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Iridium-Mediated Isomerization−Cyclization of Bicyclic Pauson−Khand Derived Allylic Alcohols

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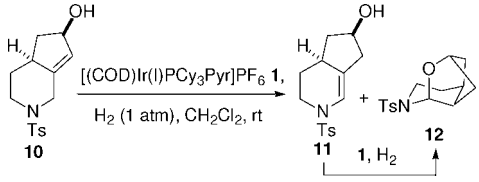
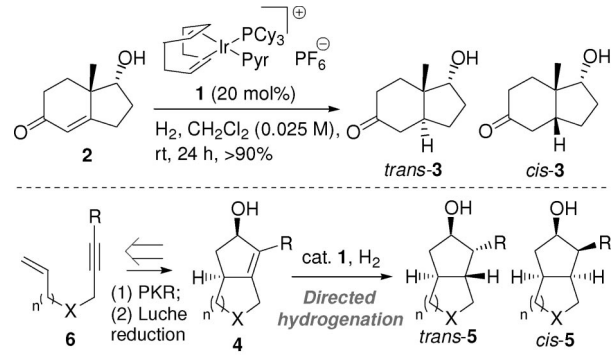
Received August 6, 2008



Treatment of 2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[2]pyrindin-6-ol **10**, accessed from the diastereoselective Luche reduction of a Pauson−Khand derived bicylic cyclopentenone, with a catalytic amount of (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate **1** (Crabtree's catalyst) under a hydrogen atmosphere resulted in the formation of 4-(toluene-4-sulfonyl)-2-oxa-4-azatricyclo[5.2.1.0^{3,8}]decane **12** as a single diastereoisomer. This process is likely to proceed via an initial Ir(I)-mediated isomerization of the alkene to form an *N*-sulfonyl enamine **11**, followed by cyclization. Evidence to support this came when, after short reaction periods, **11** was isolated, characterized spectroscopically, and on resubmission to the reaction conditions formed **12**.

Crabtree's iridium(I) catalyst **1**[1] offers both enhanced reactivity in hydrogenation reactions, often enabling sterically challenging, substituted alkenes to participate that prove unreactive under more standard, Wilkinson-type rhodium(I) catalysis and also, as a consequence of coordination, delivery of hydrogen in a diastereoselective fashion (efficient, diastereoselective delivery of hydrogen has been reported to occur even with tertiary alcohols).[1b,2,3] A classic example of the power of this approach was published by Stork and Kahne in which they demonstrated that treatment of **2** with **1**, under a hydrogen atmosphere, gave *trans*-**3** in 92% de (Scheme 1).[3] In contrast, under heterogeneous hydrogenation conditions (5 mol % Pd/C, H_2, MeOH) *cis*-**3** was selectively formed. We envisaged that

SCHEME 1. The Directed Hydrogenation of Alkenols



[where X = O, NR', CH_2 etc.; R = H, alkyl etc.; n = 1, 2]

this would be an attractive method for the synthesis of densely functionalized trans-fused bicycles, of the type *trans*-**5**, possessing 4-contiguous stereogenic centers, and as such would prove complementary to standard hydrogenation. As in the case of **2**, this type of reduction has been reported to proceed stereoselectively generating the cis-fused ring architecture where $n = 1$ (i.e. *cis*-**5**).[4] Methods for achieving the trans-architecture related to this type of system are of interest since it is found in several naturally occurring compounds.[5]

Bicyclic compounds of the type **4** may be accessed, typically in good yields, from the corresponding enyne **6** following a Pauson−Khand reaction (PKR)[6] and a Luche reduction.[7] The latter process has been shown to proceed in related systems with high levels of diastereoselectivity.[8]

To investigate the feasibility of this directed, diastereoselective reduction approach bicyclic cyclopentenone **9** was prepared in 4-steps following an initial Mitsunobu reaction between propargyl alcohol **7** and *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide.[9] Subsequent removal of the *tert*-butoxycarbonyl (Boc) group and alkylation with butenyl bromide gave enyne **8**. Pauson−Khand cycloaddition was effected under standard conditions[6] which entailed initial formation of the dicobalt hexacarbonyl−alkyne complex followed by promotion with 4-methylmorpholine *N*-oxide (NMO).[10] The resulting bicyclic cyclopentenone **9** was then treated with sodium borohydride in the presence of cerium(III) chloride heptahydrate[7,8] to stereoselectively form allylic alcohol **10**. The relative stereochemistry of the stereogenic centers was probed by nuclear Overhauser effect experiments. A degassed solution of allylic alcohol **10**

(1) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205. (b) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

(2) For reviews concerning directed reactions, including hydrogenation of alkenes see: (a) Hoveyda, A. H.; Evans, D.A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

(3) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.

(4) (a) Becker, D. P.; Nosal, R.; Zabrowski, D. L.; Flynn, D. L. *Tetrahedron* **1997**, *53*, 1. (b) Krafft, M. E.; Bonaga, L. V. R.; Wright, J. A.; Hirosawa, C. *J. Org. Chem.* **2002**, *67*, 1233.

(5) Kam, T.-S.; Yoganathan, K.; Wei, C. *J. Nat. Prod.* **1997**, *60*, 673.

(6) For reviews see: (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (b) Evans, P.; Kavanagh, Y. *Modern Approaches to the Synthesis of O- and N-Heterocycles*; Kaufman, T. S., Larghi, E. L., Eds.; Research Signpost: Kerala, India, 2007; Vol *2*, pp 33−78.

(7) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

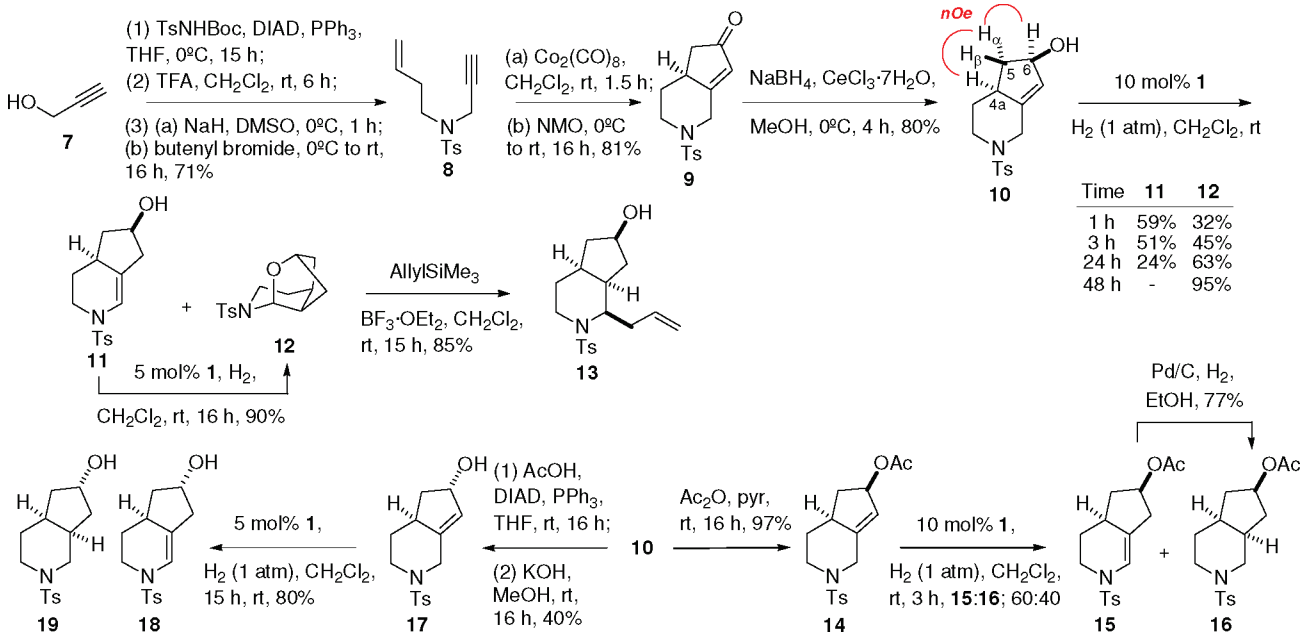
(8) (a) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396–1406. (b) Lanver, A.; Schmalz, H.-G. *Eur. J. Org. Chem.* **2005**, 1444.

(9) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745.

(10) (a) Shambayti, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204.

10.1021/jo8017439 CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/08/2008

SCHEME 2. The Iridium(I) Mediated Conversion of Pauson−Khand Derived Allylic Alcohol 10 into Tricycle 12



in dichloromethane was then treated with Crabtree's catalyst **1** (ca. 10 mol%) and stirred under an atmosphere of hydrogen gas. After 1 h the formation of a nonpolar compound was detected by thin layer chromatography. Purification of the crude reaction mixture by flash column chromatography afforded this material, which proved to be **12** (32%).[11] The second compound recovered from the column was *N*-sulfonyl enamine **11** (59%). The reaction was repeated under identical conditions, albeit for longer reaction periods, and in doing so it became clear that as the time of reaction was increased the isolated yield of the tricycle **12** increased and accordingly less of the enamine **11** was detected. For example, after 2 days **12** was obtained as the sole product (95%).

This finding seemed to indicate that **11** gradually underwent conversion into **12** as the reaction progressed, which was corroborated when a purified sample of **11** was resubmitted to the reaction in the presence of 5 mol % of **1**. In this instance, under a hydrogen atmosphere conversion of **11** into **12** (90%) was observed over 16 h. Interestingly, in the absence of either the catalyst, or indeed if the same process was carried out under a nitrogen atmosphere, no conversion of **11** was detected. Furthermore, when **10** was stirred with 10 mol % of **1** under a nitrogen atmosphere no conversion into **11** was detected. Treatment of enone **9**, under identical conditions used to convert **10** to **11**/**12**, also resulted in no change. In none of these studies were the anticipated saturated products, of the type **5**, resulting from alkene hydrogenation observed. In relation to these findings several examples of alkenyl isomerizations with **1** have been observed in which the desired hydrogenation appears to be slow.[12]

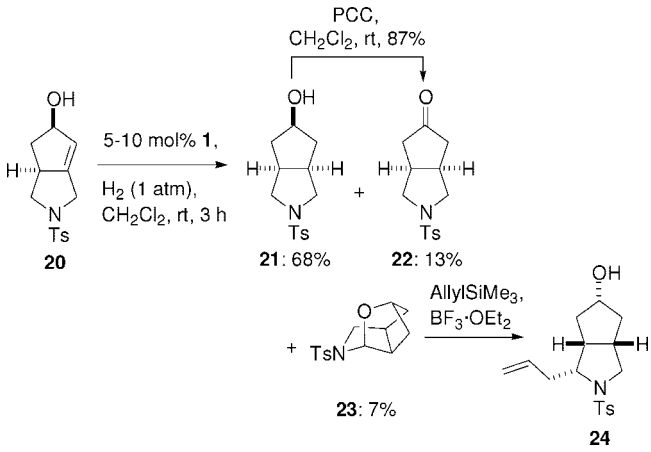
The overall conversion, **10** into **12**, represents a diastereoselective C−H activation and since it is appreciated that *N*,*O*-acetals participate in a range of further functionalization reactions[13] we were interested in considering the reactivity of **12**. To this end, **12** was treated with allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$[14] and gratifyingly **13**, the product of carbon−carbon bond formation, was isolated in good yield as a single diastereoisomer whose stereochemistry was again uncovered by the use of nuclear Overhauser effect NMR experiments.

The identity and stereochemistry of the 6-oxa functional group was next investigated (Scheme 2). Since alternative Lewis basic groups[2] have also been reported to interact with **1**, compound **10** was first acetylated under standard conditions before **14** was treated with 10 mol % of **1**. After 1 h, proton NMR spectroscopy indicated quantitative formation of **15** and after 3 h a mixture of **15** and **16** was similarly detected in a 3:2 ratio. Initially it was hoped that in the absence of the hydroxyl group responsible for the cyclization reaction **11** to **12**, directed hydrogenation might have occurred to form the trans-ring junction. However, hetereogeneous hydrogenation of this mixture gave only one compound that proved to be *cis*-**16**. A Mitsunobu sequence was then employed to invert the hydroxyl stereochemistry. Thus, **17** was prepared in 2-steps and its relative stereochemistry probed by NOE experiments and comparison to **10**. Treatment of **17** with Crabtree's catalyst **1** again gave the product **18** of isomerization in 80% yield. In this example only a trace of the reduced compound **19** was detected even after prolonged reaction periods (15 h).

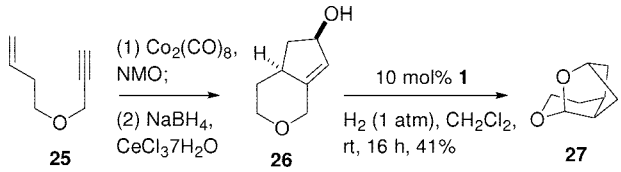
These examples clearly demonstrate that, for this type of [4.3.0]-bicyclic structure, regioselective isomerization of the trisubstituted alkene occurs more rapidly than addition of hydrogen and that, as expected, the stereochemistry and identity of the 6-oxa functionality governs any further reactivity. To compare the reactions described above with the analogous [3.3.0]-bicyclic system **20** was prepared from allylprop-2-ynylamine[15] via sulfonamide formation, PKR, followed by Luche reduction (Scheme 3). In the event, treatment of **20** with Crabtree's catalyst **1** gave a mixture of compounds **21**, **22**, and

(11) CCDC reference no. 694620.
(12) For examples of alkene isomerization with **1** see: (a) Krel, M.; Lallemand, J.-Y.; Guillou, C. *Synlett* **2005**, 2043. (b) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *24*, 5461.
(13) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.
(14) For a representative procedure see: Toumieux, S.; Compain, P.; Martin, O. R.; Selkti, M. *Org. Lett.* **2006**, *8*, 4493.
(15) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757.

SCHEME 3. Conversion of 20 into Tricycle 23



SCHEME 4. Conversion of 26 into Tricycle 27



the tricycle **23**, albeit in low yield (7%). None of the *N*-sulfonyl enamine, which, based on the study summarized in Scheme 2, presumably facilitates the formation of **23**, was detected in this example. The relative stereochemistry between the ring junction in compounds **21** and **22** was elucidated by oxidation of the alcohol **21**, which formed **22**, and hydrogenation (Pd/C, H_2, not shown) of **20** and the PKR adduct, which formed **21** and **22**, respectively.

Compound **23** possessed similar spectral properties to its congener **12** and, pleasingly, underwent a similar opening of the *N*,*O*-acetal to generate **24**, again as a single major diastereoisomer.

The formation of **21** and **22** in this sequence (these types of compounds were not observed during the studies illustrated in Scheme 2) is probably explained by the increased strain of the [3.3.0]-bicycle and the influence this has on the reactivity of the bridging trisubstituted alkene.

As Scheme 4 illustrates, the same sequence may be successfully applied to compounds possessing alternative functional groups to the *N*-sulfonyl examples previously discussed. Thus, **26** (prepared following the PKR and Luche reduction of 4-but-1-enyloxyprop-2-yne **25**)[16] gave **27** in moderate yield on treatment of with 10 mol % of **1**. The lower yields observed in this sequence may reflect the increased volatility of these lower molecular weight ether-containing compounds.

A possible mechanistic rationale, based on the sequence presented by Guillou and co-workers,[12a] may be suggested (Scheme 5). Under an atmosphere of hydrogen following reduction and subsequent loss of COD the cationic iridium(I) species **1** generates a 12 valence electron cationic Ir(I) species **28**. Association of this cationic species to the trisubstituted alkenes employed in this study serves to generate key complex **29** which may or may not be ligated to the hydroxyl group. It seems reasonable that at this stage regioselective insertion into one of two allylic carbon−hydrogen bonds serves to generate Ir(III) π-allyl complexes **30** and **32**, a step that appears to occur in competition with the oxidative addition of hydrogen to form an Ir(III) dihydride **34** required for alkenyl reduction.

Where $n = 1$ results indicate that the formation of **30** is favored and that this then undergoes conversion into **31**, which in turn may then undergo decomplexation to afford the isomerized alkene products (**11**, **15**, **18**), or evidently cyclization and hydrogen transfer to generate the tricycles **12**, **23**, and **27**. In the case of $n = 0$, presumably due to the extra strain associated with the [3.3.0] bicyclic system, **32** may also be formed, which leads to the formation of **22** on tautomerization. This sequence of events implies a relatively slow oxidative addition of hydrogen to Ir(I) forming the Ir(III) dihydride species **34** required for hydrogenation of the alkene.

An alternative pathway involving the addition of Ir(III) dihydride across the double bond followed by β-hydride elimination was also considered. However, in this instance it would appear surprising that intermediates such as **35** would not rapidly generate the products of direct hydrogenation on reductive elimination.

In summary, we have uncovered and studied an unusual isomerization−cyclization sequence that appears to be mediated by an iridium species derived from Crabtree's catalyst. The key to observing this sequence is that formal addition of two hydrogen atoms across the trisubstituted, bicyclic alkenes used in this study appears to be slow under the conditions studied. Future work involves ascertaining the role, if any, played by the heteroatom in the isomerization process and further application of these novel *N*,*O*- and *O*,*O*-acetals in the kind of ring-opening chemistry exemplified by the stereoselective transformation **12** to **13**. In relation to these future studies an enantioselective PKR-based method for the formation of this type of structure has recently been reported.[17]

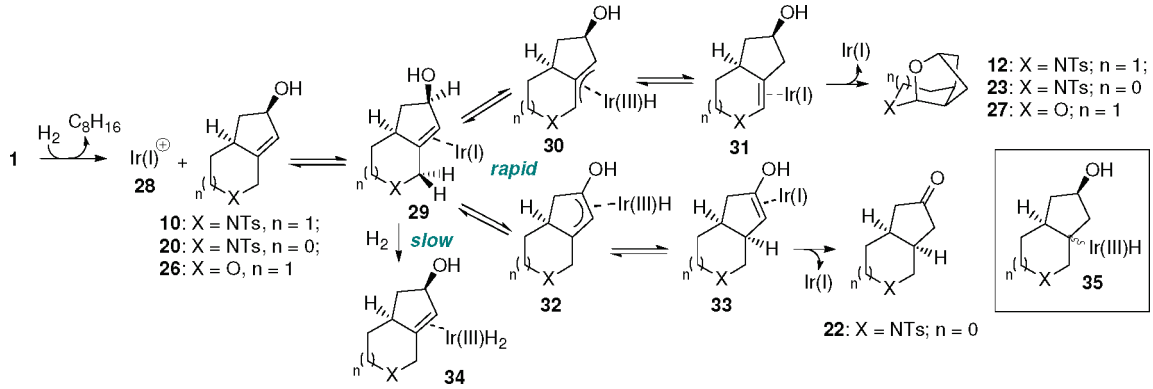
Experimental Section

(1*R,3*R**,7*S**,8*R**)-4-(Toluene-4-sulfonyl)-2-oxa-4-azatricyclo[5.2.1.0^{3,8}]-decane (12) and (4a*S**,6*R**)-2-(Toluene-4-sulfonyl)-3,4,4a,5,6,7-hexahydro-2*H*-[2]pyrindin-6-ol (11).** A solution of alcohol **10** (156 mg, 0.53 mmol, 1 equiv) in dichloromethane (20 cm^3) was degassed with a steady stream of N_2 for 10 min. To this Crabtree's catalyst **1** (20 mg, 0.025 mmol, 5 mol %) was added. Stirring was continued under an atmosphere of H_2 for 15 h. Solvent removal followed by direct purification by flash column chromatography (cyclohexane → cyclohexane−EtOAc; 1:1) afforded **12** as a colorless solid (78 mg, 51%) [crystals suitable for X-ray crystallography[11] were formed from gradual evaporation of a saturated solution of **12** in dichloromethane]: mp 108 °C; R_f 0.65 (cyclohexane−EtOAc; 1:1); δ_H (400 MHz, $CDCl_3$) 1.35−1.40 (1H, m, 10-CH_2), 1.52 (1H, d, J = 10.0 Hz, 9-CH_2), 1.67−1.72 (2H, m, 6-CH_2, 10-CH_2), 1.87−1.89 (1H, m, 9-CH_2), 1.91−1.96 (1H, m, 6-CH_2), 2.22−2.28 (2H, m, 7-CH, 8-CH), 2.42 (3H, s, CH_3), 2.78−2.85 (1H, m, 5-CH_2), 3.45−3.49 (1H, m, 5-CH_2), 4.24 (1H, s, 1-CH_2), 5.77 (1H, s, 3-CH_2), 7.28 (2H, d, J = 8.0 Hz, ArH), 7.70 (2H, d, J = 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 26.5 (CH_2), 28.8 (CH), 34.4 (CH_2), 34.8 (CH_2), 38.8 (CH_2), 41.2 (CH), 77.8 (CH), 85.6 (CH), 127.8 (CH), 129.6 (CH), 135.9 (C), 143.2 (C) ppm; υ_{max} (film) 2989, 2926, 1597, 1454, 1333, 1159, 1091, 1041, 998, 907, 867, 817, 762, 662; *m*/*z* $C_{15}H_{20}NO_3S$ requires 294.1164 (MH^+, 100%); found 294.1178 (+4.8 ppm). Further elution gave **11** as an amorphous solid (56 mg, 36%): R_f 0.30 (cyclohexane−EtOAc; 1:1); δ_H (400 MHz, $CDCl_3$) 1.13−1.19 (2H, m, 4-CH_2, 5-CH_2), 1.96−2.01 (1H, m, 4-CH_2), 2.16−2.22 (3H, m, 4-CH_2, 4a-CH,

(16) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

(17) (a) Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron: Asymmetry* **2000**, *11*, 797. (b) Gibson, S. E.; Kaufmann, K. A. C.; Loch, J. A.; Steed, J. W.; White, A. J. P. *Chem. Eur. J.* **2005**, *11*, 2566.

SCHEME 5. Possible Mechanistic Rationale for the Crabtree Catalyst Mediated Isomerization−Cyclization Sequence



7-CH_2), 2.42 (3H, s, CH_3), 2.63 (1H, dd, J = 7.0, 15.8 Hz, 7-CH_2), 2.80 (1H, dt, J = 3.0, 12.5 Hz, 3-CH_2), 3.85 (1H, dt, J = 3.0, 12.5 Hz, 3-CH_2), 4.28−4.34 (1H, m, 6-CH), 6.51 (1H, s, 1-CH), 7.29 (2H, d, J = 8.0 Hz, ArH), 7.64 (2H, d, J = 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 27.2 (CH_2), 35.3 (CH), 38.8 (CH_2), 41.4 (CH_2), 43.6 (CH_2), 71.9 (CH), 117.8 (CH), 124.6 (CH), 127.0 (CH), 129.6 (CH), 134.6 (C), 143.5 (C) ppm; υ_{max} (film) 3492, 3415, 2926, 2856, 2250, 1677, 1598, 1494, 1454, 1339, 1259, 1164, 1092, 1047, 977 cm^{-1}; m/z $C_{15}H_{20}NO_3S$ requires 294.1164 (MH^+, 100%); found 294.1151 (−4.4 ppm). Following the procedure described above alcohol **10** (42 mg; 0.140 mmol, 1 equiv) in dichloromethane (10 cm^3) was treated with **1** (11 mg, 0.014 mmol, 10 mol%) under a hydrogen atmosphere. After stirring for 48 h gradient elution flash column chromatography (cyclohexane to cyclohexane−EtOAc; 3:1) yielded **12** (40 mg, 95%) with data in accord to that reported above.

(1*S,4a*S**,6*R**,7a*R**)-1-Allyl-2-(toluene-4-sulfonyl)-octahydro-[2]pyrindin-6-ol (13).** Under an atmosphere of nitrogen, boron trifluoride·diethyletherate (0.4 cm^3, 2.96 mmol, 10 equiv) was added to a solution of the tricyclic ether **12** (87 mg, 0.29 mmol, 1 equiv) and allyltrimethylsilane (0.18 cm^3, 1.18 mmol, 4 equiv) in dichloromethane (15 cm^3) at rt. The mixture was stirred for 15 h, before $NaHCO_3$ (15 cm^3) was added. Ether (3 × 20 cm^3) was used to the extract and the combined extracts were dried over $MgSO_4$ and filtered then solvent was removed in vacuo. The crude material was purified by flash column chromatography (cyclohexane−EtOAC; 1:1) giving **13** (85 mg, 85%) as a colorless solid: mp 130 °C; R_f 0.30 (cyclohexane−EtOAc; 1:1); δ_H (400 MHz, $CDCl_3$) 1.30 (1H, dd, J = 2.0, 13.0 Hz, 5-CH_2), 1.40−1.45 (1H, m, 4-CH_2), 1.52 (1H, dq, J = 6.0, 13.0, 7-CH_2), 1.64 (1H, dq, J = 4.5, 13.0 Hz, 4-CH_2), 1.79−1.85 (1H, m, 7a-CH), 1.91−1.99 (3H, m, 4a-CH, 5-CH_2, 7-CH_2), 2.06−2.13 (1H, m, CH_2), 2.18−2.25 (1H, m, CH_2), 2.33 (3H, s, CH_3), 2.80 (1H, td, J = 3.0, 13.0 Hz, 3-CH_2), 3.56−3.61 (1H, m, 3-CH_2), 3.90 (1H, dd, J = 6.0, 9.0 Hz, 1-CH), 4.23−4.29 (1H, m, 6-CH), 4.88−4.93 (2H, m, CH_2), 5.54−5.63 (1H, m, CH), 7.20 (2H, d, J = 8.0 Hz, ArH), 7.63 (2H, d, J = 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 21.4 (CH_3), 27.4 (CH_2), 31.9 (CH), 36.3 (CH_2), 37.7 (CH_2), 39.8 (CH_2), 40.0 (CH), 41.6 (CH_2), 53.7 (CH), 72.0 (CH), 117.3 (CH_2), 126.9 (CH), 129.5 (CH), 135.0 (CH), 138.3 (C), 142.8 (C) ppm; υ_{max} (film) 3512, 3414, 3076, 2926, 2867, 2255, 1641, 1598, 1495, 1461, 1442, 1384, 1335, 1315, 1267, 1160, 1091, 1061, 1018, 969, 917, 815, 737 cm^{-1}; m/z $C_{18}H_{26}NO_3S$ requires 336.1633 (MH^+, 100%); found 336.1635 (+0.5 ppm).

Acknowledgment. We would like to acknowledge financial support from the Science Foundation Ireland and the University College Dublin. Additionally Dr. Helge Müller-Bunz is thanked for X-ray crystallography and Dr. Dilip Rai for mass spectrometry.

Supporting Information Available: Experimental details, copies of proton and carbon NMR spectra, and the X-ray structure of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8017439