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The Double Reduction of Cyclic Sulfonamides for the Synthesis of (4*S*-Phenylpyrrolidin-2*R*-yl)methanol and 2*S*-Methyl-4*S*-phenylpyrrolidine

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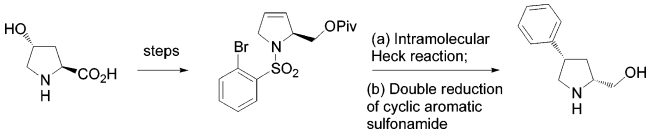
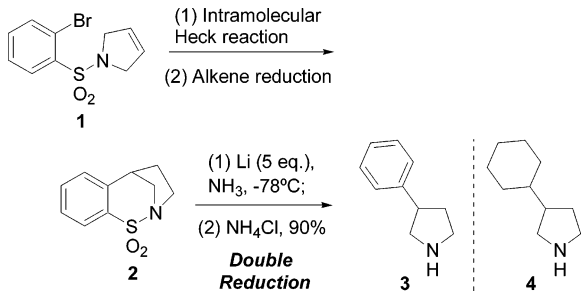
Received October 21, 2006



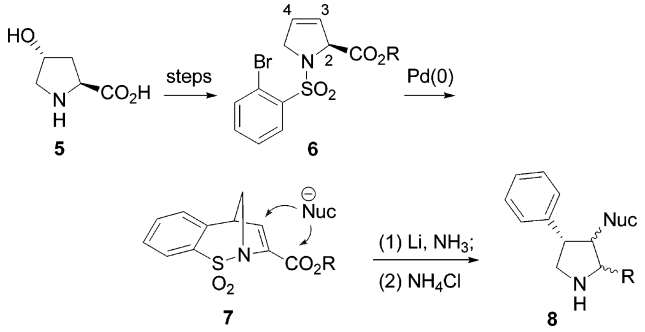
The synthesis of (4*S*-phenylpyrrolidin-2*R*-yl)methanol and 2*S*-methyl-4*S*-phenylpyrrolidine has been achieved via the double reduction of their cyclic sulfonamide precursors which themselves were prepared following the stereoselective intramolecular Heck reaction of a chiral pool derived 2,5-dihydropyrrole. We have recently described a process whereby cyclic aryl sulfonamides, such as **2**, are reductively ring-opened to furnish amino products in which the aryl group is incorporated in the final compound. (Evans, P.; McCabe, T.; Morgan, B. S.; Reau, S. *Org. Lett.* **2005**, *7*, 43.) The precursors for this reaction were assembled using an intramolecular Heck reaction followed by reduction of the alkene. Overall, this sequence represents an efficient means to construct molecules of this type in which the aryl sulfonyl moiety acts as both an N-protecting group and as an aryl donor. Use of Benkeser's stronger reducing conditions enables molecules such as **4** to be prepared in which both the sulfonamide functional group and the aromaticity of the aryl substituent have been destroyed.

The type of structural motif accessed using this reaction appears in several classes of biologically active molecules.[2,3] The angiotensin converting enzyme (ACE) inhibitor fosinopril, for example, contains 3*R*-cyclohexyl proline as a central structural motif.[4] Following on from these preliminary studies,

SCHEME 1



SCHEME 2



we decided to investigate the preparation of enantiopure 4-aryl-2-substituted pyrrolidines **8** using *anti*-4-hydroxy-L-proline **5** (Scheme 2). The proposed route utilized a selenium-based method for the preparation of the enantiopure pyrroline Heck precursor **6** and has been described for the analogous *N*-Cbz and *N*-Boc series.[5] It was expected that the intramolecular Heck reaction of **6** would proceed in a stereoselective manner and that the stereogenic center controlling this cyclization would then be lost following *syn*-β-hydride elimination. The functionalized scaffold **7** would then be amenable to further (diastereoselective) functionalization via conjugate addition/alkenyl reduction or manipulation of the ester functional group, prior to the double reduction generating species such as **8**.

Thus, 4-hydoxy proline **5** was converted to its methyl ester,[5] which was then used to prepare sulfonamide **9** (Scheme 3). Following a three-step sequence, **9** was converted into **6** in an overall yield of 69%. None of the *N*-sulfonyl enamine, resulting from a non-regioselective Cope-type elimination, was observed. The initial thionyl chloride reaction works most efficiently in methanol affording the methyl ester. In contrast, it has been reported for similar *N*-carbamate examples[5] that the mesylate displacement, under reductive formation of benzene selenonate, proceeds best in ethanol. As a consequence, trans-esterification also occurred at this stage and **6** was isolated as the ethyl ester. At this stage, we investigated the possibility of performing a stereoselective intramolecular Heck reaction directly to form **7** (Scheme 2). However, under the standard conditions used, this proved not to be possible since pyrrole **17** rapidly formed, presumably by a base-mediated sulfinate elimination−isomer-

(1) Evans, P.; McCabe, T.; Morgan, B. S.; Reau, S. *Org. Lett.* **2005**, *7*, 43.

(2) (a) Zelle, R. E.; Hancock, A. A.; Buckner, S. A.; Basha, F. Z.; Tietje, K.; DeBernardis, J. F.; Meyer, M. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1319. (b) Ahn, K. H.; Lee, S. J.; Lee, C.−H.; Hong, C. Y.; Park, T. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1379. (c) Sonesson, C.; Wikström, H.; Smith, M. W.; Svensson, K.; Carlsson, A.; Waters, N. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 241.

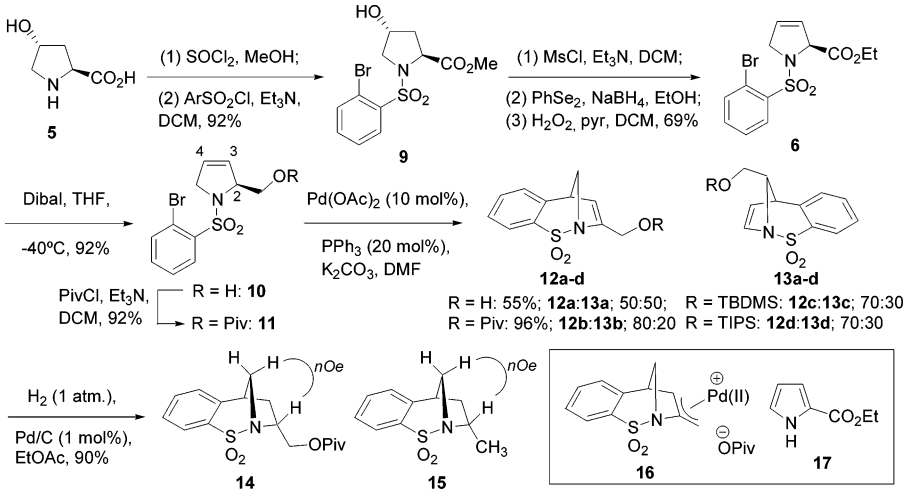
(3) (a) Parsons, A. *Tetrahedron* **1996**, *52*, 4149. (b) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2588.

(4) See: Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Lee, V. G.; Loots, M. J.; Petrillo, E. W. *J. Med. Chem.* **1990**, *33*, 1459 and references therein.

(5) (a) Robinson, J. K.; Lee, V.; Claridge, T. D. W.; Baldwin, J. E.; Schofield, C. J. *Tetrahedron* **1998**, *54*, 98l. (b) Greenwood, E. S.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **2003**, *59*, 3307.

10.1021/jo062189o CCC: $37.00
Published on Web 01/26/2007

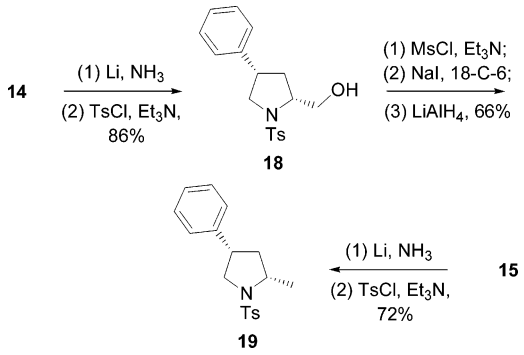
SCHEME 3



ization process.[6] Since we had been able to use 2,5-dihydropyrroles without 2-substituents effectively in this type of Heck reaction,[1] the ethyl ester **6** was reduced to the corresponding alcohol **10** using Dibal.[7] When **10** was subjected to the standard Heck reaction protocol, pleasingly none of the 2-substituted pyrrole was observed. ^{1}H NMR spectroscopy of the crude material, however, revealed the presence of two compounds (ca. 50:50) that proved to be inseparable. Although assignment of these compounds was difficult, we had a feeling that they were regioisomers **12a** and **13a** resulting from an unselective 6-*exo*-trig cyclization at both the 3- and 4-positions.

To probe this hypothesis, we converted the primary alcohol **10** into more sterically demanding derivatives in an attempt to direct the carbon−carbon bond formation toward the 4-position. Pleasingly, this proved to be the case, although the reactions were not completely regioselective. Thus, using the pivaloyl ester **11** significantly more of the 4-isomer **12b** was observed (**12b**:**13b**; 80:20), and although the compounds co-ran on chromatography, the major isomer **12b** proved crystalline and could be separated from **13b**. X-ray crystallography confirmed the structure and indicated that bond formation had occurred on the Si-face of the alkene as expected.[8] The regioisomer **13b** was not obtained in completely pure form, but we assume that bond formation occurs from the opposite face to the substituent. Similarly, using the *O*-*tert*-butyldimethylsilyl ether, or *O*-triisoproylsilyl ether derivatives, a 70:30 mixture of regioisomers **12c/d** and **13c/d** were observed which were not crystalline and again proved to be inseparable by column chromatography. Hydrogenolysis of **12b** (ca. 1 mol % Pd/C) proceeded with high stereoselectivity and **14** was obtained as a single diastereoisomer in 90% yield. NOE experiments indicated that reduction had occurred on the opposite side to the aromatic substituent and reinvestigation of the X-ray structure indicated that this is the least sterically congested face of the alkene. Interestingly, during these studies, it was noticed that reactions performed using ca. 8 mol % of palladium resulted in the formation of an additional compound. Separation of this impurity initially proved problematic but could be achieved by column chromatography using DCM as the eluent (**14**, 49%; **15**, 29%).[9] Once separated, spectroscopic data and X-ray crystallographic studies[8] indicated that this impurity was compound **15**. It seems likely that **15** arises from a π-allyl palladium species such as **16** since, as expected, **14** does not undergo reduction to **15** under the hydrogenation conditions.[10]

SCHEME 4



With the cyclic sulfonamides **14** and **15** in hand, their double reduction was investigated (Scheme 4). Thus, compound **14** was added to liquid ammonia and was stirred at −78 °C before lithium (5 equiv) was added in small pieces. Under these conditions, **14** smoothly underwent both double reduction of the aryl sulfonamide motif and *O*-pivaloyl cleavage. Treatment of *O*-pivaloyl esters with ammonia solutions represents a mild method for their cleavage.[11] The resultant amine[12] was converted to the sulfonamide **18** for characterization purposes. Similarly, the methyl compound **15** was converted into **19** in good yield.[13] To confirm the stereochemical assignment of **14**, on the basis of the NOE measurements described above, alcohol **18** was converted into **19** and the proton and carbon spectra for this material proved to be identical with those obtained from the direct reduction of **15**. This latter sequence, along with the

(6) Declerck, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372.

(7) Use of $LiAlH_4$ resulted in significant reduction of the aromatic bromide.

(8) CCDC references numbers 624659 (**12b**) and 624660 (**15**).

(9) Use of 100 mol% of Pd/C gave a 50:50 mixture of **14**:**15**.

(10) For a similar reduction of an allylic ester see: Quijano, L.; Calderón, J. S.; Ríos, T. *Chem. Lett*. **1979**, 1387.

(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(12) For a racemic synthesis see: Katsukiyo, M.; Takeshi, H.; Takahiro, N.; Tatsuyuki, T.; Akira, H. *Org. Lett.* **2000**, *2*, 385.

(13) For a racemic synthesis see: Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959.

π-allyl palladium chemistry implicated previously, illustrates the potential for the further functionalization of this series of chiral pool derived aryl substituted pyrrolidines. In summary, we have developed a concise route for the preparation of (4*S*-phenylpyrrolidin-2*R*-yl)methanol and 2*S*-methyl-4*S*-phenylpyrrolidine from 4-hydroxyproline, featuring a stereoselective intramolecular Heck cyclization and the double reduction of the aromatic cyclic sulfonamide functionality.

Experimental Section

1-(2-Bromobenzenesulfonyl)-4*S*-phenylselanylpyrrolidine-2*S*-carboxylic Acid Ethyl Ester. Under N_2, a solution of diphenyl diselenide (0.805 g, 2.58 mmol, 0.53 equiv) was treated with $NaBH_4$ (0.210 g, 5.53 mmol, 1.1 equiv) at 0 °C for 1 h. The mesylate (2.17 g, 4.91 mmol, 1 equiv) in EtOH (40 mL) was then added and the mixture was heated to reflux for 3.5 h. The reaction mixture was cooled to room temperature and stirring was continued for 18 h. The bulk of the solvent was removed under reduced pressure before Et_2O (75 mL) and saturated brine solution (75 mL) were added. Following separation, the aqueous layer was further extracted with Et_2O (2 × 50 mL) and was dried over $MgSO_4$. On filtration, silica (ca. 10 g) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography (cyclohexane-EtOAc; 9:1 → 3:1) gave the selenoether (2.05 g, 81%) as a yellow oil. $R_f = 0.35$ (cyclohexane-EtOAc; 3:1); $[\alpha]^{20}_D$ −18.8 (*c* 0.5, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3065, 2983, 1742, 1573, 1442, 1342, 1260, 1209, 1162, 1028, 913; *m*/*z* (ES$^+$) 537 (MNH_4^+, Br,^{81} 100%), 535 (MNH_4^+, Br,^{79} 100%), 520 (MH^+, Br,^{81} 80%), 518 (MH^+, Br,^{79} 80%); found 517.9526, $C_{19}H_{21}NO_4SSeBr^{79}$ requires 517.9540 (−2.7 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.14 (t, *J* = 7.0 Hz, 3H), 2.11−2.18 (m, 1H), 2.74−2.81 (m, 1H), 3.58−3.63 (m, 2H), 3.95 (dq, *J* = 7.0, 10.75 Hz, 1H), 4.01 (dq, *J* = 7.0, 10.75 Hz, 1H), 4.08−4.16 (m, 1H), 4.59 (dd, *J* = 6.5, 8.5 Hz, 1H), 7.28−7.32 (m, 3H), 7.37 (dt, *J* = 2.0, 7.5 Hz, 1H), 7.42 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.51−7.55 (m, 2H), 7.73 (dd, *J* = 1.5, 7.5 Hz, 1H), 8.10 (dd, *J* = 2.0, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 13.9 (CH_3), 37.3 (CH), 37.9 (CH_2), 55.6 (CH_2), 60.6 (CH), 61.5 (CH_2), 120.4 (C), 127.4 (CH), 127.6 (C), 128.3 (CH), 129.3 (CH), 132.1 (CH), 133.6 (CH), 134.9 (CH), 135.5 (CH), 139.2 (C), 171.1 (CO).

1-(2-Bromobenzenesulfonyl)-2,5-dihydro-1*H*-pyrrole-2*S*-carboxylic Acid Ethyl Ester 6. A solution of the selenoether (4.30 g, 8.43 mmol, 1 equiv) and pyridine (0.85 mL, 10.57 mmol, 1.25 equiv) in DCM (50 mL) was cooled to 0 °C before 30% w/v H_2O_2 (2.15 mL, 18.97 mmol, 2.25 equiv) was added. The reaction was stirred and warmed to room temperature over 15 h. DCM (50 mL), H_2O (50 mL), and 1 M HCl solution (10 mL) were added. On separation, the resultant aqueous layer was further extracted with DCM (2 × 50 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration, solvent removal, and purification by flash column chromatography (cyclohexane-EtOAc; 3:1) gave **6** (2.71 g, 91%) as a colorless viscous oil which solidified at 5 °C. Mp 69−71 °C; $R_f = 0.3$ (cyclohexane-EtOAc; 3:1); $[\alpha]^{20}_D$ −143.8 (*c* 3.0, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3091, 2983, 2928, 2873, 1750, 1571, 1446, 1343, 1263, 1167, 1027; *m*/*z* (ES$^+$) 379 (MNH_4^+, Br,^{81} 45%), 377 (MNH_4^+, Br,^{79} 45%), 362 (MH^+, Br,^{81} 100%), 360 (MH^+, Br,^{79} 100%); found 359.9897, $C_{13}H_{14}NO_4SBr^{79}$ requires 359.9905 (−2.3 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.20 (t, *J* = 7.0 Hz, 3H), 4.04−4.08 (m, 2H), 4.34 (dddd, app. dq, *J* = 2.25, 14.25 Hz, 1H), 4.43 (dddd, app. ddt, *J* = 2.0, 5.75, 14.25 Hz, 1H), 5.33−5.36 (m, 1H), 5.76−5.80 (m, 1H), 5.95−5.98 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 13.9 (CH_3), 55.7 (CH_2), 61.7 (CH_2), 68.7 (CH), 120.5 (C), 124.8 (CH), 127.5 (CH), 128.5 (CH), 131.8 (CH), 133.6 (CH), 135.6 (CH), 139.0 (C), 169.5 (CO); found C, 43.03; H, 3.82; N, 3.69%, $C_{13}H_{14}NO_4SBr$ requires C, 43.35; H, 3.92; N, 3.89%.

[1-(2-Bromobenzenesulfonyl)-2,5-dihydro-1*H*-pyrrol-2*S*-yl]-methanol 10. Under N_2, a solution of 1 M Dibal in hexanes (2.00 mL, 2.00 mmol, 2.2 equiv) was added dropwise to a solution of **6** (0.330 g, 0.92 mmol, 1 equiv) in THF (8 mL) at −78 °C. The reaction mixture was allowed to warm to 0 °C over 1 h. Saturated NH_4Cl (25 mL) and Et_2O (25 mL) were added. Following separation, the resultant aqueous layer was further extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and were filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (cyclohexane-EtOAc; 1:1) gave **10** (0.267 mg, 92%) as a colorless oil. R_f = 0.3 (cyclohexane-EtOAc; 1:1); $[\alpha]^{20}_D$ −86.0 (*c* 3.0, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3518, 3427, 3087, 2923, 2875, 1693, 1570, 1444, 1427, 1334, 1164, 1109; *m*/*z* (ES$^+$) 320 (MH^+, Br,^{81} 100%), 318 (MH^+, Br,^{79} 100%); found 317.9814, $C_{11}H_{12}NO_3SBr^{79}$ requires 317.9800 (+4.6 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.42−2.61 (s(br), 1H), 3.65 (dd, *J* = 4.5, 12.0 Hz, 1H), 3.73 (dd, *J* = 3.25, 12.0 Hz, 1H), 4.24 (dddd, app. ddt, *J* = 2.0, 5.75, 14.5 Hz, 1H), 4.39 (dddd, app. dq, *J* = 2.25, 14.5 Hz, 1H), 4.74−4.78 (m, 1H), 5.67−5.71 (m, 1H), 5.85−5.89 (m, 1H), 7.41 (dt, *J* = 1.75, 7.5 Hz, 1H), 7.45 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.76 (dd, *J* = 1.5, 7.5 Hz, 1H), 8.01 (dd, *J* = 1.75, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 56.4 (CH_2), 64.9 (CH_2), 69.3 (CH), 120.4 (C), 126.7 (CH), 127.1 (CH), 127.8 (CH), 131.5 (CH), 133.8 (CH), 136.0 (CH), 138.1 (C).

2,2-Dimethylpropionic Acid 1-(2-Bromobenzenesulfonyl)-2,5-dihydro-1*H*-pyrrol-2*S*-yl Methyl Ester 11. At room temperature, alcohol **10** (475 mg, 1.494 mmol, 1 equiv) in DCM (10 mL) was treated with pivaloyl chloride (0.23 mL, 1.862 mmol, 1.25 equiv) and triethylamine (0.31 mL, 2.224 mmol, 1.5 equiv). After 15 h, the silica (ca. 3 g) was added and the solvent was removed under reduced pressure. The residue was then purified by flash column chromatography (cyclohexane-EtOAc; 9:1 → 3:1) which gave **11** (0.553 mg, 92%) as a colorless oil. R_f = 0.15 (cyclohexane-EtOAc; 9:1); $[\alpha]^{20}_D$ −129.7 (*c* 4.2, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3089, 2972, 2874, 1729, 1571, 1453, 1342, 1283, 1165; *m*/*z* (ES$^+$) 421 (MNH_4^+, Br,^{81} 100%), 419 (MNH_4^+, Br,^{79} 100%), 404 (MH^+, Br,^{81} 90%), 402 (MH^+, Br,^{79} 90%); found 402.0378, $C_{16}H_{21}NO_4SBr^{79}$ requires 402.0375 (+0.8 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.18 (s, 9H), 4.03 (dd, *J* = 4.75, 11.5 Hz, 1H), 4.22 (dddd, *J* = 2.0, 2.5, 5.5, 14.5 Hz, 1H), 4.32−4.37 (m, 2H), 4.96−5.01 (m, 1H), 5.66−5.69 (m, 1H), 5.83−5.87 (m, 1H), 7.38 (dt, *J* = 2.0, 7.5 Hz, 1H), 7.45 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.74 (dd, *J* = 1.5, 7.5 Hz, 1H), 8.02 (dd, *J* = 2.0, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.1 (CH_3), 38.7 (C), 55.9 (CH_2), 64.6 (CH_2), 66.2 (CH), 120.4 (C), 126.7 (CH), 126.9 (CH), 127.7 (CH), 131.1 (CH), 133.6 (CH), 135.9 (CH), 139.0 (C), 177.9 (CO).

2,2-Dimethylpropionic Acid 1*S*-8,8-Dioxo-8λ^6-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6,10-tetraen-10-yl Methyl Ester 12b. Under N_2, a mixture of **11** (411 mg, 1.02 mmol, 1 equiv), $Pd(OAc)_2$ (23 mg, 0.102 mmol, 10 mol %), PPh_3 (54 mg, 0.206 mmol, 20 mol %), and K_2CO_3 (212 mg, 1.53 mmol, 1.5 equiv) in DMF (25 mL) was heated to 60 °C (oil bath temperature). The reaction was stirred at this temperature for 15 h before cooling and addition of Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was further extracted with Et_2O (4 × 30 mL) and the combined organics were dried over $MgSO_4$. Filtration, solvent removal, and purification by flash column chromatography (cyclohexane-EtOAc; 3:1) gave regioisomers **12b** and **13b** (313 mg, 96%) as an inseparable mixture (80:20). The major isomer **12b** was obtained as a colorless solid (ca. 200 mg) following crystallization. Mp 122 °C (EtOAc-cyclohexane; 1:1); R_f = 0.15 (cyclohexane-EtOAc; 9:1); $[\alpha]^{20}_D$ −38.5 (*c* 1.3, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3075, 2973, 2876, 1733, 1654, 1476, 1340, 1340, 1283, 1164; *m*/*z* (ES$^+$) 339 (MNH_4^+, 50%), 322 (MH^+, 100%); found 322.1100, $C_{16}H_{20}NO_4S$ requires 322.1113 (−4.1 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.19 (s, 9H), 3.30 (dd, app. t, *J* = 3.75 Hz, 1H), 4.15 (dd, *J* = 3.75, 11.75 Hz, 1H), 4.54 (d, *J* = 11.75 Hz, 1H), 4.91 (ddd, *J* = 0.75, 1.75,

15.0 Hz, 1H), 4.93 (dd, J = 1.5, 15.0 Hz, 1H), 6.44−6.47 (m, 1H), 7.13 (dd, J = 1.5, 7.5 Hz, 1H), 7.39 (dt, J = 1.5, 7.5 Hz, 1H), 7.47 (dt, J = 1.5, 7.5 Hz, 1H), 7.72 (dd, J = 1.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.1 (CH_3), 38.2 (C), 42.5 (CH), 60.9 (CH_2), 64.8 (CH_2), 125.5 (CH), 127.3 (CH), 129.9 (CH), 131.7 (CH), 131.8 (CH), 134.5 (C), 140.5 (C), 144.0 (C), 177.7 (CO); found C, 59.85; H, 5.96; N, 4.25%, $C_{16}H_{19}NO_4S$ requires C, 59.80; H, 5.96; N, 4.36%.

2,2-Dimethyl-propionic Acid 1*S*-8,8-Dioxo-8λ^6-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-10*R*-yl Methyl Ester 14 and 1*S*,10*S*-Methyl-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene 8,8-Dioxide 15. 10% w/w Pd/C (84 mg, ca. 0.08 mmol, 8 mol %) was added to a solution of **12b** (316 mg, 0.984 mmol, 1 equiv) in EtOAc (20 mL). The mixture was stirred under H_2 (1 atm) for 15 h. Filtration through Celite, washing EtOAc (2 × 25 mL), and solvent removal followed by purification and by flash column chromatography (cyclohexane-DCM: 1:2 → DCM) gave initially **15** (63 mg, 29%) as a colorless solid followed by **14** (155 mg, 49%) as a viscous oil. Data for **15**: Mp 148−150 °C (EtOAc); R_f = 0.5 (DCM); $[\alpha]^{20}_D$ −17.2 (*c* 1.7, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3045, 2985, 2923, 1449, 1329, 1264, 1168; *m*/*z* (ES$^+$) 224 (MH$^+$, 100%); found 224.0740, $C_{11}H_{14}NO_2S$ requires 224.0745 (−2.3 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.46−1.54 (m, 1H), 1.50 (d, J = 7.5 Hz, 3H), 2.54−2.62 (m, 1H), 3.24 (dd, J = 3.25, 7.0 Hz, 1H), 3.32 (dd, J = 3.25, 12.75 Hz, 1H), 3.83−3.39 (m, 1H), 4.41 (dd, J = 2.5, 12.75 Hz, 1H), 7.17 (dd, J = 1.5, 7.5 Hz, 1H), 7.38 (dt, J = 1.5, 7.5 Hz, 1H), 7.44 (dt, J = 1.5, 7.5 Hz, 1H), 7.78 (dd, J = 1.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 19.4 (CH_3), 39.9 (CH_2), 41.4 (CH), 58.8 (CH_2), 59.0 (CH), 125.7 (CH), 127.1 (CH), 128.2 (CH), 132.6 (CH), 136.7 (C), 142.7 (C); found C, 59.04; H, 5.85; N, 6.11%, $C_{11}H_{13}NO_2S$ requires C, 59.15; H, 5.87; N, 6.30%. Data for **14**: R_f = 0.45 (DCM); $[\alpha]^{20}_D$ −33.8 (*c* 1.7, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3055, 2965, 2875, 1727, 1476, 1334, 1285, 1168; *m*/*z* (ES$^+$) 324 (MH$^+$, 100%); found 324.1255, $C_{16}H_{22}NO_4S$ requires 324.1270 (−4.5 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.16 (s, 9H), 1.71 (ddd, J = 2.0, 6.5, 13.0 Hz, 1H), 2.52 (ddd, J = 7.0, 9.75, 13.0 Hz, 1H), 3.31 (dd, J = 3.25, 7.0 Hz, 1H), 3.34 (dd, J = 3.25, 12.5 Hz, 1H), 3.99−4.07 (m, 1H), 4.28 (dd, J = 7.0, 12.0 Hz, 1H), 4.39 (dd, J = 2.25, 12.5 Hz, 1H), 4.65 (dd, J = 6.5, 12.0 Hz, 1H), 7.19 (dd, J = 1.5, 7.5 Hz, 1H), 7.38 (dt, J = 1.5, 7.5 Hz, 1H), 7.44 (dt, J = 1.5, 7.5 Hz, 1H), 7.77 (dd, J = 1.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 27.0 (CH_3), 37.1 (CH_2), 38.6 (C), 39.3 (CH), 58.8 (CH_2), 60.8 (CH), 63.4 (CH_2), 126.0 (CH), 127.1 (CH), 128.4 (CH), 132.8 (CH), 136.2 (C), 142.0 (C), 177.8 (CO).

[4*S*-Phenyl-1-(toluene-4-sulfonyl)pyrrolidin-2*R*-yl]methanol 18. A solution of **14** (86 mg, 0.266 mmol, 1 equiv) in THF (10 mL) was added to NH_3 (ca. 250 mL) at −78 °C. The mixture was stirred for 0.25 h before small pieces of Li (9 mg, 1.29 mmol, 4.8 equiv) were added. Stirring was continued for 0.5 h before solid NH_4Cl (ca. 5 g) was added. Following evaporation of ammonia, Et_2O (50 mL) and 1 M KOH (50 mL) were added. The resultant aqueous phase was further extracted with Et_2O (4 × 25 mL) and the combined organic phases were dried over $MgSO_4$. Filtration and solvent removal gave the crude product which was taken up in DCM (3 mL). TsCl (51 mg, 0.268 mmol, 1 equiv) and triethylamine (56 μL, 0.402 mmol, 1.5 equiv) were added and the mixture was stirred for 15 h. Silica (ca. 1 g) was added and the solvent was removed under reduced pressure before purification by flash column chromatography (cyclohexane-EtOAc; 3:1) gave **18** (78 mg, 89%) as a colorless oil. R_f = 0.15 (cyclohexane-EtOAc; 3:1); $[\alpha]^{20}_D$ −79.7 (*c* 2.3, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3475, 3061, 3031, 2928, 2889, 1599, 1495, 1452, 1339, 1158, 1092, 1034; *m*/*z* (ES$^+$) 332 (MH$^+$, 100%); found 332.1309, $C_{18}H_{22}NO_3S$ requires 332.1320 (−3.4 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.84−1.95 (m, 1H), 2.21−2.29 (m, 1H), 2.43 (s, 3H), 2.51−2.62 (m, 1H), 3.36 (dd, app. t, J = 11.75 Hz, 1H), 3.73 (dd, J = 5.5, 11.0 Hz, 1H), 3.74−3.81 (m, 1H), 3.86 (dd, J = 2.75, 11.0 Hz, 1H), 3.89 (ddd, J = 1.5., 7.5, 11.75 Hz, 1H), 7.07 (d, J = 7.0 Hz, 2H), 7.21 (t, J = 7.0 Hz, 1H), 7.26 (t, J = 7.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.6 (CH_3), 36.2 (CH_2), 42.7 (CH), 56.0 (CH_2), 62.8 (CH), 65.6 (CH_2), 126.9 (CH), 127.2 (CH), 127.5 (CH), 128.6 (CH), 130.0 (CH), 134.4 (C), 138.9 (C), 144.1 (C).

2*S*-Methyl-4*S*-phenyl-1-(toluene-4-sulfonyl)pyrrolidine 19. As described above, **15** (53 mg, 0.238 mmol, 1 equiv) was converted into **19** (54 mg, 72%) which was isolated following purification by flash column chromatography (cyclohexane-EtOAc: 6:1) as a colorless oil. R_f = 0.25 (cyclohexane-EtOAc: 6:1); $[\alpha]^{20}_D$ −114.0 (*c* 0.6, $CHCl_3$); υ_{max} (neat/cm^{-1}) 3031, 2972, 2927, 2878, 1599, 1494, 1454, 1339, 1158, 1091; *m*/*z* (ES$^+$) 316 (MH$^+$, 100%); found 316.1358, $C_{18}H_{22}NO_2S$ requires 316.1371 (−4.2 ppm); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.46 (d, J = 6.0 Hz, 3H), 1.65−1.74 (m, 1H), 2.31−2.39 (m, 1H), 2.45 (s, 3H), 2.61−2.70 (m, 1H), 3.35 (dd, app. t, J = 11.5 Hz, 1H), 3.72−3.81 (m, 1H), 3.74 (ddd, J = 1.25, 7.5, 11.5 Hz, 1H), 7.09−7.12 (m, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.6 (CH_3), 22.7 (CH_3), 42.2 (CH_2), 43.0 (CH), 55.0 (CH_2), 57.1 (CH), 126.9 (CH), 127.0 (CH), 127.5 (CH), 128.6 (CH), 129.8 (CH), 135.4 (C), 139.7 (C), 143.4 (C).

Alcohol **18** (75 mg, 0.227 mmol, 1 equiv) in DCM (10 mL) was treated with MsCl (25 μL, 0.323 mmol, 1.4 equiv) and triethylamine (63 μL, 0.452 mmol, 2 equiv), and stirring was continued at room temperature for 15 h. Diethyl ether (15 mL) and 1 M HCl solution (15 mL) were added and the resultant aqueous phase was re-extracted with diethyl ether (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and were filtered, and the solvent was removed under reduced pressure. The mesylate (ca. 0.227 mmol) was directly dissolved in acetone (15 mL), and NaI (340 mg, 2.267 mmol, 10 equiv) and 18-crown-6 (ca. 5 mg) were added. The mixture was heated to reflux for 24 h. On cooling, acetone was removed under reduced pressure before diethyl ether (20 mL) and water (20 mL) were added. The aqueous layer was extracted with diethyl ether (20 mL) and the combined extracts were dried over $MgSO_4$ and were filtered, and the solvent was removed. The crude iodide (ca. 0.227 mmol) was taken up in dry THF (10 mL) and LAH (86 mg, 2.263 mmol, 10 eq.) was added. The mixture was heated to reflux and was stirred for 1 h. After cooling to room temperature, saturated NH_4Cl (20 mL) and diethyl ether (20 mL) were added. On phase separation, the aqueous layer was further extracted with diethyl ether (2 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration, solvent removal, and purification by flash column chromatography (cyclohexane-EtOAc: 6:1) gave **19** (47 mg, 66%) whose data were identical to that described above.

Acknowledgment. Dr. H. Mueller-Bunz (UCD) is thanked for X-ray crystallography and UCD is thanked for their financial support.

Supporting Information Available: Proton and carbon NMR spectra and the X-ray structures of **12a** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062189O