e** was coupled with vinyltributylstannane, (50 °C, for 16 h). Column chromatography (1:20 and then 1:10 ethyl acetate/light petroleum ether, on SiO_2) gave **4e** as a colorless oil (40%): IR 1598 cm^{-1}; ^1H NMR (400 MHz) δ 7.63 (2 H, d, J = 8.2), 7.28 (2 H, d, J = 8.2), 6.46 (1 H, dd, J = 17.7, 11.5), 5.40 (1 H, dd, J = 11.2, 1.4), 5.36 (1 H, dd, J = 17.5, 1.4), 4.78 (1 H, s), 4.01 (1 H, dq, J = 9.6, 7.0), 3.65 (1 H, dq, J = 9.6, 7.0), 2.60 (1 H, brd, J = 13.0), 2.41 (3 H, s), 2.19 (1 H, dd, J = 12.8, 4.5), 1.92 (1 H, td, J = 8.7, 4.4), 1.76 (1 H, brd, J = 12.4), 1.57 (2 H, m), 1.22 (3 H, t, J = 6.8), 1.17 (1 H, m), 0.82 (1 H, m), −0.37 (1 H, qd, J = 12.7, 3.6); ^{13}C NMR (100 MHz) δ 143.6 (s), 134.8 (s), 132.5 (s), 129.2 (2d), 129.0 (s), 128.5 (d), 128.0 (2d), 118.0 (t), 94.5 (d), 63.1 (t), 53.3 (d), 30.6 (t), 27.8 (t), 25.9 (t), 25.6 (t), 21.5 (q), 15.0 (q); MS (FAB) 370 $(MNa)^+$ (20), 348 $(MH)^+$ (15); HRMS calcd for $C_{19}H_{26}NO_3S$ 348.1633, found 348.1662.

5-Ethoxy-2-(2-ethoxyvinyl)-1-*p*-toluenesulfonyl-2,3-dihydropyrrole (5a). A solution of triflate **2a** (0.097 g, 0.233 mmol) and $Pd(PPh_3)_2Cl_2$ (8.2 mg, 11.7 μmol, 0.05 equiv) in dry DMF (2 mL) was stirred at rt for 10 min, and then 1-(ethoxyvinyl)tributylstannane (102 μL, 0.303 mmol) was added and the solution stirred at 40 °C for 18 h. Saturated aqueous KF (1 mL) was added and the solution stirred for 1 h. Ethyl acetate (5 mL) was added and the solution filtered through Celite to remove the precipitated tin salts (which were washed with further ethyl acetate). The combined organic filtrate was washed with water (5 × 5 mL) and brine (5 mL) and then dried and solvent removed *in vacuo*. Column chromatography (1:20 and then 1:7 ethyl acetate/light petroleum ether, on SiO_2) gave **5a** as a colorless oil (0.049 g, 62%): IR 1590 cm^{-1}; ^1H NMR (400 MHz) δ 7.60 (2 H, d, J = 8.2), 7.26 (2 H, d, J = 8.0), 5.61 (1 H, dd, J = 2.2, 2.1), 5.39 (1 H, d, J = 5.7), 4.61 (1 H, d, J = 2.2), 4.32 (1 H, d, J = 2.2), 4.00 (1 H, dq, J = 9.8, 7.1), 3.89 (1 H, dq, J = 9.3, 7.0), 3.79 (1 H, dq, J = 9.3, 7.0), 3.67 (1 H, dq, J = 9.8, 7.1), 2.41 (3 H, s), 2.07 (1 H, dd, J = 18.0, 3.6), 1.94 (1 H, ddd, J = 18.0, 5.7, 1.9), 1.32 (3 H, t, J = 7.0), 1.22 (3 H, t, J = 7.1); ^{13}C NMR (100 MHz) δ 154.1 (s), 143.8 (s), 139.2 (s), 134.9 (s), 129.3 (2d), 127.5 (2d), 117.7 (d), 93.0 (d), 87.4 (t), 63.4 (t), 62.88 (t), 35.8 (t), 21.5 (q), 14.9 (q), 14.1 (q), MS 337 M^+ (65); HRMS calcd for $C_{17}H_{23}NO_4S$ 337.1347, found 337.1380.

6-Ethoxy-2-(2-ethoxyvinyl)-1-*p*-toluenesulfonyl-1,4,5,6-tetrahydropyridine (5b). A similar protocol transformed triflate **2b** into **5b**. Column chromatography (1:20 and then 1:7 ethyl acetate/light petroleum ether, on SiO_2) gave **5b** as a colorless oil (67%): IR 1600 cm^{-1}; ^1H NMR (400 MHz) δ 7.69 (2 H, d, J = 8.3), 7.28 (2 H, d, J = 8.3), 5.75 (1 H, t, J = 4.1), 5.26 (1 H, t, J = 3.0), 4.32 (1 H, d, J = 1.9), 4.06 (1 H, d, J = 1.9), 3.87 (1 H, dq, J = 9.8, 7.2), 3.84 (1 H, dq, J = 9.2, 7.1), 3.74 (1 H, dq, J = 9.2, 7.0), 3.55 (1 H, dq, J = 9.8, 7.0), 2.42 (3 H, s), 2.13 (1 H, m), 1.71 (2 H, m), 1.31 (3 H, t, J = 7.0), 1.15 (3 H, t, J = 7.0), 1.14 (1 H, m); ^{13}C NMR (100 MHz) δ 160.6 (s), 143.3 (s), 136.2 (s), 132.0 (s), 129.3 (2d), 127.4 (2d), 119.9 (d), 88.7 (t), 82.8 (d), 63.4 (t), 62.9 (t), 25.6 (t), 21.4 (q), 18.6 (t), 14.6 (q), 14.4 (q); MS (FAB) 374 $(MNa)^+$ (100), 352 $(MH)^+$ (61); HRMS calcd for $C_{18}H_{26}NO_4S$ 352.1583, found 352.1616.

5-Ethoxy-2-(2-methyl-1-oxopropyl)-1-*p*-toluenesulfonyl-2,3-dihydropyrrole (7). A solution of triflate **2a** (0.267 g, 0.643 mmol), stannane **6**[10] (0.415 g, 0.958 mmol), and $Pd(PPh_3)_2Cl_2$ (8.2 mg, 11.7 μmol, 0.05 equiv) in dry DMF (7 mL) was stirred at 40 °C for 16 h. After cooling to rt, saturated aqueous KF (2 mL) was added and the solution stirred for 1 h. Ethyl acetate (15 mL) was added and the solution filtered through Celite to remove the precipitated tin salts (which were washed with further ethyl acetate). The combined organic filtrate was washed with water (3 × 10 mL) and brine (10 mL) and then dried and solvent removed *in vacuo*. Column chromatography (1:20 and then 1:7 ethyl acetate/light petroleum ether, on SiO_2) gave **7** as an off white low melting solid containing traces of tin residues (0.084 g, 40%). For pure material an additional column was run, mp 88−91 °C: IR 1694 cm^{-1}; ^1H NMR (400 MHz) δ 7.63 (2 H, d, J = 8.3), 7.29 (2 H, d, J = 8.3), 6.01 (1 H, dd, J = 3.4, 2.2), 5.24 (1 H, d, J = 5.6), 4.03 (1 H, dq, J = 9.6, 7.1), 3.64 (1 H, dq, J = 9.6, 7.0), 3.49 (1 H, septet, J = 7.2), 2.42 (3 H, s), 2.16 (1 H, dd, J = 18.6, 3.5), 1.93 (1 H, ddd, J = 18.6, 5.6, 2.1), 1.22 (3 H, t, J = 7.0), 1.17 (3 H, d, J = 6.5), 1.11 (3 H, d, J = 7.4); ^{13}C NMR (100 MHz) δ 201.5 (s), 144.7 (s), 142.4 (s), 133.9 (s), 129.8 (2d), 127.9 (2d), 125.6 (d), 92.9 (d), 63.2 (t), 38.0 (d), 36.8 (t), 21.8 (q), 19.3 (q), 16.5 (q), 15.0 (q); MS 337 M^+ (28); HRMS calcd for $C_{17}H_{23}NO_4S$ 337.1348, found 337.1364. Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15. Found: C, 59.90; H, 6.56; N, 4.18.

Diels−Alder Reaction between Diene 4a and Dieneophile *N*-Methyl Maleimide: Cycloadduct 8. A solution of **4a** (0.062 g, 0.212 mmol) and *N*-methyl maleimide (0.118 g, 1.058 mmol, 5 equiv) in THF (2 mL) was heated at reflux for 2 h. After cooling to rt, the solvent was removed *in vacuo*. Column chromatography (1:3 → 1:1 ethyl acetate/light petroleum ether, on SiO_2) gave **8** as a colorless oil and a single diastereomer (0.061 g, 71%): IR 1697, 1598 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.53 (2 H, d, J = 8.3), 6.68 (2 H, d, J = 8.0), 5.72 (1 H, dt, J = 6.8, 2.6), 5.48 (1 H, d, J = 5.4), 3.98 (1 H, dq, J = 9.7, 7.0), 3.63 (1 H, dq, J = 9.7, 7.0), 2.63 (1 H, tdt, J = 10.7, 8.0, 2.5), 2.63 (1 H, ddd, J = 15.4, 7.5, 1.4), 2.38 (1 H, ddd, J = 13.1, 11.3, 5.5), 2.22 (3 H, s), 2.17 (1 H, td, J = 8.5, 3.5), 2.09 (1 H, m), 1.96 (1 H, dd, J = 13.2, 7.6), 1.81 (3 H, s), 1.55 (1 H, ddt, J = 15.4, 7.0, 2.5), 1.12 (3 H, t, J = 7.0); ^{13}C NMR (100 MHz) δ 178.8 (s), 176.8 (s), 143.8 (s), 139.8 (s), 137.3 (s), 130.1 (2d), 128.5 (2d), 102.0 (d), 93.2 (d), 64.6 (t), 41.8 (d), 41.1 (d), 37.2 (d), 33.7 (t), 25.1 (q), 24.1 (t), 21.7 (q), 15.7 (q); MS (FAB) 427 $(MNa)^+$ (90), 404 M^+ (75); HRMS calcd for $C_{20}H_{25}N_2O_5S$ 405.1484, found 405.1483.

2-Carbomethoxy-5-ethoxy-1-*p*-toluenesulfonyl-2,3-dihydropyrrole (9a). The known[3a] ester **9a** was prepared by an identical route to **9b** in 79% yield. Data has not previously been reported: IR 1730 cm^{-1}; ^1H NMR (400 MHz) δ 7.74 (2 H, d, J = 8.3), 7.30 (2 H, d, J = 8.3), 6.23 (1 H, m), 5.38 (1 H, m), 3.87 (1 H, dq, J = 9.6, 7.1), 3.85 (3 H, s), 3.53 (1 H, dq, J = 9.6, 7.0), 2.42 (3 H, s), 2.23 (2 H, m), 1.17 (3 H, t, J = 7.0); ^{13}C NMR (100 MHz) δ 162.4 (s), 144.2 (s), 135.5 (s), 134.9 (s), 129.6 (2d), 127.7 (2d), 127.3 (d), 92.4 (d), 63.0 (t), 52.4 (q), 36.8 (t), 21.6 (q), 14.8 (q).

2-Carbomethoxy-6-ethoxy-1-*p*-toluenesulfonyl-1,4,5,6-tetrahydropyridine (9b). Full details of the preparation and characterization of **9b** (61%, partially crystallizing oil) (from **2b**) have been previously reported.[3c]

2-((2-Iodophenoxy)carbonyl)-6-ethoxy-1-*p*-toluenesulfonyl-1,4,5,6-tetrahydropyridine (9c). Prepared from triflate **2b** in an identical manner to ester **9b** by substituting MeOH (40 equiv) for 2-iodophenol (5 equiv). Column chromatography (1:5 ethyl acetate/light petroleum ether, on SiO_2) followed by recrystallization (to remove traces of the phenol) gave **9c** (40%) as white crystals, mp 136−138 °C from ethyl acetate/pentane: IR 1747 cm^{-1}; ^1H NMR (400 MHz) δ 7.87 (2 H, d, J = 8.3), 7.84 (1 H, d, J = 7.7), 7.41 (2 H, d, J = 3.9), 7.31 (2 H, d, J = 8.3), 7.00 (1H, ddd, J = 8.1, 5.0, 3.8), 6.75 (1 H, t, J = 3.7), 5.03 (1 H, t, J = 2.6), 3.72 (1 H, dq, J = 9.5, 7.1), 3.20 (1 H, dq, J = 9.5, 7.0), 2.43 (3 H, s), 2.39 (1 H, m), 2.17 (1 H, ddd, J = 20.1, 6.7, 4.1), 1.86 (1 H, dd, J = 13.1, 8.6), 1.48 (1 H, m), 1.06 (3 H, t, J = 7.0); ^{13}C NMR (100 MHz) δ 163.1 (s), 151.1 (s), 144.3 (s), 139.1 (d), 135.0 (s), 129.6 (2d), 129.6 (d), 129.5 (d), 128.1 (2d), 127.5 (d), 126.6 (s), 123.3 (d), 89.7 (s), 81.7 (d), 63.1 (t), 24.9 (t), 21.5 (q), 19.1 (t), 14.7 (q); MS (FAB) 550 $(MNa)^+$ (30); HRMS calcd for $C_{21}H_{23}NO_5SI$ 528.0342, found 528.0340. Anal. Calcd for $C_{21}H_{22}NO_5SI$: C, 47.83; H, 4.20; N, 2.66. Found: C, 47.92; H, 4.19; N, 2.62.

6-Ethoxy-1-*p*-toluenesulfonyl-1,4,5,6-tetrahydropyridine-2-carboxylic Acid 2-Bromoanilide (9d). Prepared from triflate **2b** in an identical manner to ester **9b** by substituting MeOH (40 equiv) for 2-iodoaniline (3 equiv). Column chromatography (1:5 ethyl acetate/light petroleum ether, on SiO_2) followed by recrystallization gave **9d** (61%) as white crystals, mp 118−122 °C from ethyl acetate/pentane: IR 1688 cm^{-1}; ^1H NMR (400 MHz) δ 8.51 (1 H, dd, J = 8.3, 1.3), 8.26 (1 H, s), 7.77 (2 H, d, J = 8.2), 7.55 (1 H, dd, J = 8.0, 1.3), 7.34 (1 H, m), 7.32 (2 H, d, J = 8.2), 6.98 (1 H, td, J = 8.0, 1.4), 6.45 (1 H, t, J = 3.7), 5.18 (1 H, t, J = 2.6), 3.96 (1 H, dq, J = 9.6, 7.1), 3.56 (1 H, dq, J = 9.6, 7.1), 2.44 (3 H, s), 2.25 (1 H, ddt, J = 15.4, 7.8, 3.8), 1.91 (1 H, m), 1.72 (1 H, dd, J = 14.0, 7.7), 1.17 (3 H, t, J = 7.1), 1.12 (1 H, m); ^{13}C NMR (100 MHz) δ 163.8 (s), 144.6 (s), 135.8 (s), 134.1 (s), 132.1 (d), 131.1 (s), 129.7 (2d), 128.3 (d), 128.1 (2d), 127.0 (d), 124.8 (d), 121.4 (d), 113.3 (s), 83.0 (d), 63.8 (t), 24.6 (t), 21.6 (q), 18.7 (t), 14.8 (q); MS (FAB) 503 $(MNa^{81}Br)^+$ (37), 501 $(MNa^{79}Br)^+$ (34), 480 $(M^{81}Br)^+$ (18), 478 $(M^{79}Br)^+$ (15); HRMS calcd for $C_{21}H_{23}N_2O_4SBr$ 480.0543 (^{81}Br) and 478.0562 (^{79}Br), found 480.0568 and 478.0565 respectively. Anal. Calcd for $C_{21}H_{23}N_2O_4SBr$: C, 52.62; H, 4.84; N, 5.84. Found: C, 52.69; H, 5.16; N, 5.87.

5-Ethoxy-2-phenyl-1-*p*-toluenesulfonyl-2,3-dihydropyrrole (10a). The known[3a] enamide **10a** was prepared by an identical route to **10b** in 90% yield. Data has not previously been reported: IR 1595 cm^{-1}; ^1H NMR (400 MHz) δ 7.52 (4 H, m), 7.34 (3 H, m), 7.24 (2 H, d, J = 8.0), 5.52 (1 H, d, J = 5.7), 5.46 (1 H, dd, J = 3.4, 2.0), 4.15 (1 H, dq, J = 9.8, 7.1), 3.77 (1 H, dq, J = 9.7, 7.0), 2.42 (3 H, s), 2.21 (1 H, dd, J = 17.8, 3.5), 2.08 (1 H, ddd, J = 17.8, 5.8, 1.9), 1.29 (3 H, t, J = 7.0); ^{13}C NMR (100 MHz) δ 143.8 (s), 143.0 (s), 134.8 (s), 133.3 (s), 129.4

(2d), 128.6 (1d), 127.8 (2d), 127.5 (4d), 116.3 (d), 93.1 (d), 62.9 (t), 36.3 (t), 21.6 (q), 15.0 (q).

6-Ethoxy-2-phenyl-1-*p*-toluenesulfonyl-1,4,5,6-tetrahydropyridine (10b). A solution of triflate **2b** (0.109 g, 0.253 mmol) and $Pd(PPh_3)_4$ (0.014 g, 12.6 μmol, 0.05 equiv) in THF (2 mL) was stirred at rt for 10 min. A solution of PhZnCl (0.883 mmol) in THF (ca. 4.8 mL) [Prepared *in situ* as follows: to $ZnCl_2$ (1.77 mL of a 0.5 M solution in THF, 0.883 mmol) in additional THF (3 mL) was added PhLi (0.49 mL of a 2 M solution in cyclohexane, 0.883 mmol) and the mixture stirred at rt for 15 min] was added dropwise, and the solution was stirred for 1 h. Saturated aqueous ammonium chloride (2 mL) followed by water (5 mL) and ethyl acetate (8 mL) were added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 8 mL), the combined organics were dried, and solvent was removed *in vacuo*. Column chromatography (1:4 ethyl acetate/light petroleum ether, on SiO_2) gave **10b** as a colorless oil (0.072 g, 80%): IR 3030, 1599 cm^{-1}; ^1H NMR (400 MHz) δ 7.52 (2 H, d, J = 8.2), 7.37 (2 H, m), 7.29 (5 H, m), 5.50 (1 H, t, J = 3.7), 4.45 (1 H, t, J = 2.8), 4.03 (1 H, dq, J = 9.7, 7.1), 3.74 (1 H, dq, J = 9.7, 7.0), 2.42 (3 H, s), 2.24 (1 H, m), 1.81 (2 H, m), 1.23 (3 H, t, J = 7.0), 1.20 (1 H, m); ^{13}C NMR (100 MHz) δ 143.8 (s), 140.7 (s), 136.1 (s), 135.6 (s), 129.6 (2d), 128.0 (2d), 127.7 (2d), 127.6 (d), 127.1 (2d), 120.4 (d), 83.9 (d), 63.7 (t), 25.8 (t), 21.8 (q), 19.3 (t), 15.1 (q); MS 357 M^+ (38). HRMS calcd for $C_{20}H_{23}NO_3S$ 357.1399, found 357.1407.

5-Ethoxy-1-*p*-toluenesulfonyl-2-(trimethylstannyl)-2,3-dihydropyrrole (11a). A solution of triflate **2a** (0.019 g, 0.046 mmol), $Pd(MeCN)_2Cl_2$ (0.6 mg, 2.3 μmol, 0.05 equiv), and triphenylarsine (2.8 mg, 9.2 μmol, 0.2 equiv) in THF (2 mL) was stirred at rt for 10 min. Me_6Sn_2 (0.014 g, 0.044 mmol, 0.95 equiv) in THF (0.5 mL) was added and the solution stirred at 40 °C until TLC indicated consumption of starting material (3.5 h). Ethyl acetate (5 mL) was added, the organic solution washed with water (2 × 5 mL) and brine (5 mL) and then dried, and solvent removed *in vacuo*. Column chromatography (1:25 and then 1:12 ethyl acetate/light petroleum ether, on SiO_2) gave **11a** as a colorless oil (0.010 g, 48%): IR 1599 cm^{-1}; ^1H NMR (400 MHz) δ 7.61 (2 H, d, J = 8.3), 7.25 (2 H, d, J = 8.3), 5.45 (1 H, t, J = 2.8; J_{Sn} = 20.3), 5.23 (1 H, dd, J = 5.8, 1.8), 3.90 (1 H, dq, J = 9.7, 7.0), 3.60 (1 H, dq, J = 9.7, 7.0), 2.40 (3 H, s), 2.28 (2 H, m), 1.18 (3 H, t, J = 7.0), 0.31 (9 H, s; J_{Sn} = 56.4); ^{13}C NMR (100 MHz) δ 145.4 (s), 143.3 (s), 136.4 (s), 129.5 (2d), 126.8 (2d), 126.0 (d), 90.2 (d), 62.6 (t), 39.0 (t), 21.5 (q), 15.0 (q), −7.4 (3q); MS (FAB) 432 $(MH^{120}Sn)^+$ (5); HRMS calcd for $C_{16}H_{26}NO_3S^{120}Sn$ 432.0657, found 432.0635.

6-Ethoxy-1-*p*-toluenesulfonyl-2-(trimethylstannyl)-1,4,5,6-tetrahydropyridine (11b). A solution of triflate **2b** (0.202 g, 0.471 mmol), Pd_2dba_3 (22 mg, 23.3 μmol, 0.05 equiv), and triphenylarsine (61 mg, 93.2 μmol, 0.2 equiv) in THF (13 mL) was stirred at rt for 10 min. Me_6Sn_2 (0.146 g, 0.447 mmol, 0.95 equiv) in THF (1 mL) was added and the solution stirred at 55 °C until TLC indicated consumption of starting material (2 h). Ethyl acetate (25 mL) was added, the organic solution washed with water (2 × 10 mL) and brine (10 mL) and then dried, and solvent removed *in vacuo*. Column chromatography (1:25 and then 1:9 ethyl acetate/light petroleum ether, on SiO_2) gave **11b** as a colorless oil (0.129 g, 62%): IR 1340 cm^{-1}; ^1H NMR (400 MHz) δ 7.59 (2 H, d, J = 8.2), 7.28 (2 H, d, J = 8.1), 5.40 (1 H, brs; J_{Sn} = 45.2), 5.17 (1 H, t, J = 2.7), 3.78 (1 H, dq, J = 10.0, 7.2), 3.64 (1 H, dq, J = 10.0, 7.2), 2.41 (3 H, s), 2.16 (1 H, dddd, J = 18.2, 13.0, 6.9, 2.6), 1.74 (1 H, dt, J = 18.3, 5.2), 1.68 (1 H, m), 1.19 (3 H, t, J = 7.0), 0.81 (1 H, tdd, J = 13.9, 7.4, 3.4), 0.27 (9 H, s; J_{Sn} = 54.4); ^{13}C NMR (100 MHz) δ 143.1 (s), 136.9 (s), 136.3 (s), 129.5 (2d), 126.7 (2d), 125.6 (d), 81.6 (d), 62.5 (t), 24.9 (t), 21.4 (q), 19.0 (t), 14.8 (q), −6.3 (3q); MS (FAB) 468 $(M^{120}SnNa)^+$ (8); HRMS calcd for $C_{17}H_{28}NO_3S^{120}Sn$ 446.0814, found 446.0703.

6-Ethoxy-1-*p*-toluenesulfonyl-2-(1-hydroxy-1-methylethyl)-1,4,5,6-tetrahydropyridine (12). To a solution of stannane **11b** (0.024 g, 0.053 mmol) in diethyl ether (1 mL) at −30 °C was added MeLi (36 μL of a 1.6 M solution in diethyl ether, 0.059 mmol, 1.1 equiv) and the solution warmed to −10 °C over 2 h. After cooling to −78 °C, dry acetone (25 μL, 0.265 mmol, 5 equiv) was added and the solution warmed to rt. Solvent removal *in vacuo* followed by column chromatography (1:5 → 1:4 ethyl acetate/light petroleum ether, on SiO_2) gave **12** as a colorless oil (0.011 g, 60%): IR 3505 cm^{-1}; ^1H NMR (400 MHz) δ 7.75 (2 H, d, J = 8.3), 7.28 (2 H, d, J = 8.3), 6.00 (1 H, dd, J = 6.3, 3.4), 5.29 (1 H, dd, J = 5.7, 3.7), 4.63 (1 H, s), 3.87 (1 H, dq, J = 9.7, 7.1), 3.53 (1 H, dq, J = 9.6, 7.0), 2.42 (3 H, s), 1.78 (1 H, ddt, J = 17.1, 7.3, 6.5), 1.63 (1 H, m), 1.54 (3 H, s), 1.48 (3 H, s), 1.46 (1 H, m), 1.15 (3 H, t, J = 7.0), 1.03 (1 H, dtd, J = 17.2, 7.3, 3.5); ^{13}C NMR (100 MHz) δ 144.1 (s), 142.1 (s), 136.1 (s), 129.6 (2d), 127.5 (2d), 124.6 (d), 86.2 (d), 71.6 (s), 63.6 (t), 30.2 (q), 30.0 (q), 28.8 (t), 21.6 (q), 18.7 (t), 14.7 (q); MS (FAB) 362 $(MNa)^+$ (49), 340 $(MH)^+$ (70); HRMS calcd for $C_{17}H_{26}NO_4S$ 340.1583, found 340.1578.

2,2′-Bi(6-ethoxy-1-*p*-toluenesulfonyl-1,4,5,6-tetrahydropyridine) (13). A solution of triflate **2b** (0.044 g, 0.101 mmol, 0.9 equiv), stannane **11b** (0.050 g, 0.113 mmol), and $Pd(PPh_3)_2Cl_2$ (7.9 mg, 11.3 μmol, 0.1 equiv) in DMF (2 mL) was stirred at 50 °C for 16 h. Saturated aqueous KF (1 mL) was added and the solution stirred for 1 h. Ethyl acetate (10 mL) was added and the solution filtered through Celite to remove the precipitated tin salts (which were washed with further ethyl acetate). The combined organic filtrate was washed with water (5 × 5 mL) and brine (5 mL) and then dried and solvent removed *in vacuo*. Column chromatography (1:20 then 1:6 ethyl acetate/light petroleum ether, on SiO_2) and recrystallization gave **13** (0.020 g, 35%) as white crystals, mp 162−163 °C from diethyl ether/pentane: IR 1598 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 8.33 (2 H, d, J = 8.3), 6.86 (2 H, d, J = 8.2), 6.33 (1 H, brs), 5.36 (1 H, brs), 4.04 (1 H, m), 3.76 (1 H, dq, J = 9.7, 7.0), 2.03 (1 H, m), 1.85 (3 H, s), 1.56 (1 H, m), 1.42 (1 H, m), 1.05 (3 H, t, J = 7.0), 0.86 (1 H, m) [all peaks broadened by hindered rotation]; ^{13}C NMR (100 MHz) δ 144.1 (s), 138.1 (s), 135.0 (s), 130.6 (2d), 129.4 (2d), 119.4 (d), 85.2 (d), 64.6 (t), 26.5 (t), 21.8 (q), 19.8 (t), 15.7 (q); MS (FAB) 560 M^+ (74); HRMS calcd for $C_{28}H_{37}N_2O_6S_2$ 561.2093, found 561.2052. An X-ray crystal structure was obtained: monoclinic, $C2/c$, a = 23.6471(8), b = 9.5357(9), c = 22.597(7) Å, β = 102.52(1)°, v = 2871(1) Å,^{3} Z = 2, D_x = 1.30 g cm^{-1}, λ (Cu Kα) = 1.5418 Å, μ (Cu Kα) = 19.96 cm^{-1}, $F(000)$ = 1192, rt. Final R = 0.052 for 2162 observed reflections. Full details are given in Supporting Information.

(*S*)-5-(((1,1,2-Trimethylpropyldimethylsilyl)oxy)methyl)-1-*p*-toluenesulfonyl-2-pyrrolidinone (14). Prepared according to general procedure 1. Column chromatography (1:4 ethyl acetate/light petroleum ether, on SiO_2) gave **14** (63%) as a colorless oil:^1H NMR (400 MHz) δ 7.96 (2 H, d, J = 8.4), 7.31 (2 H, d, J = 8.1), 4.43 (1 H, d, J = 7.5), 3.99 (1 H, dd, J = 10.7, 3.8), 3.73 (1 H, dd, J = 10.7, 2.2), 2.67 (1 H, dt, J = 17.4, 10.2), 2.42 (3 H, s), 2.29 (1 H, ddd, J = 17.4, 9.9, 1.7), 2.18 (1 H, m), 2.03 (1 H, m), 1.53 (1 H, septet, J = 6.8), 0.80 (3 H, d, J = 6.8), 0.80 (3 H, d, J = 6.9), 0.76 (6 H, s), 0.09 (3 H, s), 0.02 (3 H, s); ^{13}C NMR (50 MHz) δ 174.2 (s), 144.8 (s), 136.2 (s), 129.5 (2d), 128.2 (2d), 64.9 (t), 60.8 (d), 34.0 (d), 31.6 (t), 25.0 (s), 22.4 (t), 21.6 (q), 20.2 (q), 20.1 (q), 18.4 (q), 18.4 (q), −3.6 (q), −3.8 (q).

(*S*)-5-((((1,1,2-Trimethylpropyl)dimethylsilyl)oxy)methyl)-1-*p*-toluenesulfonyl-2-((trifluoromethanesulfonyl)oxy)-2,3-dihydropyrrole (15). The title triflate was prepared from lactam **14** by an identical procedure to that used for triflate **2b**.[3c] Column chromatography (1:5 → 1:1 CH_2Cl_2/light petroleum ether, on SiO_2) yielded **15** as a colorless oil 82−98% (This triflate was somewhat unstable, and so the last 5 mL of solvent remaining after chromatography was routinely removed at 0 °C and the cold triflate immediately used in the following reaction): ^1H NMR (250 MHz, C_6D_6) δ 7.77 (2 H, d, J = 8.2), 7.37 (2 H, d, J = 8.1), 5.07 (1 H, brs), 4.13 (1 H, m), 3.79 (1 H, dd, J = 10.1, 4.6), 3.63 (1 H, dd, J = 10.0, 8.6), 2.47 (3 H, s), 2.35 (1 H, dt, J = 16.8, 2.9), 2.17 (1 H, dd, J = 16.8, 9.2), 1.61 (1 H, septet, J = 6.8), 0.88 (3 H, s), 0.86 (3 H, s), 0.84 (6 H, s), 0.13 (3 H, s), 0.12 (3 H, s).

(*S*)-2-Carbomethoxy-5-((((1,1,2-Trimethylpropyl)dimethylsilyl)oxy)methyl)-1-*p*-toluenesulfonyl-2,3-dihydropyrrole (16). A solution of triflate **15** (0.780 g, 1.458 mmol), Pd_2dba_3 (0.034 g, 0.036 mmol, 0.03 equiv), and triphenylarsine (0.092 g, 0.302 mmol, 0.12 equiv) in DMF (10 mL) was flushed with carbon monoxide for 10 min. Triethyl-

amine (0.84 mL, 6.04 mmol, 4 equiv) and methanol (2.44 mL, 60.42 mmol, 40 equiv) were added, and the solution was attached to a balloon of carbon monoxide and stirred for 12 h. After flushing with nitrogen, ethyl acetate (20 mL) and water (10 mL) were added, and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 × 20 mL), the combined organics were washed with brine (2 × 10 mL) and dried, and the solvent was removed *in vacuo*. Column chromatography (1:5 ethyl acetate/light petroleum ether, on SiO_2) afforded **16** as a colorless oil (0.348 g, 53%): $[\alpha]_D$ −117 (*c* 0.9 $CHCl_3$); IR 1736 cm^{-1}; ^1H NMR (250 MHz) δ 7.74 (2 H, d, J = 8.0), 7.32 (2 H, d, J = 8.0), 6.08 (1 H, t, J = 2.4), 4.14 (1 H, m), 3.85 (3 H, s), 3.68 (1 H, dd, J = 10.1, 4.4), 3.53 (1 H, dd, J = 10.1, 7.8), 2.44 (3 H, s), 2.31 (1 H, dt, J = 18.3, 2.7), 2.13 (1 H, ddd, J = 18.3, 8.6, 1.4), 1.58 (1 H, septet, J = 6.8), 0.85 (3 H, s), 0.83 (3 H, s), 0.80 (6 H, s), 0.09 (3 H, s), 0.07 (3 H, s); ^{13}C NMR (100 MHz) δ 162.6 (s), 144.1 (s), 136.9 (s), 134.1 (s), 129.5 (2d), 128.0 (2d), 127.0 (d), 64.5 (t), 63.1 (d), 52.3 (q), 34.1 (d), 31.4 (t), 25.1 (s), 21.6 (q), 20.2 (2q), 18.5 (2q), −3.5 (q), −3.6 (q); MS (FAB) 454 $(MH)^+$ (69); HRMS calcd for $C_{22}H_{36}NO_5SSi$ 454.2083, found 454.2082.

(*S*)-2-Carbomethoxy-5-(hydroxymethyl)-1-*p*-toluenesulfonyl-2,3-dihydropyrrole (17). To a solution of **16** (0.230 g, 0.508 mmol) in THF (2 mL) was added TBAF (1 mL of a 1 M solution in THF) and the solution stirred for 1.5 h. Ethyl acetate (15 mL) was added, the organic solution washed with water (2 × 8 mL) and brine (8 mL) and dried, and the solvent removed *in vacuo*. Column chromatography (ethyl acetate, on SiO_2) afforded **17** as a colorless oil (0.120 g, 76%): $[\alpha]_D$ −122 (c 0.6 $CHCl_3$); IR 3566, 1733 cm^{-1}; ^1H NMR (400 MHz) δ 7.73 (2 H, d, J = 8.2), 7.33 (2 H, d, J = 8.1), 6.10 (1 H, dd, J = 3.4, 2.3), 4.16 (1 H, m), 3.87 (3 H, s), 3.56 (2 H, m), 2.44 (3 H, s), 2.30 (1 H, brs), 2.15 (1 H, ddt, J = 18.3, 8.6, 2.2), 2.03 (1 H, dt, J = 18.3, 3.2); ^{13}C NMR (100 MHz) δ 162.5 (s), 144.5 (s), 136.5 (s), 133.2 (s), 129.7 (2d), 128.1 (2d), 127.4 (d), 64.6 (t), 63.8 (d), 52.5 (q), 31.4 (t), 21.6 (q); MS 311 M^+ (35); HRMS calcd for $C_{14}H_{17}NO_5S$ 311.0827, found 311.0852.

(5*S*)-2-Carbomethoxy-5-(hydroxymethyl)-1-*p*-toluenesulfonylpyrrolidine (18). A solution of **17** (0.100 g, 0.322 mmol) and Pd/C (10%, 18 mg) in MeOH (6 mL) was stirred under a balloon of H_2 for 3 days. The solvent was removed *in vacuo* and then ethyl acetate (5 mL) added. The solution was filtered through Celite and the solvent removed *in vacuo*. Column chromatography (ethyl acetate, on SiO_2) afforded **18** as a colorless oil (0.096 g, 96%) and a 93:7 mixture of inseparable diastereomers: $[\alpha]_D$ +37.9 (*c* 0.47 $CHCl_3$); IR 3487, 1740 cm^{-1}; ^1H NMR (400 MHz) δ (major only) 7.75 (2 H, d, J = 8.3), 7.34 (2 H, d, J = 8.3), 4.33 (1 H, dd, J = 8.5, 5.3), 3.94 (1 H, dd, J = 11.8, 3.0), 3.85 (1 H, m), 3.78 (3 H, s), 3.57 (1 H, dd, J = 11.8, 3.4), 2.44 (3 H, s), 2.08 (1 H, m), 1.92 (2 H, m), 1.73 (1 H, m) [OH not observed]; ^{13}C NMR (100 MHz) δ 173.5 (s), 144.1 (s), 134.4 (s), 129.9 (2d), 127.4 (2d), 64.9 (t), 63.0 (d), 61.7 (d), 52.7 (q), 29.8 (t), 27.5 (t), 21.5 (q); MS 282 $(M - OMe)^+$ (81); HRMS calcd for $C_{13}H_{16}NO_4S$ 282.0805, found 282.0800.

(2*S*)-2,5-Bis(hydroxymethyl)-1-*p*-toluenesulfonylpyrrolidine (19). To a solution of **18** (0.025 g, 0.080 mmol) in THF (1 mL) at 0 °C was added DIBALH (0.40 mL of a 1 M solution in THF, 0.4 mmol, 5 equiv), and the solution was warmed to rt. After 12 h, the reaction was carefully quenched with saturated aqueous Rochelle's salt. Water (3 mL) was added, and the solution was extracted with ethyl acetate (4 × 7 mL). The combined extracts were dried, and the solvent was removed *in vacuo*. Column chromatography (ethyl acetate, on SiO_2) afforded a diol product as a colorless oil (0.014 g, 63%). This compound was immediately protected as the corresponding bis-methyl ether before characterization using the method of Somfai:[4b] to a solution of this diol (0.014 g, 0.049 mmol) in THF (1 mL) at 0 °C was added NaH (10 mg of a 35% dispersion in mineral oil, 0.146 mmol, 3 equiv) and the solution stirred at rt for 1 h. After cooling to 0 °C, MeI (18.3 μL, 0.294 mmol, 6 equiv) was added and the solution warmed to rt and stirred for 16 h. Ethyl acetate (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 5 mL), the combined organics were dried, and solvent was removed *in vacuo*. ^1H NMR analysis confirmed the product to be a 93:7 mixture of diastereomers. Column chromatography (1:4 ethyl acetate/light petroleum ether, on SiO_2) afforded **19** as a colorless oil (0.014 g, 90%) in two fractions. The first contained a 1:3 mixture of major and minor isomers respectively (1.5 mg), and the second fraction the pure major isomer (12.3 mg, used for the following data: $[\alpha]_D$ 0; IR 3027, 1326 cm^{-1}; ^1H NMR (400 MHz) δ 7.73 (2 H, d, J = 8.2), 7.31 (2 H, d, J = 8.2), 3.70 (2 H, m), 3.66 (2 H, dd, J = 9.1, 3.9), 3.37 (6 H, s), 3.34 (2 H, t, J = 8.8), 2.43 (3 H, s), 1.79 (2 H, m), 1.51 (2 H, m); ^{13}C NMR (100 MHz) δ 143.6 (s), 134.3 (s), 129.7 (2d), 127.6 (2d), 75.4 (2t), 60.3 (2d), 59.2 (2q), 27.4 (2t), 21.5 (q); MS (FAB) 314 $(MH)^+$ (100); HRMS calcd for $C_{15}H_{23}NO_4S$ 314.1426, found 314.1452.

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Supporting Information Available: ^1H NMR spectra of all new compounds lacking combustion analysis (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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