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Stereocontrolled preparation of bicyclic alkaloid analogues: an approach towards the kinabalurine skeleton

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ABSTRACT

An approach towards the construction of bicyclic analogues of monoterpene alkaloids belonging to the kinabalurine, incarvilline and skytanthine families of natural products is reported. These syntheses rely on a stereoselective intramolecular Pauson–Khand cyclisation of a chiral pool-derived enyne in order to prepare the bicyclic core. Stereoselective further elaboration generates diastereomeric analogues of the naturally occurring alkaloids.

1. Introduction

In 1997 a new class of monoterpene alkaloids, named the kinabalurines, was isolated from *Kopsia pauciflora*.[1] This species belongs to a larger family of trees and shrubs that are widespread throughout Asia. The structures of this group of diastereomeric compounds, exemplified by kinabalurines A **1**, B **2** and F **3**, were determined by X-ray crystallography and NMR spectroscopy. These compounds appear to belong to a wider family bearing a close structural resemblance to other bicyclic alkaloids isolated from different plant sources. For example, the incarvilline series was isolated recently from *Incarvillea sinensis* Lam. and members of this compound class exhibit analgesic properties.[2] Recently reports concerning the stereoselective synthesis of the incarvilline **4** family of compounds have appeared.[3] Tecomanine **5** from *Tecoma stans* Juss. possesses hypoglycaemic properties.[4] Tecostanine **6** is an isomer of incarvilline **4** in which the oxidation is found on the methyl substituent as opposed to the five-membered ring.[5]

The majority of compounds, shown in Figure 1, possesses a characteristic fused bicyclic ring structure and oxygenation in the five-membered carbocyclic ring. Another structurally related class of compounds that have generated interest are the skytanthine alkaloids **7** that lack this oxygenation in the five-membered ring but display the same structural framework.[6] Similarly, related compounds are found in which the heterocyclic ring is present as a pyridine, exemplified by actinidine **8**.[7] In a more general sense, since many natural products and pharmaceutically active agents possess substituted piperidine ring systems the synthesis of this class of functionalised heterocyclic compound remains of interest to the general synthetic chemistry community.[8]

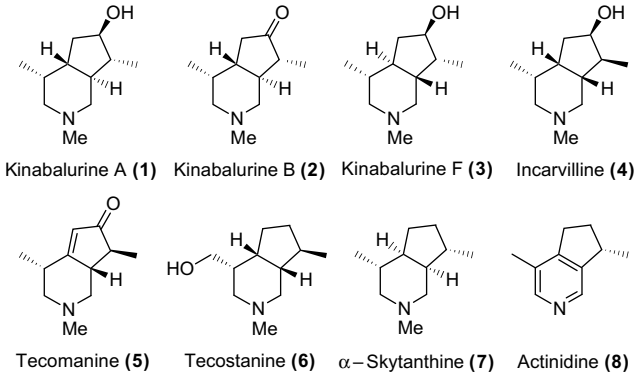

Figure 1. Bicyclic monoterpene alkaloids.

In terms of the kinabalurine family, the presence of 5-contiguous stereocentres and the *trans*-stereochemistry of the **4a**/**7a** ring junction represents an interesting and challenging synthetic problem. Consequently, based on both their structure and potential biological properties we considered this family of compounds as interesting targets and envisaged using an intramolecular Pauson–Khand cyclisation[9] to install the bicyclic ring architecture (Fig. 2).

Retrosynthetically, from the target compound(s), manipulation of the nitrogen-protecting group and two stereocontrolled reductions lead to the cyclopentenone Pauson–Khand adduct **9**. Ever since Magnus' seminal studies involving the intramolecular Pauson–Khand reaction it has been well appreciated that a stereogenic centre adjacent to either the propargylic, or the allylic reactive group typically engenders good stereocontrol on cyclisation.[9–11] Finally, it was felt that the acyclic PKR precursor **10** would be readily available following standard synthetic steps. Recently, Honda and

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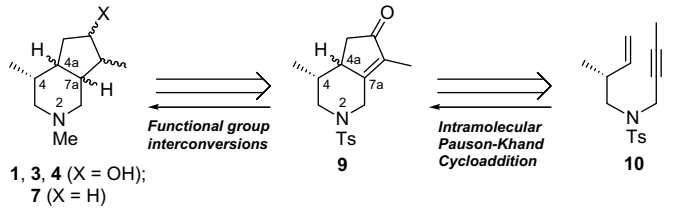


Figure 2. Retrosynthetic analysis of bicyclic alkaloids based on an intramolecular Pauson–Khand reaction.

Kaneda have reported a similar PKR based strategy as a means to prepare both (−)-incarvilline and (+)-α-skytanthine as single stereoisomers.[12]

2. Results and discussion

Scheme 1 illustrates the preparation of the enyne PKR precursor **10** and its subsequent intramolecular PKR. Starting from the enantiopure, chiral pool-derived alcohol **11**, often termed the Roche ester, a Mitsunobu reaction using a Weinreb-type reagent, under standard conditions,[13] installed the protected nitrogen atom. When 1 equiv of alcohol **11** was employed only moderate yields of adduct **12** were encountered (ca. 40–60%). It seems likely that these low yields arise from a competitive elimination reaction, facilitated by the ester functional group. Based on this hypothesis the use of 2 equiv of **11** significantly improved the isolated yield of **12** (94%). The methyl ester moiety was then reduced using $LiAlH_4$ to afford the primary alcohol **13**. This apparently straightforward reduction proved troublesome and following initial attempts the desired product **13** was formed in only moderate yield in conjunction with compound **14** in which the *tert*-butyloxycarbamate group has been lost. However, the formation of this side product can be minimised if the reaction is conducted at low temperature and for only short periods. Oxidation of the primary alcohol **13** to the aldehyde **15**, using PCC, proceeded smoothly and this material was converted into the terminal alkene **16** using a standard Wittig reaction. An excess of the phosphonium salt was used to ensure that the aldehyde **15**, with its vulnerable asymmetric carbon, did not come into contact with the base. However, under a variety of conditions only moderated yields of **16** were obtained. Removal of the carbamate protecting group with TFA and alkylation using but-2-ynyl bromide proceeded without event and afforded the PKR precursor **10** in good yield. This compound was treated under standard intramolecular PKR conditions:[11,14] thus, $Co_2(CO)_8$ was added to a solution of **10** in dichloromethane and the mixture was stirred for 1 h at room temperature. TLC analysis indicated the consumption of **10** and the formation of a less-polar, brown spot. The reaction mixture was then cooled to 0 °C and NMO·H_2O was added. Following purification of the crude reaction mixture, **9a** was isolated (80%) along with its diastereomeric adduct **9b** (10%). Under these conditions the PKR proceeds in a diastereoselective manner and the stereochemistry of the newly formed chiral centre was confirmed by NOE and X-ray crystallography.[15]

During this sequence we were somewhat concerned with the integrity of the stereogenic methyl substituent since several compounds potentially possess a labile proton. However, based on the Flack parameters[15,16] obtained for the X-ray structure and the consistent optical rotation values obtained for the bulk material (**9a**: $[\alpha]_D^{20}=-74.2$) we believe that this fear was unfounded and that minimal epimerisation occurs following this sequence. Thus, adduct **9a** may be prepared from **11** in seven linear steps (31% overall yield) and isolated as a single diastereoisomer. The preferential formation of **9a** is consistent with a reactive conformer resembling *exo*-**18** (X=H) in which the alkene moiety occupies a *pseudo*-equatorial orientation (Fig. 3). Although this stereochemistry is present in the natural product kinabalurine F (**3**), most members of this family of compounds possess a *cis*-relationship between H-4 and H-4a (see Fig. 1). Therefore, we wished to investigate whether the presence of a sulfonyl substituted alkene would reverse the stereochemical outcome of the intramolecular PKR following work from Carretero's group.[17] In these studies good to excellent levels of diastereoselectivity were achieved, particularly during the formation of [3.3.0]bicyclic cyclopentenones. The rationale used to explain the change in stereochemical course for a series of enynes was that according to the Magnus mechanistic model, the presence of

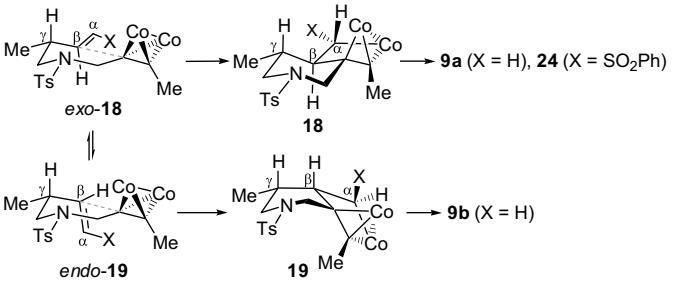
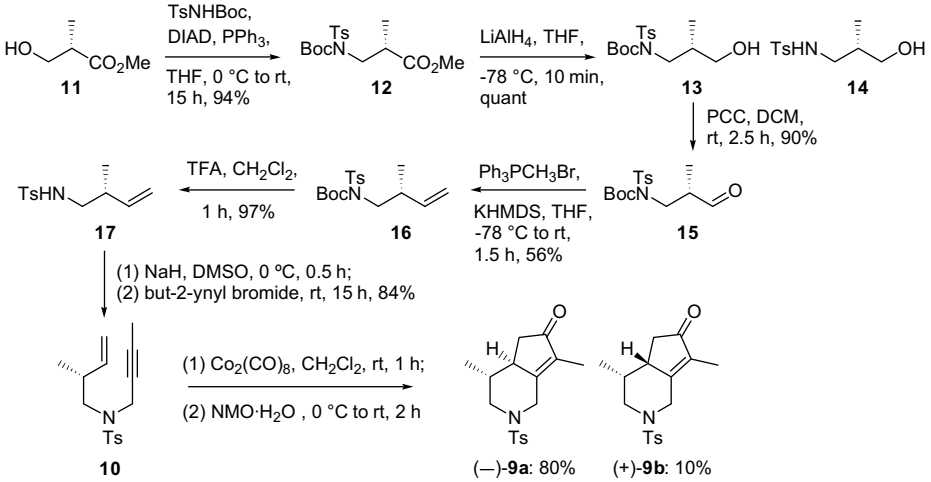
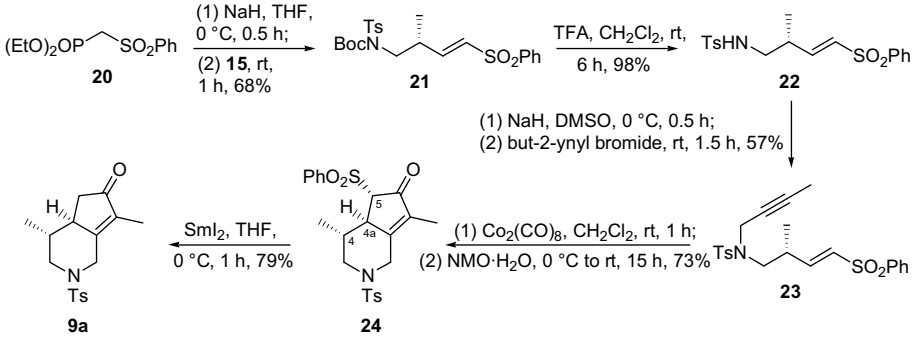


Figure 3. Possible explanation for observed stereochemistry (cobalt CO ligands omitted for clarity).



Scheme 1. Preparation of enyne **10** and its stereoselective intramolecular Pauson–Khand reaction.



Scheme 2. Intramolecular Pauson–Khand reaction of vinyl sulfone **23**.

a sulfinyl, or sulfonyl alkenyl substituent leads to a developing steric interaction between the allylic substituent in the proposed transition state forming **18** when X=SO_2Ph. In contrast, it was argued that in the *pseudo*-axial conformer *endo*-**19** when X=SO_2Ph such steric interactions between the substituents are minimised on formation of **19** (Fig. 3).

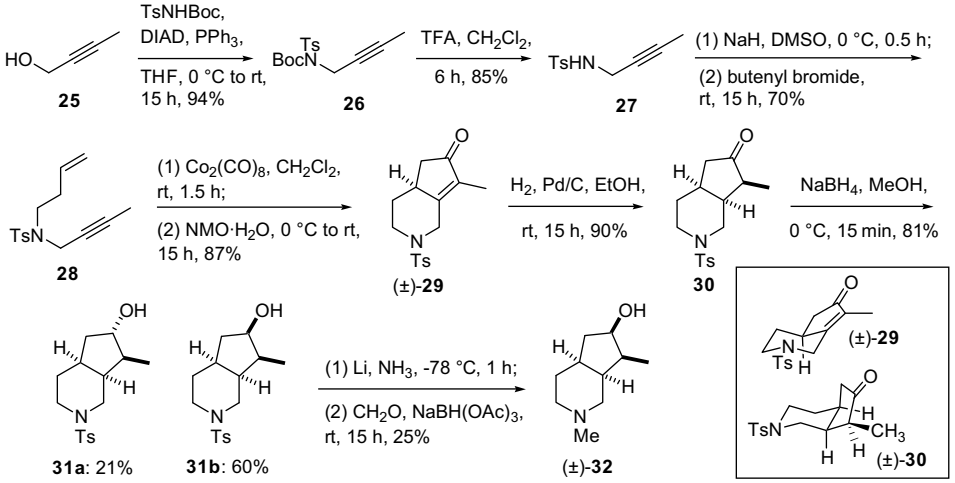
As Scheme 2 illustrates, PK precursor, enyne **23** was prepared over three steps from aldehyde **15**. A standard Horner–Wadsworth–Emmons reaction between **20**[18] and **15** afforded the α,β-unsaturated sulfone **21** in reasonable yield with good control of alkenyl geometry (*E*:*Z*; >95:5). This compound was converted into enyne **23** in two steps. The alkylation of **22** proved problematic and only moderate yields of **23** were obtained. The main side product formed from this reaction was *trans*-3-methyl(buta-1,3-diene-1-sulfonyl)benzene, resulting from elimination of the amino containing group. Use of alternative conditions such as Cs_2CO_3 did not improve this yield.[19] Notwithstanding, enyne **23** underwent an efficient intramolecular PKR and compound **24** was isolated in 73% yield and no diastereomeric products were detected following this reaction.

The relative stereochemistry of **24** was uncovered by two means; firstly, NOE experiments indicated an enhancement to H-5 to when H-4 was irradiated and to the 4-methyl substituent when H-4a was irradiated. Secondly, this was further confirmed on conversion of **24** into **9a** on treatment with 2 equiv of SmI_2. Measurement of optical rotation value of the material isolated following this sequence proved to be identical to values recorded from material prepared via Scheme 1, again confirming the integrity of the stereogenic centre bearing the methyl substituent.

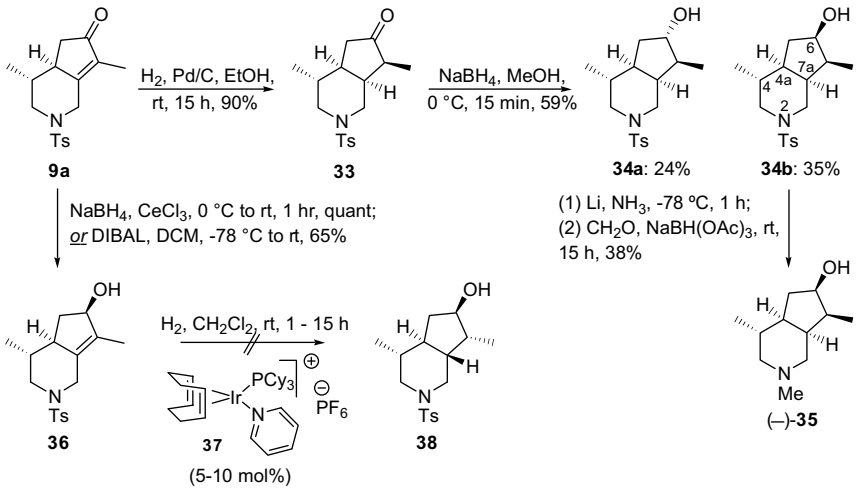
Thus, clearly in the case of our particular substrate **23** the ability of an α,β-unsaturated sulfone to reverse the stereochemistry of an intramolecular PKR was not observed.[17] Possible explanations for this could be that allylic strain serves to minimise the population of the reactive conformer *endo*-**19**,[20] or alternatively the formation of the metallocycle intermediate **19** may force the newly formed piperidine ring into an unfavourable boat conformation.

With compound **9a** in hand its conversion into the types of natural products illustrated in Figure 1 was considered. To this end a racemic model system, **29**, not containing the stereogenic methyl substituent present in **9a** was prepared using an analogous PK based route (Scheme 3). But-2-ynol **25** smoothly participated in a Mitsunobu reaction with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide and, in this case, equimolar amounts of the reaction partners delivered adduct **26** in good yield. The *tert*-butoxycarbonyl protecting group was removed with TFA and the resultant sulfonamide **27** underwent alkylation with butenyl bromide to generate the PKR precursor **28**. Standard oxidative PK conditions using NMO·H_2O afforded the racemic fused cyclopentenone **29** (four steps, 49%).

Compound **29** stereoselectively underwent a palladium-catalysed hydrogenation to generate **30**, whose relative stereochemistry, again, was probed using NOE experiments [irradiation of H-7a enhanced H-4a and H-7]. In contrast, subsequent 1,2-reduction of **30** with sodium borohydride resulted in a non-stereoselective reaction in which significant levels of **31a** were formed in addition to the expected diastereoisomer, **31b** [irradiation of H-7 enhancement to H-6 and H-7a]. Attempts to optimise the stereochemical outcome of this reaction were not performed and the major diastereoisomer was converted into the *N*-methyl analogue (±)-**32** over a two-step sequence involving reductive desulfonylation followed by reductive amination using aqueous formaldehyde and



Scheme 3. Stereoselective synthesis of bicyclic alkaloid analogue (±)-**32**.



Scheme 4. Stereoselective synthesis of (−)-**35**.

sodium triacetoxyborohydride.[21] The drastic change in the stereofacial efficiency between the alkenyl reduction of **29** and the carbonyl reduction of **30** appears to be consistent with the shift from an sp^2 hybridised junction, between the bicyclic system, to an sp^3 hybridised *cis*-ring junction and can be understood on the basis of their likely, respective conformations (as shown in Scheme 3).

Following the model study outlined in Scheme 3 attention was turned towards the chiral pool-derived cyclopentenone **9a** (Scheme 4). As observed in Scheme 3, hydrogenation occurred stereoselectively to afford the *cis*-fused bicyclic ring architecture **33** and subsequent non-stereoselective carbonyl reduction gave a mixture of **34a** and **34b** [NOE main diastereoisomer: irradiation of H-7a enhancement to H-7 and H-4a; irradiation of H-7 enhancement to H-6; irradiation of H-6 enhancement to CH_{2A}-5 and irradiation of CH_{2A}-5 enhancement to H-4a]. The low yields observed for the purified diastereomers **34a** and **34b** reflect the difficulty in obtaining pure samples by column chromatography. Diastereomer **34b** was converted into compound **35**, a diastereoisomer of kinabalurine F (**3**), following *N*-sulfonyl deprotection and methylation.

Since only 3 of the 5 stereocentres present in compound **35** are consistent with those of the natural product kinabalurine F (**3**) we then attempted to make use of the intrinsic stereofacial bias of compound **9a**, observed in the palladium-catalysed hydrogenation, by reducing the carbonyl group prior to alkenyl reduction. Pleasingly, when **9a** was treated under either DIBAL, or Luche[22] reduction conditions only one diastereoisomer was isolated, which proved to possess the correct stereochemistry [NOE: irradiation of H-6 enhancement CH_{2A}-5, which when irradiated showed an enhancement to H-4a, irradiation of CH_{2B}-5 showed enhancement only to CH_{2A}-5]. We felt that allylic alcohol **36** was now a perfect candidate for a directed diastereoselective hydrogenation,[23] which has been reported to occur under the influence of Crabtree's iridium hydrogenation catalyst **37**, even in cases involving sterically challenging substrates.[24] Thus, we hoped that following this reaction we would install the remaining stereocentres required to complete the synthesis of **3**. However, unfortunately under standard conditions (1–4 atm H_2, 5–10 mol % **37**), several attempts only led to the formation of unidentified material and none of the hoped for product **38**.

Apart from the sterically hindered nature of the tetrasubstituted alkene present in **36** an additional explanation for the failure of this key reaction concerns our recent finding that related PKR derived bicycles undergo rapid alkene isomerisation in the presence of **37** affording the corresponding *N*-sulfonyl enamine.[25] The conjugate reduction of enone **9** under dissolved metal conditions was also briefly investigated based on the possibility that this mechanistically distinct process might lead to the formation of the desired **4a**/**7a** *trans*-stereochemistry.[24b,26] However, due to concomitant *N*-sulfonyl deprotection the results obtained from these studies proved difficult to interpret.

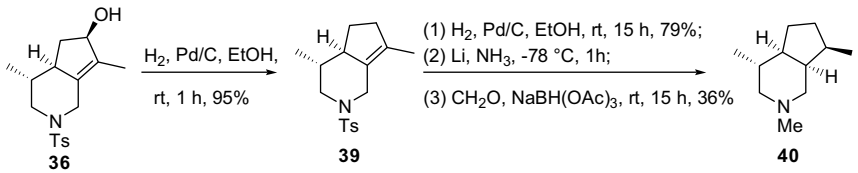
An interesting observation was encountered when allylic alcohol **36** was treated under standard hydrogenation conditions (Scheme 5). Following short reaction periods, loss of the secondary hydroxyl group occurred more rapidly than addition of hydrogen to the hindered alkene. The product **39**, of this uncommon allylic reduction (hydrogenolysis) was subsequently converted into **40**, a diastereoisomer of the deoxygenated skytanthine monoterpene alkaloid **7**.

In summary, the stereoselective synthesis of a series of bicyclic analogues related to naturally occurring monoterpene alkaloids has been achieved employing the intramolecular Pauson–Khand reaction. The majority of the bicyclic compounds belonging to this class of natural product possesses the opposite stereochemistry at C-4a, therefore, further synthetic studies will be focussed on investigating the stereoselectivity of the Pauson–Khand cyclisation.

3. Experimental

3.1. General

THF was dried over sodium-benzophenone under an atmosphere of nitrogen. Dichloromethane was distilled under nitrogen from calcium hydride. Dimethyl sulfoxide (DMSO) was dried over 4 Å molecular sieves. Reagents were obtained from commercial



Scheme 5. Synthesis of (−)-**40**.

sources and were used without additional purification. *N*-Methylmorpholine *N*-oxide (NMO) was used as its monohydrate. ^{1}H and ^{13}C NMR spectra were referenced to either residual ($CHCl_3$, δ_H 7.27 ppm; $CDCl_3$, δ_C 77.0 ppm), or internal trimethylsilane (TMS, δ_H 0.00 ppm). Spectral assignments reported were based on DEPT and 2D correlation spectroscopy. Optical rotation measurements, recorded in spectrophotometric grade chloroform, were performed at 20 °C and are given in units of deg cm^2 g^{-1}.

3.2. (+)-Methyl 3-[*N*-(*tert*-butoxycarbonyl)-*N*-(4-methylphenylsulfamido)]-2*S*-methyl propanoate 12[27]

Under N_2 *S*-**11** (1.00 cm^3, 9.08 mmol, 2 equiv) was added to a solution of *N*-(*tert*-butyoxycarbonyl)-*p*-toluenesulfonamide (1.23 g, 4.54 mmol, 1 equiv), triphenylphosphine (1.78 g, 6.81 mmol, 1.5 equiv) and diisopropylazodicarboxylate (1.43 cm^3, 7.26 mmol, 1.6 equiv) in THF (100 cm^3) in a dropwise fashion at 0 °C. The reaction mixture was then stirred at room temperature for 15 h. The solvent was removed under reduced pressure. Hexane (100 cm^3) was added to the resultant yellow mixture and a white solid precipitate removed by filtration. The remaining solution was preabsorbed on silica gel (ca. 15 g) and purified by flash column chromatography (Hex–EtOAc; 9:1→3:1) affording the product **12** as a colourless solid (1.59 g, 94%); mp=64–66 °C; R_f=0.35 (Hex–EtOAc; 3:1); $[\alpha]_D^{20}$ +24.0 (*c* 0.36, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.5 Hz, CH_3), 1.34 (9H, s, CH_3), 2.46 (3H, s, CH_3), 2.99–3.08 (1H, m, CH), 3.70 (3H, s, CH_3), 3.94 (1H, dd, *J* 7.5, 14.5 Hz, CH_2), 4.11 (1H, dd, *J* 7.5, 14.5 Hz, CH_2), 7.32 (2H, d, *J* 8.5 Hz, ArH) and 7.81 (2H, d, *J* 8.5 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 21.6 (CH_3), 27.8 (CH_3), 39.8 (CH), 49.1 (CH_2), 51.8 (CH_3), 84.5 (C), 127.9 (CH), 129.2 (CH), 137.1 (C), 144.2 (C), 150.9 (C) and 174.7 (C) ppm; ν_{max} (film) 2980, 2926, 2853, 1732, 1597, 1496, 1458, 1435, 1358, 1292, 1256, 1170, 1148 and 1088 cm^{-1}; *m*/*z* $C_{17}H_{25}NO_6SNa$ requires 394.1315 (MNa^+, 100%); found 394.1300 (+3.7 ppm); CHN analysis: $C_{17}H_{25}NO_6S$ requires C 54.99%, H 6.74%, N 3.77%; found C 55.04%, H 6.77%, N 3.76%.

3.3. (+)-*tert*-Butyl *N*-(3-hydroxy-2*S*-methylpropyl)-*N*-(toluene-4-sulfonyl)carbamate 13[27]

Under N_2 a solution of **12** (6.186 g, 16.67 mmol, 1 equiv), in THF (150 cm^3), at −78 °C was treated with solid $LiAlH_4$ (2.53 g, 66.6 mmol, 4 equiv) in one portion. Stirring was continued for 10 min before TLC analysis indicated consumption of the starting material. Saturated aqueous NH_4Cl (100 cm^3) was cautiously added at −78 °C. The mixture was stirred at room temperature before extraction with ether (4×50 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex–EtOAc; 3:1) afforded the alcohol **13** as a colourless oil (5.71 g, 100%); R_f=0.20 (Hex–EtOAc; 3:1); $[\alpha]_D^{20}$ +6.4 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 7.0 Hz, CH_3), 1.32 (9H, s, CH_3), 2.08–2.21 (1H, m, CH), 2.46 (3H, s, CH_3), 2.57 (1H, s(br), OH), 3.52 (1H, dd, *J* 4.0, 11.5 Hz, CH_2), 3.73 (1H, dd, *J* 4.0, 11.5 Hz, CH_2), 3.77 (1H, dd, *J* 5.5, 15.0 Hz, CH_2), 3.88 (1H, dd, *J* 9.5, 15.0 Hz, CH_2), 7.35 (2H, d, *J* 8.0 Hz, ArH) and 7.77 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 21.6 (CH_3), 27.8 (CH_3), 36.4 (CH), 49.1 (CH_2), 63.5 (CH_2), 85.0 (C), 127.7 (CH), 129.3 (CH), 137.1 (C), 144.4 (C) and 152.0 (C) ppm; ν_{max} (film) 3543, 3429, 2978, 2878, 1726, 1597, 1456, 1354, 1290, 1257, 1154 and 1088 cm^{-1}; *m*/*z* $C_{16}H_{25}NO_5SNa$ requires 366.1359 (MNa^+, 100%); found 366.1310 (+2.1 ppm).

3.4. (+)-*tert*-Butyl *N*-(2*S*-methyl-3-oxopropyl)-3-(toluene-4-sulfonyl)carbamate 15

A solution of the alcohol **13** (1.28 g, 3.73 mmol, 1 equiv) in dichloromethane (60 cm^3) was treated with PCC (2.00 g, 9.33 mmol, 2.5 equiv). Stirring was continued for 2.5 h at room temperature. TLC analysis indicated the consumption of starting material. Solvent was removed under reduced pressure and the residue purified by rapid flash column chromatography (Hex–EtOAc; 5:1). Thus the aldehyde **15** (1.14 g, 90%) was obtained as a colourless viscous oil and was used immediately in the following step; R_f=0.35 (Hex–EtOAc; 3:1); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 7.0 Hz, CH_3), 1.32 (9H, s, CH_3), 2.45 (3H, s, CH_3), 2.89–2.95 (1H, m, CH), 3.95 (1H, dd, *J* 7.0, 15.0 Hz, CH_2), 4.16 (1H, dd, *J* 7.0, 15.0 Hz, CH_2), 7.32 (2H, d, *J* 8.0 Hz, ArH), 7.78 (2H, d, *J* 8.0 Hz, ArH) and 9.71 (1H, d, *J* 2.5 Hz, CHO); δ_C (100 MHz, $CDCl_3$) 11.6 (CH_3), 21.6 (CH_3), 27.7 (CH_3), 47.1 (CH), 47.2 (CH_2), 84.9 (C), 127.9 (CH), 129.4 (CH), 136.9 (C), 144.6 (C), 150.9 (C) and 202.7 (CH) ppm; ν_{max} (film) 3419, 2982, 2938, 1730, 1598, 1496, 1458, 1395, 1369, 1355, 1292, 1257, 1179, 1149 and 1088 cm^{-1}; *m*/*z* $C_{16}H_{23}NO_5SNa$ requires 364.1204 (MNa^+, 100%); found 364.1195 (+2.6 ppm).

3.5. (+)-*tert*-Butyl *N*-(2*R*-methylbut-3-enyl)-*N*-(toluene-4-sulfonyl)carbamate 16

Under N_2 a slurry of Ph_3PCH_3Br (1.76 g, 4.92 mmol, 1.5 equiv) in THF (30 cm^3) was treated with a 0.5 M solution of KHMDS in toluene (8.2 cm^3, 4.10 mmol, 1.25 equiv) at −78 °C. The yellow/orange solution was warmed to room temperature over 1 h before recooling to −78 °C and addition of the aldehyde **15** (1.12 g, 3.28 mmol, 1 equiv) in THF (10 cm^3). Stirring was continued for 0.5 h at −78 °C before warming to room temperature over 1 h. Saturated NH_4Cl (50 cm^3) was added and the mixture was extracted with ether (3×50 cm^3). The combined organic extracts were dried over $MgSO_4$ followed by filtration, solvent removal under reduced pressure and purification by flash column chromatography (Hex–EtOAc; 5:1). Thus, the alkene **16** (630 mg, 56%) was isolated as a viscous, slightly yellow oil; R_f=0.35 (Hex–EtOAc; 5:1); $[\alpha]_D^{20}$ +7.6 (*c* 0.95, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.5 Hz, CH_3), 1.34 (9H, s, CH_3), 2.43 (3H, s, CH_3), 2.69–2.77 (1H, m, CH), 3.73–3.84 (2H, m, CH_2), 5.02–5.11 (2H, m, CH_2), 5.70–5.79 (1H, m, CH), 7.31 (2H, d, *J* 8.0 Hz, ArH) and 7.80 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 16.9 (CH_3), 21.1 (CH_3), 27.4 (CH_3), 38.3 (CH), 51.5 (CH_2), 83.6 (C), 114.9 (CH_2), 127.5 (CH), 128.6 (CH), 137.1 (C), 140.3 (CH), 143.5 (C) and 150.6 (C) ppm; ν_{max} (film) 3079, 2978, 2932, 1723, 1643, 1598, 1456, 1421, 1367, 1356, 1157 and 1088 cm^{-1}; *m*/*z* $C_{17}H_{25}NO_4SNa$ requires 362.1408 (MNa^+, 100%); found 362.1402 (+1.7 ppm).

3.6. (−)-4-Methyl-*N*-(2*R*-methylbut-3-enyl)benzenesulfonamide 17[27]

At room temperature a solution of the alkene **16** (428 mg, 1.31 mmol, 1 equiv) in dichloromethane (20 cm^3) was treated with TFA (1.01 cm^3, 13.11 mmol, 10 equiv) in a dropwise fashion. Stirring was continued for 1 h before a saturated solution of $NaHCO_3$ (50 cm^3) was added. Extraction with ether (3×50 cm^3) and drying of the combined organic extracts over $MgSO_4$, filtration and solvent removal in vacuo gave the crude product. Purification by flash column chromatography (Hex–EtOAc; 5:1) gave **17** as a colourless viscous oil (287 mg, 97%); R_f=0.15 (Hex–EtOAc; 5:1); $[\alpha]_D^{20}$ −2.3 (*c* 0.258, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.5 Hz, CH_3), 2.25–2.32 (1H, m, CH), 2.45 (3H, s, CH_3), 2.72–2.77 (1H, m, CH_2), 2.94–3.01 (1H, m, CH_2), 4.44 (1H, t, *J* 5.0 Hz, NH), 5.01–5.05 (2H, m CH_2), 5.48–5.57 (1H, m, CH), 7.33 (2H, d, *J* 8.0 Hz, ArH) and 7.75 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 17.1 (CH_3), 21.1 (CH_3), 37.5 (CH), 47.5 (CH_2), 116.0 (CH_2), 126.7 (CH), 129.3 (CH), 136.5 (C), 139.9 (CH) and 143.1 (C) ppm; ν_{max} (film) 3340, 3293, 3109, 2971, 2928, 2872, 1642, 1453, 1423, 1324, 1306, 1289, 1160 and 1093 cm^{-1}; *m*/*z* $C_{12}H_{18}NO_2S$ requires 240.1054 (MH^+, 100%); found 240.1058 (−1.8 ppm).

3.7. (+)-*N*-But-2-ynyl-4-methyl-*N*-(2*R*-methylbut-3-enyl)benzenesulfonamide 10

At room temperature a solution of the alkene **17** (435 mg, 1.91 mmol, 1 equiv) in DMSO (40 cm^3) was treated with 60% w/w NaH in mineral oil (115 mg, 2.87 mmol, 1.5 equiv). The mixture was stirred for 0.5 h before 1-bromobut-2-yne (0.34 cm^3, 3.83 mmol, 2 equiv) was added dropwise. After stirring for 1 h the mixture was extracted with ether (4×50 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (Hex–EtOAc; 9:1→Hex–EtOAc; 1:1) afforded **10** (470 mg, 84%) as a colourless oil; R_f=0.35 (Hex–EtOAc; 5:1); $[\alpha]_D^{20}$ +6.8 (*c* 0.302, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.5 Hz, CH_3), 1.53 (3H, t, *J* 1.5 Hz, CH_3), 2.42 (3H, s, CH_3), 2.45–2.52 (1H, m, CH), 3.00–3.10 (2H, m, CH_2), 4.00–4.12 (2H, m, CH_2), 5.02–5.11 (2H, m, CH_2), 5.70–5.79 (1H, m, CH), 7.29 (2H, d, *J* 8.0 Hz, ArH) and 7.73 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 3.1 (CH_3), 17.4 (CH_3), 21.4 (CH_3), 36.0 (CH), 37.1 (CH_2), 51.4 (CH_2), 71.5 (C), 81.5 (C), 114.8 (CH_2), 127.7 (CH), 129.1 (CH), 136.0 (C), 140.9 (CH) and 143.0 (C) ppm; ν_{max} (film) 3095, 2972, 2921, 2868, 2224, 1598, 1495, 1346, 1331, 1306, 1183, 1158, 1118 and 1090 cm^{-1}; *m*/*z* $C_{16}H_{22}NO_2S$ requires 292.1371 (MH^+, 100%); found 292.1371 (−0.2 ppm).

3.8. (−)-(4*R*,4a*R*)-4,7-Dimethyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro[2]pyrindin-6-one 9a and (+)-(4*R*,4a*S*)-4,7-dimethyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro[2]pyrindin-6-one 9b

At room temperature a solution of the enyne **10** (215 mg, 0.739 mmol, 1 equiv) in dichloromethane (25 cm^3, 0.03 M) was degassed with a steady stream of N_2 for approximately 0.5 h. $Co_2(CO)_8$ (316 mg, 0.924 mmol, 1.25 equiv) was added in one portion. Stirring was continued for 1 h before TLC analysis indicated the formation of the cobalt complex [brown spot; R_f=0.45 (Hex–EtOAc; 5:1)]. The solution was cooled to 0 °C before $NMO \cdot H_2O$ (435 mg, 3.22 mmol, 4.5 equiv) was added in one portion. Stirring was continued at 0 °C to room temperature over 2 h. TLC analysis indicated the formation of a more polar spot. Silica (ca. 5 g) was added and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (Hex–EtOAc; 3:1→1:1). Thus, the title compound **9a** (188 mg, 80%) was isolated as a colourless solid; crystals were formed from evaporation of a saturated solution of **9a** in dichloromethane; mp=120 °C (CH_2Cl_2); R_f=0.40 (Hex–EtOAc; 1:1); $[\alpha]_D^{20}$ −74.2 (*c* 0.225, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.5 Hz, 4-CH_3), 1.49–1.53 (1H, m, 4-CH), 1.74 (3H, d, *J* 1.0 Hz, 7-CH_3), 1.99 (1H, d, *J* 18.5 Hz, 5-CH_2), 2.08–2.13 (1H, m(br), 4a-CH), 2.19 (1H, dd (app. t), *J* 12.0 Hz, 3-CH_2), 2.45 (3H, s, CH_3), 2.55 (1H, dd, *J* 6.5, 18.5 Hz, 5-CH_2), 3.07 (1H, d, *J* 13.5 Hz, 1-CH_2), 3.85 (1H, ddd, *J* 2.0, 3.5, 12.0 Hz, 3-CH_2), 4.76 (1H, d, *J* 13.5 Hz, 1-CH_2), 7.36 (2H, d, *J* 8.0 Hz, ArH), 7.71 and (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 7.9 (CH_3), 17.3 (CH_3), 21.5 (CH_3), 37.7 (CH), 38.9 (CH_2), 44.8 (CH), 45.2 (CH_2), 52.2 (CH_2), 127.6 (CH), 129.8 (CH), 132.9 (C), 135.6 (C), 144.8 (C), 163.3 (C) and 205.1 (C) ppm; ν_{max} (film) 3042, 2960, 2925, 1705, 1666, 1597, 1457, 1344 and 1169 cm^{-1}; *m*/*z* $C_{17}H_{22}NO_3S$ requires 320.1331 (MH^+, 100%); found 320.1320 (+3.3 ppm). The other diastereoisomer **9b** was also isolated (25 mg, 10%) as a viscous oil; R_f=0.30 (Hex–EtOAc; 1:1); $[\alpha]_D^{20}$ +49.8 (*c* 1.016, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.5 Hz, 4-CH_3), 1.74 (3H, s, 7-CH_3), 2.13–2.21 (2H, m, 4-CH, 5-CH_2), 2.34 (1H, d, *J* 6.5 Hz, 5-CH_2), 2.44 (3H, s, CH_3), 2.63 (1H, dd, *J* 2.5, 12.0 Hz, 3-CH_2), 2.72 (1H, s(br), 4a-CH), 3.05 (1H, d, *J* 13.5, 1-CH_2), 3.74 (1H, d, *J* 12.0, 3-CH_2), 4.69 (1H, d, *J* 13.5, 1-CH_2), 7.35 (2H, d, *J* 8.0 Hz, ArH), and 7.68 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 7.8 (CH_3), 10.7 (CH_3), 21.5 (CH_3), 31.2 (CH), 36.7 (CH_2), 41.5 (CH), 45.7 (CH_2), 52.1 (CH_2), 127.6 (CH), 129.8 (CH), 132.7 (C), 136.8 (C), 143.9 (C), 161.6 (C) and 208.2 (C) ppm; ν_{max} (film) 3020, 2966, 2924, 1702, 1634, 1597, 1454, 1344, 1305 and 1159 cm^{-1}; *m*/*z* $C_{17}H_{20}NO_3S$ requires 318.1164 (M−H^+, 100%); found 318.1176 (+3.8 ppm).

3.9. (+)-*trans*-*tert*-Butyl *N*-(2*R*-methyl-4-(phenylsulfonyl)but-3-enyl)-*N*-(toluene-4-sulfonyl) carbamate 21

Solid 60% w/w NaH in mineral oil (100 mg; 2.52 mmol, 1.1 equiv) was added portionwise to a solution of phosphonate ester **20**[28] (770 mg, 2.52 mmol, 1.1 equiv) in THF (100 cm^3) at 0 °C. After 0.5 h aldehyde **15** (782 mg, 2.29 mmol, 1 equiv) was added at ambient temperature. After stirring for 1 h a saturated solution of NH_4Cl (50 cm^3) was added, and the mixture was extracted with ether (4×50 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (cyclohexane–EtOAc; 1:1) afforded **21** (743 mg, 68%) as a colourless oil; R_f=0.40 (cyclohexane–EtOAc; 3:1); $[\alpha]_D^{20}$=+17 (*c* 0.511, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.5 Hz, CH_3), 1.25 (9H, s, CH_3), 2.35 (3H, s, CH_3), 2.82–2.87 (1H, m, CH), 3.72–3.82 (2H, m, CH_2), 6.30 (1H, dd, *J* 1.0, 15.0 Hz, CH), 6.87 (1H, dd, *J* 8.0 and 15.0 Hz, CH), 7.21 (2H, d, *J* 8.0 Hz, ArH), 7.43–7.47 (2H, m, ArH), 7.52–7.35 (1H, m ArH), 7.67 (2H, d, *J* 8.0 Hz, ArH) and 7.81–7.83 (2H, m, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 16.6 (CH_3), 21.6 (CH_3), 27.8 (CH_3), 37.1 (CH), 50.9 (CH_2), 84.0 (C), 127.7 (CH), 127.8 (CH), 129.2 (CH), 129.3 (CH), 130.9 (CH), 133.3 (CH), 137.1 (C), 140.4 (C), 144.4 (CH), 147.9 (C) and 150.9 (C); ν_{max} (film) 3060, 2980, 2933, 1729, 1598, 1626, 1447, 1355, 1317, 1147, 1086 and 1008 cm^{-1}; *m*/*z* $C_{23}H_{29}NO_6SNa$ requires 502.1334 (MNa^+, 100%); found 502.1317 (−3.4 ppm).

3.10. (+)-*trans*-*N*-(4-Benzenesulfonyl-2*R*-methylbut-3-enyl)-4-methylbenzene sulfonamide 22

At room temperature a solution of the alkene **21** (3.34 g, 6.99 mmol, 1 equiv) in dichloromethane (110 cm^3) was treated with TFA (5.35 cm^3, 69.9 mmol, 10 equiv) in a dropwise fashion. Stirring was continued for 6 h before a saturated solution of $NaHCO_3$ (150 cm^3) was added. Extraction with ether (3×100 cm^3) and drying of the combined organic extracts over $MgSO_4$, filtration and solvent removal in vacuo gave the crude product. Purification by flash column chromatography (cyclohexane–EtOAc; 3:1) gave **22** as a colourless viscous oil (2.65 g; 98%); R_f=0.25 (cyclohexane–EtOAc; 3:1); $[\alpha]_D^{20}$ +8.9 (*c* 0.725, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.05 (3H, d, *J* 7.0 Hz, CH_3), 2.43 (3H, s, CH_3), 2.53–2.62 (1H, m, CH), 2.89–3.02 (2H, m, CH_2), 4.83 (1H, t, *J* 7.0 Hz, NH), 6.29 (1H, dd, *J* 1.5, 15.0 Hz, CH), 6.83 (1H, dd, *J* 7.0, 15.0 Hz, CH), 7.30 (2H, d, *J* 8.0 Hz, ArH), 7.56 (2H, t, *J* 7.5 Hz, ArH), 7.62–7.65 (1H, m, ArH), 7.72 (2H, d, *J* 8.0 Hz, ArH) and 7.88 (2H, d, *J* 7.5 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 16.4 (CH_3), 21.5 (CH_3), 36.4 (CH), 47.4 (CH_2), 127.0 (CH), 127.6 (CH), 129.4 (CH), 129.3 (CH), 131.4 (CH), 133.5 (CH), 136.8 (C), 140.8 (C), 143.6 (C) and 147.5 (CH) ppm; ν_{max} (film) 3277, 2969, 2926, 2360, 1736, 1625, 1446, 1320, 1306, 1299, 1146 and 1086 cm^{-1}; *m*/*z* $C_{18}H_{20}NO_4S_2$ requires 378.0829 (M−H^+, 100%); found 378.0834 (−1.3 ppm).

3.11. (+)-*trans*-*N*-(4-Benzenesulfonyl-2*R*-methylbut-3-enyl)-*N*-(but-2-ynyl)-4-methyl benzenesulfonamide 23

At 0 °C a solution of the alkene **22** (42 mg, 0.11 mmol, 1 equiv) in DMSO (6 cm^3) was treated with 60% w/w NaH in mineral oil (4 mg, 0.11 mmol, 1 equiv). The mixture was stirred for 0.5 h before 1-bromobut-2-yne (0.02 cm^3, 0.22 mmol, 2 equiv) was added dropwise. After stirring for 1.5 h the mixture was extracted with ether (3×20 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (cyclohexane→cyclohexane–EtOAc; 1:1) afforded **23** (27 mg, 57%) as a colourless oil; R_f=0.50 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ +2.35 (*c* 1.70, $CHCl_3$); δ_H (400 MHz,

$CDCl_3$) 1.10 (3H, d, *J* 7.0 Hz, CH_3), 1.53 (3H, t, *J* 2.5 Hz, CH_3), 2.41 (3H, s, CH_3), 2.71–2.78 (1H, m, CH), 3.05–3.16 (2H, m, CH_2), 3.89–3.93 (2H, m, CH_2), 6.36 (1H, dd, *J* 1.5, 15.0 Hz, CH), 6.94 (1H, dd, *J* 7.5, 15.0 Hz, CH), 7.28 (2H, d, *J* 8.0 Hz, ArH), 7.52–7.55 (2H, m, ArH), 7.59–7.63 (1H, m, ArH), 7.67 (2H, d, *J* 8.0 Hz, ArH) and 7.89 (2H, d, *J* 7.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 3.2 (CH_3), 16.4 (CH_3), 21.4 (CH_3), 35.1 (CH), 37.9 (CH_2), 50.9 (CH_2), 71.2 (C), 82.2 (C), 127.6 (CH), 127.7 (CH), 129.2 (CH), 129.3 (CH), 130.8 (CH), 133.3 (CH), 135.5 (CH), 140.2 (C), 143.5 (C) and 148.3 (C) ppm; ν_{max} (film) 3405, 3058, 2967, 2921, 1626, 1598, 1446, 1347, 1318, 1161, 1087 and 1024 cm^{-1}; *m/z* $C_{22}H_{26}NO_4S_2$ requires 432.1305 (MH^+, 100%); found 432.1318 (+3.4 ppm).

3.12. (−)-(4*R*,4a*R*,5*S*)-5-Benzenesulfonyl-4,7-dimethyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro[2]pyridin-6-one 24

At room temperature a solution of the enyne **23** (666 mg, 1.54 mmol, 1 equiv) in dichloromethane (200 cm^3) was degassed with a steady stream of N_2 for approximately 0.5 h. $Co_2(CO)_8$ (792 mg, 2.31 mmol, 1.5 equiv) was then added in one portion. Stirring was continued for 1 h before TLC analysis indicated the formation of the cobalt complex [brown spot; R_f=0.80 (cyclohexane–EtOAc; 1:1)]. The solution was cooled to 0 °C before $NMO \cdot H_2O$ (903 mg, 6.69 mmol, 4.5 equiv) was added in one portion. The reaction was stirred from 0 °C to room temperature over 15 h. TLC analysis indicated the formation of a more polar spot. Silica (ca. 7 g) was added the solvent removed under reduced pressure and the residue purified by flash column chromatography (cyclohexane→cyclohexane–EtOAc; 1:1). Thus, the title compound **24** (518 mg, 73%) was isolated as a colourless solid; mp=87 °C; R_f=0.60 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ −33.6 (*c* 1.15, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.13 (3H, d, *J* 7.0 Hz, 4-CH_3), 1.57–1.64 (1H, m, 4-CH), 1.74 (3H, s, 7-CH_3), 2.31 (1H, t, *J* 12.0 Hz, 3-CH_2), 2.46 (3H, s, CH_3), 2.86 (1H, d, *J* 11.0 Hz, 4a-CH), 3.13 (1H, d, *J* 13.5 Hz, 1-CH_2), 3.61 (1H, d, *J* 2.0 Hz, 5-CH), 3.87–3.90 (1H, m, 3-CH_2), 4.74 (1H, d, *J* 13.5 Hz, 1-CH_2), 7.36 (2H, d, *J* 8.0 Hz, ArH), 7.57 (2H, t, *J*, 8.0 Hz, ArH), 7.69 (3H, d, *J* 8.0 Hz, ArH) and 7.85 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 8.3 (CH_3), 17.4 (CH_3), 21.6 (CH_3), 37.8 (CH), 45.3 (CH_2), 45.6 (CH), 52.4 (CH_2), 70.1 (CH), 127.6 (CH), 129.0 (CH), 129.3 (CH), 129.9 (CH), 132.9 (C), 134.3 (CH), 135.5 (C), 137.6 (C), 144.3 (C), 163.6 (C) and 195.9 (C) ppm; ν_{max} (film) 3026, 2964, 2927, 2360, 1715, 1665, 1598, 1448, 1387, 1346, 1309, 1163, 1008 and 1001 cm^{-1}; *m/z* $C_{23}H_{25}NO_5S_2$ requires 460.1252 (MH^+, 100%); found 460.1233 (−4.2 ppm).

3.13. (+)-(4*R*,4a*R*)-4,7-Dimethyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro[2]pyridin-6-one 9a

A solution of the enone **24** (49 mg, 0.106 mmol, 1 equiv) in THF (5 cm^3) was degassed under a steady stream of N_2 for 10 min. A 0.1 M solution of SmI_2 in hexanes (2.24 cm^3, 0.224 mmol, 2.1 equiv) was added dropwise at 0 °C. After stirring for 1 h, $NaHCO_3$ (10 cm^3) was added and the mixture extracted with diethyl ether (3×10 cm^3). The extract was dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by flash column chromatography (cyclohexane→cyclohexane–EtOAc; 1:1) yielded **9a** as a colourless solid (27 mg, 79%) whose data was in agreement with that described above.

3.14. *tert*-Butyl *N*-but-2-ynyl(toluene-4-sulfonyl)-carbamate 26

Under N_2, diisopropylazodicarboxylate (4.40 cm^3, 22.3 mmol, 1.2 equiv) was added to a solution of *N*-(*tert*-butyoxycarbonyl)-*p*-toluenesulfonamide (5.06 g, 18.6 mmol, 1 equiv), triphenylphosphine (5.86 g, 22.3 mmol, 1.2 equiv) and 2-butyn-1-ol **25** (1.53 cm^3, 20.5 mmol, 1.1 equiv) in THF (250 cm^3) in a dropwise fashion at 0 °C. The reaction mixture was then stirred at room temperature for 15 h. The solvent was removed under reduced pressure. Cyclohexane (100 cm^3) was added to the resultant yellow mixture and the white precipitate was filtered. The remaining solution was pre-absorbed on silica gel (ca. 15 g) and purified by flash column chromatography (cyclohexane→cyclohexane–EtOAc; 3:1) affording the product **26** as a white solid (6.02 g, 100%); mp=103 °C; R_f=0.40 (cyclohexane–EtOAc; 3:1); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, CH_3), 2.35 (3H, t, *J* 2.5 Hz, CH_3), 2.41 (3H, s, CH_3), 4.54 (2H, q, *J* 2.5 Hz, CH_2), 7.27 (2H, d, *J* 8.0 Hz, ArH) and 7.87 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 3.3 (CH_3), 21.4 (CH_3), 27.7 (CH_3), 36.1 (CH_2), 74.2 (C), 79.8 (C), 84.5 (C), 128.1 (CH), 128.9 (CH), 136.8 (C), 144.1 (C) and 150.2 (C) ppm; ν_{max} (film) 3035, 2982, 2923, 2233, 1919, 1729, 1598, 1496, 1457, 1359, 1313, 1280, 1246, 1173, 1089 and 1067 cm^{-1}; *m/z* $C_{16}H_{22}NO_4S$ requires 324.1270 (MH^+, 100%); found 324.1285 (+4.8 ppm).

3.15. *N*-But-2-ynyl-4-methylbenzenesulfonamide 27

At room temperature a solution of the alkyne **26** (1.65 g, 5.09 mmol, 1 equiv) in dichloromethane (100 cm^3) was treated with TFA (3.9 cm^3, 50.9 mmol, 10 equiv) in a dropwise fashion. Stirring was continued for 6 h before a saturated solution of $NaHCO_3$ (100 cm^3) was added. Extraction with ether (3×75 cm^3) and drying of the combined organic extracts over $MgSO_4$, filtration and solvent removal in vacuo gave the crude product. Purification by flash column chromatography (cyclohexane–EtOAc; 3:1) gave **27** as a colourless solid (1.07 g; 95%); mp=61 °C; R_f=0.35 (cyclohexane–EtOAc; 3:1); δ_H (500 MHz, $CDCl_3$) 1.47 (3H, t, *J* 2.5 Hz, CH_3), 2.32 (3H, s, CH_3), 3.64–3.67 (2H, m, CH_2), 5.11 (1H, t, *J* 5.5 Hz, NH), 7.20 (2H, d, *J* 8.5 Hz, ArH) and 7.69 (2H, d, *J* 8.5 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 3.0 (CH_3), 21.2 (CH_3), 33.1 (CH_2), 73.2 (C), 80.7 (C), 127.2 (CH), 129.3 (CH), 136.7 (C) and 143.3 (C) ppm; ν_{max} (film) 3258, 3063, 2954, 2919, 2851, 2299, 2228, 1598, 1494, 1325, 1245, 1160, 1092 and 1046 cm^{-1}; *m/z* $C_{11}H_{14}NO_2S$ requires 224.1745 (MH^+, 100%); found 224.0751 (+0.6 ppm).

3.16. *N*-But-3-enyl-*N*-but-2-ynyl-4-methylbenzenesulfonamide 28

Under N_2 a solution of the alkyne **27** (1.16 g, 5.20 mmol, 1 equiv) in DMSO (70 cm^3) was treated with 60% w/w NaH in mineral oil (260 mg, 6.50 mmol, 1.25 equiv) at ambient temperature. The mixture was stirred for 0.5 h before 4-bromobut-1-ene (0.79 cm^3, 7.80 mmol, 1.5 equiv) was added dropwise. After stirring for 15 h saturated aqueous NH_4Cl (100 cm^3) was added. The mixture was extracted with ether (4×75 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (cyclohexane→cyclohexane–EtOAc; 3:1) afforded **28** (1.01 g, 70%) as a colourless oil; R_f=0.60 (cyclohexane–EtOAc; 3:1); δ_H (500 MHz, $CDCl_3$) 1.55 (3H, t, *J* 2.5 Hz, CH_3), 2.30–2.35 (2H, m, CH_2), 2.41 (3H, s, CH_3), 3.23 (2H, t, *J* 7.5 Hz, CH_2), 4.05–4.06 (2H, m, CH_2), 5.03–5.12 (2H, m, CH_2), 5.73–5.81 (1H, m, CH), 7.28 (2H, d, *J* 8.0 Hz, ArH) and 7.22 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 3.1 (CH_3), 21.4 (CH_3), 32.2 (CH_2), 36.8 (CH_2), 45.7 (CH_2), 71.7 (C), 81.4 (C), 116.9 (CH_2), 127.7 (CH), 129.2 (CH), 134.6 (C), 136.1 (C) and 143.1 (CH) ppm; ν_{max} (film) 3077, 2978, 2921, 2867, 2298, 2224, 1920, 1642, 1598, 1495, 1455, 1325, 1288, 1233, 1170, 1092 and 1046 cm^{-1}; *m/z* $C_{15}H_{20}NO_2S$ requires 278.1215 (MH^+, 100%); found 278.1210 (−1.7 ppm).

3.17. (±)-7-Methyl-2-(toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro-[2]pyrindin-6-one 29

At room temperature a solution of the enyne **28** (824 mg, 2.97 mmol, 1 equiv) in dichloromethane (100 cm^3, 0.029 M) was

degassed with a steady stream of N_2 for approximately 0.5 h. $Co_2(CO)_8$ (1.52 g, 4.45 mmol, 1.5 equiv) was added in one portion. Stirring was continued for 1.5 h before TLC analysis indicated the formation of the cobalt complex [brown spot; R_f=0.9 (cyclohexane–EtOAc; 1:1)]. The solution was cooled to 0 °C before NMO·H_2O (2.60 g, 19.26 mmol, 6.5 equiv) was added in two portions. Stirring was continued at 0 °C to room temperature overnight. Silica (ca. 12 g) was added, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (cyclohexane–EtOAc; 1:1) to afford the colourless solid **29** (790 mg, 87%); mp=116 °C; R_f=0.35 (cyclohexane–EtOAc; 1:1); δ_H (400 MHz, $CDCl_3$) 1.32–1.43 (1H, m, 4-CH_2), 1.74 (3H, s, 7-CH_3), 1.95 (1H, d, *J* 16.5 Hz, 5-CH_2), 2.10 (1H, d(br), *J* 15.0 Hz, 4-CH_2), 2.45 (3H, s, CH_3), 2.53–2.59 (3H, m, 3-CH_2, 4a-CH_2, 5-CH_2), 3.13 (1H, d, *J* 13.5 Hz, 1-CH_2), 3.93 (1H, d, *J* 12.0 Hz, 3-CH_2), 4.75 (1H, d, *J* 13.5 Hz, 1-CH_2), 7.37 (2H, d, *J* 8.0 Hz, ArH) and 7.68 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 7.6 (CH_3), 21.3 (CH_3), 31.8 (CH_2), 37.3 (CH_2), 40.1 (CH), 45.5 (CH_2), 45.7 (CH_2), 127.4 (CH), 129.6 (CH), 132.8 (C), 135.4 (C), 143.8 (C), 163.6 (C) and 207.4 (C) ppm; ν_{max} (film) 3064, 2956, 2923, 2847, 1712, 1629, 1598, 1494, 1464, 1410, 1342, 1228, 1199, 1164, 1103 and 1004 cm^{-1}; *m/z* $C_{16}H_{20}NO_3S$ requires 306.1164 (MH^+, 100%); found 306.1159 (−1.6 ppm).

3.18. (±)-(4a*S*,7*S*,7a*S*)-7-Methyl-2-(toluene-4-sulfonyl)octahydro[2]pyrindin-6-one 30

A solution of enone **29** (233 mg, 0.76 mmol, 1 equiv) in ethanol (20 cm^3) was degassed with a steady stream of N_2 for 20 min. To this, Pd/C 10% w/w catalyst (81 mg, 10 mol %) was added. Stirring was continued overnight under an atmosphere of H_2. Filtration through Celite, followed by purification by flash column chromatography (cyclohexane–EtOAc; 1:1) afforded **30** as colourless solid (211 mg, 90%); mp=119 °C; R_f=0.55 (cyclohexane–EtOAc; 1:1); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 7.5 Hz, 7-CH_3), 1.72–1.77 (2H, m, 1-CH_2, 4-CH_2), 1.86–1.94 (1H, m, 5-CH_2), 2.02–2.10 (1H, m, 4-CH_2), 2.17–2.31 (2H, m, 3-CH_2, 5-CH_2), 2.39–2.48 (5H, m, 4a-CH, 7-CH, CH_3), 2.56–2.63 (1H, m, 7a-CH), 3.61–3.65 (2H, m, 1-CH_2, 3-CH_2), 7.32 (2H, d, *J* 8.0 Hz, ArH) and 7.60 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 8.2 (CH_3), 21.3 (CH_3), 25.7 (CH_2), 30.3 (CH), 36.8 (CH_2), 38.9 (CH), 40.9 (CH_2), 43.7 (CH_2), 48.7 (CH), 127.6 (CH), 129.6 (CH), 132.6 (C), 143.6 (C) and 218.3 (C) ppm; ν_{max} (film) 3041, 2968, 2945, 2925, 1737, 1596, 1492, 1453, 1388, 1325, 1308, 1295, 1180, 1154, 1092, 1076, 1035 and 1005 cm^{-1}; *m/z* $C_{16}H_{22}NO_3S$ requires 308.1320 (MH^+, 100%); found 308.1311 (−3.1 ppm).

3.19. (±)-(4a*S*,6*R*,7*S*,7a*S*)-7-Methyl-2-(toluene-4-sulfonyl)octahydro[2]pyrindin-6-ol 31b and (±)-(4a*S*,6*S*,7*S*,7a*S*)-7-methyl-2-(toluene-4-sulfonyl)octahydro[2]pyrindin-6-ol 31a

Sodium borohydride (44 mg, 1.15 mmol, 2.5 equiv) was added to a solution of ketone **30** (141 mg, 0.46 mmol, 1 equiv) in methanol (40 cm^3) at −78 °C. After stirring for 15 min, water (30 cm^3) was added and the mixture was extracted with ether (3×25 cm^3). The organic layer was washed with brine (20 cm^3), dried over $MgSO_4$ and filtered. Purification by flash column chromatography (cyclohexane→cyclohexane–EtOAc; 3:1) yielded **31b** as a colourless oil (85 mg, 60%); R_f=0.30 (cyclohexane–EtOAc; 1:1); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 7.5 Hz, 7-CH_3), 1.32–1.39 (1H, m, 5-CH_2), 1.58 (1H, d, *J* 13.5 Hz, 4-CH_2), 1.91–2.16 (5H, m, 4-CH_2, 4a-CH, 5-CH_2, 7-CH, 7a-CH), 2.42 (3H, s, CH_3), 2.43–2.52 (2H, m, 1-CH_2, 3-CH_2), 3.53–3.57 (2H, m, 1-CH_2, 3-CH_2), 4.14–4.18 (1H, m, 6-CH), 7.29 (2H, d, *J* 8.0 Hz, ArH) and 7.63 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 8.9 (CH_3), 21.4 (CH_3), 26.1 (CH_2), 34.7 (CH), 36.8 (CH_2), 41.5 (CH), 41.6 (CH_2), 42.3 (CH), 44.2 (CH_2), 74.0 (CH), 127.4 (CH), 129.6 (CH), 133.9 (C) and 143.2 (C) ppm; ν_{max} (film) 3513, 3060, 2928, 2857, 2360, 1727, 1638, 1598, 1531, 1464, 1342, 1267, 1161, 1094 and 1025 cm^{-1}; *m/z* $C_{16}H_{24}NO_3S$ requires 310.1477 (MH^+, 100%); found 310.1470 (−2.2 ppm). The other diastereoisomer **31a** was isolated as a colourless oil (30 mg, 21%); R_f=0.25 (cyclohexane–EtOAc; 1:1); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 7.5 Hz, CH_3), 1.51–1.59 (2H, m, 4-CH_2, 5-CH_2), 1.79–1.98 (4H, m, 1-CH_2, 4-CH_2, 5-CH_2, 7-CH), 2.17–2.23 (1H, m, 7a-CH), 2.38–2.41 (2H, m, 3-CH_2, 4a-CH), 2.44 (3H, s, CH_3), 3.46–3.54 (2H, m, 1-CH_2, 3-CH_2), 3.81–3.86 (1H, m, 6-CH), 7.34 (2H, d, *J* 8.0 Hz, ArH) and 7.64 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 12.9 (CH_3), 21.5 (CH_3), 26.2 (CH_2), 34.1 (CH), 36.2 (CH_2), 41.7 (CH_2), 41.8 (CH), 44.2 (CH_2), 46.7 (CH_2), 78.6 (CH), 127.5 (CH), 129.6 (CH), 133.5 (C) and 143.4 (C) ppm; ν_{max} (film) 3497, 3401, 2923, 1648, 1598, 1463, 1340, 1162, 1092, 1057 and 1003 cm^{-1}; *m/z* $C_{16}H_{24}NO_3S$ requires 310.1477 (MH^+, 100%); found 310.1472 (−1.6 ppm).

3.20. (±)-(4a*S*,6*R*,7*S*,7a*S*)-2,7-Dimethyloctahydro[2]pyrindin-6-ol 32

Alcohol **31b** (70 mg, 0.23 mmol, 1 equiv) in THF (5 cm^3) was added dropwise to a solution of lithium (59 mg, 8.42 mmol, 38 equiv) in NH_3 (40 cm^3) at −78 °C. Stirring was continued at −78 °C for 40 min. Solid NH_4Cl (ca. 10 mg) was added and the mixture was stirred at room temperature for 1 h. Water (10 cm^3) and dichloromethane (15 cm^3) were added and the solution was basified to pH 14 (1 M NaOH) and extracted with dichloromethane (3×15 cm^3). The combined extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. Mass spectrometry confirmed the presence of the amine [$C_9H_{18}NO$ requires 156.1388 (MH^+, 100%); found 156.1381 (−4.7 ppm)]. The residue was taken up in THF (5 cm^3). To this, formaldehyde, 38% in water (19 mg, 0.25 mmol, 1.1 equiv) was added. The mixture was stirred for 10 min before sodium triacetoxyborohydride (72 mg, 0.34 mmol, 1.5 equiv) was added. After 15 h water (10 cm^3) and dichloromethane (10 cm^3) were added. Basification of the water layer from pH of 5–14 (1 M NaOH) was followed by extraction with dichloromethane (3×15 cm^3). The combined extracts were dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by flash column chromatography (CH_2Cl_2→CH_2Cl_2–MeOH; 1:1) gave the tertiary amine **32** as a yellow oil (9 mg, 25%); R_f=0.10 (CH_2Cl_2–MeOH; 1:1); δ_H (500 MHz, $CDCl_3$) 0.99 (3H, d, *J* 7.0 Hz, 7-CH_3), 1.56–1.64 (2H, m, 4-CH_2, 5-CH_2), 1.86–1.96 (1H, m, 4-CH_2), 1.98–2.23 (5H, m, 1-CH_2, 4a-CH, 5-CH_2, 7-CH, 7a-CH), 2.27 (3H, s, 2-CH_3), 2.38 (1H, dt, *J* 4.5, 12.0 Hz, 3-CH_2), 2.47–2.53 (2H, m, 1-CH_2, 3-CH_2) and 4.08–4.12 (1H m, 6-CH) ppm; δ_C (125 MHz, $CDCl_3$) 9.5 (CH_3), 25.8 (CH_2), 33.6 (CH), 38.5 (CH_2), 42.2 (CH), 42.9 (CH), 46.3 (CH_3), 50.1 (CH_2), 52.1 (CH_2) and 74.5 (CH) ppm; ν_{max} (film) 3401, 2926, 2780, 2684, 2229, 1659, 1454, 1334, 1263, 1117 and 1034 cm^{-1}; *m/z* $C_9H_{20}NO$ requires 170.1545 (MH^+, 100%); found 170.1543 (−1.1 ppm).

3.21. (+)-(4a*S*,4a*R*,7*S*,4a*S*)-4,7-Dimethyl-2-(toluene-4-sulfonyl)octahydro[2]pyrindin-6-one 33

A solution of enone **9a** (135 mg, 0.42 mmol, 1 equiv) in ethanol (15 cm^3) was degassed under a steady stream of N_2 for 20 min. To this Pd/C 10% w/w (45 mg, 10 mol %) was added. Stirring was continued overnight under an atmosphere of H_2. Filtration through Celite, followed by purification by flash column chromatography (cyclohexane→cyclohexane–EtOAc; 1:1) afforded **33** as colourless solid (122 mg, 90%); mp (decomp.)=117 °C; R_f=0.65 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ +39.5 (*c* 2.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 7.5 Hz, 7-CH_3), 1.22 (3H, d, *J* 7.5 Hz, 4-CH_3), 1.86–1.95 (3H, m, 4-CH, 5-CH_2, 1-CH_2), 2.09–2.16 (1H, m, 4a-CH), 2.22–2.29 (1H, m, 5-CH_2), 2.32–2.39 (1H, m, 7-CH), 2.42 (3H, s, CH_3), 2.54 (1H, dd, *J* 3.0, 11.5 Hz, 3-CH_2), 2.68–2.76 (1H, m, 7a-CH), 3.26 (1H, d, *J* 11.5 Hz,

3-CH_2), 3.56 (1H, dd, *J* 5.5, 12.0 Hz, 1-CH_2), 7.30 (2H, *J* 8.0 Hz, ArH) and 7.58 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 8.8 (CH_3), 18.4 (CH_3), 21.4 (CH_3), 30.0 (CH), 35.7 (CH), 37.7 (CH), 38.6 (CH_2), 41.2 (CH_2), 47.1 (CH_2), 48.2 (CH), 127.3 (CH), 129.7 (CH), 132.9 (C), 143.6 (C) and 218.4 (C) ppm; ν_{max} (film) 2962, 2925, 2854, 1738, 1598, 1463, 1379, 1344, 1306, 1261, 1163, 1091, 1067 and 1018 cm^{-1}; *m*/*z* $C_{17}H_{24}NO_3S$ requires 322.1477 (MH^+, 100%); found 322.1469 (−2.5 ppm).

3.22. (+)-(4*R*,4a*R*,6*R*,7*S*,7a*S*)-4,7-Dimethyl-2-(toluene-4-sulfonyl)octahydro[2]pyrindin-6-ol 34b and (+)-(4*R*,4a*S*,6*R*,7*S*,7a*S*)-4,7-dimethyl-2-(toluene-4-sulfonyl)octahydro[2]pyrindin-6-ol 34a

Sodium borohydride (11 mg, 0.29 mmol, 1.2 equiv) was added to a solution of ketone **33** (78 mg, 0.24 mmol, 1 equiv) in methanol (10 cm^3) at −78 °C. After stirring for 15 h, water (15 cm^3) was added and the mixture extracted with ether (3×20 cm^3). The organic layer was washed with brine (10 cm^3), dried over $MgSO_4$ and filtered. Purification by flash column chromatography (cyclohexane–EtOAc; 1:1→cyclohexane–EtOAc; 3:1) yielded **34b** as a colourless oil (35 mg, 45%); R_f=0.60 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ +13.7 (*c* 2.15, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 7.0 Hz, 7-CH_3), 1.11 (3H, d, *J* 7.0 Hz, 4-CH_3), 1.31–1.41 (1H, m, 5-CH_2), 1.65–1.72 (1H, m, 4a-CH), 1.74–1.80 (1H, m, 4-CH), 1.95–2.00 (1H, m, 7-CH), 2.13–2.24 (2H, m, 5-CH_2, 7a-CH), 2.43 (3H, s, CH_3), 2.66 (1H, t, *J* 11.5 Hz, 1-CH_2), 2.76 (1H, dd, *J* 3.5, 11.5 Hz, 3-CH_2), 3.09–3.14 (1H, m, 3-CH_2), 3.45 (1H, dd, *J* 6.5, 11.5 Hz, 1-CH_2), 4.11–4.16 (1H, m, 6-CH), 7.30 (2H, d, *J* 8.0 Hz, ArH) and 7.63 (2H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 9.3 (CH_3), 19.3 (CH_3), 21.5 (CH_3), 31.2 (CH), 37.9 (CH_2), 38.6 (CH), 42.0 (CH), 42.1 (CH), 44.2 (CH_2), 48.1 (CH_2), 74.1 (CH), 127.4 (CH), 129.5 (CH), 134.2 (C) and 143.1 (C) ppm; ν_{max} (film) 3530, 3025, 2961, 2928, 1598, 1462, 1337, 1260, 1225, 1160, 1092 and 1024 cm^{-1}; *m*/*z* $C_{17}H_{26}NO_3S$ requires 324.1633 (MH^+, 100%); found 324.1629 (−1.4 ppm). The other diastereoisomer **34a** was isolated as a colourless oil (24 mg, 31%); R_f=0.45 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ +15.3 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.03–1.07 (6H, m, 4-CH_3, 7-CH_3), 1.63–1.68 (2H, m, 4-CH, 4a-CH), 1.79–1.87 (2H, m, 5-CH_2), 1.91–1.97 (1H, m, 7-CH), 2.32–2.42 (2H, m, 1-CH_2, 7a-CH), 2.44 (3H, s, CH_3), 2.84–2.86 (2H, m, 3-CH_2), 3.28 (1H, q, *J* 4.5, Hz, 1-CH_2), 3.83–3.88 (1H, m, 6-CH), 7.32 (2H, d, *J* 8.0 Hz, ArH) and 7.64 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 13.6 (CH_3), 18.9 (CH_3), 21.5 (CH_3), 31.8 (CH), 37.6 (CH), 38.5 (CH_2), 41.6 (CH_2), 44.4 (CH_2), 46.1 (CH), 48.6 (CH), 78.6 (CH), 127.5 (CH), 129.6 (CH), 133.6 (C) and 143.3 (C) ppm; ν_{max} (film) 3512, 3035, 2958, 2977, 2301, 1598, 1462, 1341, 1162, 1092, 1066 and 1019 cm^{-1}; *m*/*z* $C_{17}H_{26}NO_3S$ requires 324.1633 (MH^+, 100%); found 324.1624 (−2.9 ppm).

3.23. (+)-(4*R*,4a*R*,6*R*,7*S*,7a*S*)-2,4,7-Trimethyl-octahydro[2]pyrindin-6-ol 35

Lithium (8 mg, 1.08 mmol, 10 equiv) was added to a solution of alcohol **34b** (35 mg, 0.1 mmol, 1 equiv) in THF (5 cm^3) and NH_3 (30 cm^3) at −78 °C. The mixture was stirred at −78 °C for 1 h. Solid NH_4Cl (ca. 10 mg) was added, and stirring was continued at room temperature for 1 h. Water (7 cm^3) and dichloromethane (10 cm^3) were added. The water layer was basified to pH 14 (1 M NaOH) and extracted with dichloromethane (3×10 cm^3). The combined extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. Mass spectrometry confirmed the presence of the amine [$C_{10}H_{20}NO$ requires 170.1545 (MH^+, 100%); found 170.1538 (−4.1 ppm)]. The residue was taken up in THF (5 cm^3) and 38% aqueous formaldehyde (9 mg, 0.12 mmol, 1.2 equiv) was added. The mixture was stirred for 10 min before sodium triacetoxyborohydride (34 mg, 0.16 mmol, 1.5 equiv) was added. After 15 h water (10 cm^3) and dichloromethane (10 cm^3) were added. Basification of the water layer from pH of 6–14 (1 M NaOH) was followed by extraction with dichloromethane (3×10 cm^3). The extracts were dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by flash column chromatography (CH_2Cl_2→CH_2Cl_2–MeOH; 1:1) gave the tertiary amine **35** as an oil (8 mg, 38%); R_f=0.10 (CH_2Cl_2–MeOH; 1:1); $[\alpha]_D^{20}$ −5.6 (*c* 0.16, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.00 (3H, d, *J* 7.5 Hz, 7-CH_3), 1.12 (3H, d, *J* 7.5 Hz, 4-CH_3), 1.55–1.61 (1H, m, 5-CH_2), 1.70–1.76 (1H, m, 4a-CH), 1.77–1.83 (1H, m, 4-CH), 1.95–2.02 (1H, m, 7-CH), 2.12–2.19 (3H, m, 1-CH_2, 5-CH_2, 7a-CH), 2.23–2.29 (4H, m, 2-CH_3, 3-CH_2), 2.43–2.46 (2H, m, 1-CH_2, 3-CH_2) and 4.11–4.15 (1H, m, 6-CH) ppm; δ_C (125 MHz, $CDCl_3$) 9.5 (CH_3), 21.7 (CH_3), 31.3 (CH), 38.9 (CH), 39.5 (CH_2), 41.2 (CH), 42.5 (CH), 46.9 (CH_3), 53.7 (CH_2), 57.9 (CH_2) and 74.2 (CH) ppm; ν_{max} (film) 3581, 3412, 2926, 2880, 2970, 1645, 1598, 1458, 1381, 1339, 1256, 1202, 1129 and 1037 cm^{-1}; *m*/*z* $C_{11}H_{22}NO$ requires 184.1701 (MH^+, 100%); found 184.1706 (+2.5 ppm).

3.24. (−)-(4*R*,4a*R*,6*R*)-4,7-Dimethyl-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[2]pyrindin-6-ol 36

Cerium(III) chloride heptahydrate (347 mg, 0.93 mmol, 2 equiv) was added to a solution of the enone **9a** (150 mg, 0.47 mmol, 1 equiv) in methanol (35 cm^3), at −78 °C. After stirring for 10 min, sodium borohydride (21 mg, 0.56 mmol, 1.2 equiv) was added. The mixture was allowed to warm up to ambient temperature over a period of 1 h before water (20 cm^3) was added. This was extracted using ether (3×20 cm^3). The combined organic extracts were washed with brine (15 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (cyclohexane–EtOAc; 1:1) yielded **36** as a colourless solid (150 mg, 100%); mp (decomp.)=130 °C; R_f=0.35 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ −38.3 (*c* 2.45, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.5 Hz, 4-CH_3), 1.07–1.13 (1H, m, 5-CH_2), 1.42–1.53 (1H, m, 4-CH), 1.71 (3H, d, *J* 1.0 Hz, 7-CH_3), 1.75–1.78 (1H, m, 4a-CH), 2.01 (1H, t, *J* 12.0 Hz, 3-CH_2), 2.43 (3H, s, CH_3), 2.54–2.62 (1H, m, 5-CH_2), 2.76–2.79 (1H, m, 1-CH_2), 3.73–3.77 (1H, m, 3-CH_2), 4.45 (1H, d, *J* 13.0 Hz, 1-CH_2), 4.54 (1H, s(br), 6-CH), 7.33 (2H, d, *J* 8.0 Hz, ArH) and 7.67 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 10.7 (CH_3), 16.9 (CH_3), 21.5 (CH_3), 38.5 (CH_2), 38.9 (CH), 44.8 (CH_2), 48.3 (CH), 52.5 (CH_2), 79.3 (CH), 127.7 (CH), 129.6 (CH), 132.0 (C), 133.3 (C), 135.1 (C) and 143.5 (C) ppm; ν_{max} (film) 3412, 3029, 2921, 2852, 1598, 1453, 1342, 1088, 1039 and 1003 cm^{-1}; *m*/*z* $C_{17}H_{24}NO_3S$ requires 322.1477 (MH^+, 100%); found 322.1489 (+3.8 ppm).

3.25. (−)-(4*R*,4a*R*)-4,7-Dimethyl-2-(toluene-4-sulfonyl)-2,3,4,4a,5,6-hexahydro-1*H*-[2]pyrindine 39

A solution of alcohol **36** (99 mg, 0.31 mmol, 1 equiv) in ethanol (15 cm^3) was degassed under a steady stream of N_2 for 15 min. To this solution Pd/C 10% w/w (33 mg, 10 mol %) was added. Stirring was continued for 45 min under an atmosphere of H_2. Filtration through Celite, followed by purification by flash column chromatography (cyclohexane–EtOAc; 3:1) afforded **39** as a colourless solid (89 mg, 95%); mp (decomp.)=106 °C; R_f=0.75 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ −36.8 (*c* 2.17, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.5 Hz, 4-CH_3), 1.21–1.28 (1H, m, 5-CH_2), 1.31–1.34 (1H, m, 4-CH), 1.64 (3H, s, 7-CH_3), 1.90–1.99 (2H, m, 3-CH_2, 4a-CH), 2.00–2.04 (1H, m, 5-CH_2), 2.19–2.25 (2H, m, 6-CH_2), 2.41 (3H, s, CH_3), 2.71 (1H, d, *J* 12.5 Hz, 1-CH_2), 3.69 (1H, dd, *J* 2.5, 11.5 Hz, 3-CH_2), 4.43 (1H, d, *J* 12.5 Hz, 1-CH_2), 7.30 (2H, d, *J* 8.0 Hz, ArH) and 7.65 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 16.9 (CH_3), 21.4 (CH_3), 27.3 (CH_2), 37.1 (CH_2), 38.9 (CH), 45.1 (CH_2), 51.7 (CH), 52.5 (CH_2), 127.7 (CH), 128.7 (C), 129.5 (CH), 133.2 (C), 133.4 (C) and 143.3 (C) ppm; ν_{max} (film) 3035, 2957, 2928, 1710, 1598, 1495, 1458, 1342, 1226, 1160, 1090 and 1023 cm^{-1}; *m*/*z* $C_{17}H_{24}NO_2S$ requires 306.1528 (MH^+, 100%); found 306.1522 (−1.9 ppm).

3.26. (+)-(4*R*,4a*R*,7*R*,7a*R*)-4,7-Dimethyl-2-(toluene-4-sulfonyl)octahydro[2]pyrindine

A solution of **39** (358 mg, 1.16 mmol, 1 equiv) in ethanol (40 cm^3) was degassed with a steady stream of N_2 for 15 min. To this Pd/C 10% w/w catalyst (250 mg, 20 mol %) was added. Stirring was continued for 72 h, under an atmosphere of H_2. Filtration through Celite, followed by purification by flash column chromatography (cyclohexane–EtOAc; 3:1) afforded the title compound as an amorphous solid (285 mg, 79%); R_f=0.75 (cyclohexane–EtOAc; 1:1); $[\alpha]_D^{20}$ +13.9 (*c* 2.28, $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 0.94 (3H, d, *J* 7.0 Hz, 7-CH_3), 1.08 (3H, d, *J* 6.5 Hz, 4-CH_3), 1.08–1.91 (1H, m, 6-CH_2), 1.33–1.40 (1H, m, 5-CH_2), 1.59–1.66 (1H, m, 5-CH_2), 1.68–1.71 (1H, m, 4-CH), 1.72–1.77 (2H, m, 4a-CH, 6-CH_2), 2.02–2.07 (1H, m, 7-CH), 2.11–2.15 (1H, m, 7a-CH), 2.25 (1H, t, *J* 11.5 Hz, 1-CH_2), 2.43 (3H, s, CH_3), 2.71 (1H, dd, *J* 3.5, 11.5 Hz, 3-CH_2), 3.03 (1H, dd, *J* 3.5, 11.5 Hz, 3-CH_2), 3.34 (1H, dd, *J* 5.5, 11.5 Hz, 1-CH_2), 7.31 (2H, d, *J* 8.0 Hz, ArH) and 7.63 (2H, d, *J* 8.0 Hz, ArH) ppm; δ_C (150 MHz, $CDCl_3$) 15.6 (CH_3), 19.4 (CH_3), 21.4 (CH_3), 26.9 (CH_2), 30.4 (CH_2), 30.9 (CH), 36.6 (CH), 38.9 (CH_2), 43.7 (CH), 44.2 (CH), 48.1 (CH_2), 127.5 (CH), 129.5 (CH), 133.8 (C) and 143.1 (C) ppm; *m*/*z* $C_{17}H_{26}NO_2S$ requires 308.1684 (MH^+, 100%); found 308.1685 (+0.2 ppm).

3.27. (−)-(4*R*,4a*R*,7*R*,7a*R*)-2,4,7-Trimethyloctahydro-[2]pyrindine 40

Lithium (33 mg, 4.51 mmol, 10 equiv) was added to a solution of the above dimethylpyridine (139 mg, 0.45 mmol, 1 equiv) in THF (5 cm^3) and NH_3 (30 cm^3) at −78 °C. The mixture was stirred at −78 °C for 1 h. Solid NH_4Cl (ca. 15 mg) was added, and stirring continued at room temperature for 1 h. Water (10 cm^3) and dichloromethane (15 cm^3) were added. The water layer was basified to pH 14 (1 M NaOH) and extracted with dichloromethane (3×15 cm^3). The combined extracts were dried over $MgSO_4$, filtered and the solvent removed in vacuo. High resolution mass spectrometry confirmed the presence of the intermediate amine [$C_{10}H_{20}N$ requires 154.1596 (MH^+, 100%); found 154.1589 (−4.4 ppm)]. The residue was taken up in THF (5 cm^3). To this, formaldehyde, 38% in water (39 mg, 0.49 mmol, 1.1 equiv), was added. The mixture was stirred for 10 min before sodium triacetoxyborohydride (144 mg, 0.68 mmol, 1.5 equiv) was added. At 2 h water (15 cm^3) and dichloromethane (20 cm^3) were added. Basification of the water layer from pH of 6–14 (1 M NaOH) was followed by extraction with dichloromethane (3×15 cm^3). The extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (CH_2Cl_2→CH_2Cl_2–MeOH; 1:1) gave the tertiary amine **40** as an oil (27 mg, 36%); R_f=0.25 (CH_2Cl_2–MeOH; 1:1); $[\alpha]_D^{20}$ −5.04 (*c* 1.35, $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 0.93 (3H, d, *J* 7.0 Hz, 7-CH_3), 1.14 (3H, d, *J* 7.0 Hz, 4-CH_3), 1.28–1.32 (1H, m, 6-CH_2), 1.53–1.59 (1H, m, 5-CH_2), 1.66–1.70 (2H, m, 4-CH, 5-CH_2), 1.75–1.81 (3H, m, 1-CH_2, 4a-CH, 6-CH_2), 2.02–2.06 (1H, m, 7-CH), 2.13–2.16 (1H, m, 7a-CH), 2.24–2.28 (1H, m, 3-CH_2), 2.27 (3H, s, 2-CH_3), 2.38 (1H, d, *J* 12.0 Hz, 3-CH_2) and 2.55 (1H, dd, *J* 5.0, 11.0 Hz, 1-CH_2) ppm; δ_C (150 MHz, $CDCl_3$) 15.4 (CH_3), 21.0 (CH_3), 27.3 (CH_2), 30.4 (CH_2), 31.2 (CH), 37.1 (CH), 39.1 (CH), 43.8 (CH), 47.1 (CH_3), 53.5 (CH_2) and 57.8 (CH_2) ppm; ν_{max} (film) 2952, 2941, 2783, 1745, 1664, 1462, 1376, 1250, 1153, 1041, 886 and 829 cm^{-1}; *m*/*z* $C_{11}H_{22}N$ requires 168.1752 (MH^+, 70%); found 168.1744 (−4.9 ppm).

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References and notes

1. Kam, T.-S.; Yoganathan, K.; Wei, C. *J. Nat. Prod.* **1997**, *60*, 673–676.
2. Chi, Y. M.; Yan, W. M.; Chen, D. C.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *Phytochemistry* **1992**, *31*, 2930–2932.
3. (a) Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2004**, *126*, 16553–16558; (b) Ichikawa, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2327–2329.
4. Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron* **2003**, *59*, 5377–5381 and references therein.
5. Costantino, L.; Lins, A. P.; Barlocco, D.; Celotti, F.; El-Abady, S. A.; Brunetti, T.; Maggi, R.; Antolini, L. *Pharmazie* **2003**, *58*, 140–142.
6. Ernst, M.; Helmchen, G. *Synthesis* **2002**, 1953–1955 and references therein.
7. Robert, N.; Hoarau, C.; Marsais, F. *Tetrahedron* **2007**, *63*, 3702–3706.
8. (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729; (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681, a substructure search for the piperidine ring in the MDL drug data report indicated 12,000 discrete piperidines entries for compounds involved in both preclinical and clinical studies for the period 1988–1998.
9. (a) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851–4854; (b) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861–5869; (c) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483–1486.
10. (a) Breczinski, P. M.; Stumpf, A.; Hope, H.; Krafft, M. E.; Casalnuovo, J. A.; Schore, N. E. *Tetrahedron* **1999**, *55*, 6797–6812; (b) Yoo, S. E.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968–6972; (c) For a related example in which an allylic methyl group controls the axial stereochemistry of a Vollhardt cyclisation see: Stará, I. G.; Alexandrová, Z.; Teplý, F.; Sehnal, P.; Starý, I.; Šaman, D.; Budešínsky, M.; Cvačka, J. *Org. Lett.* **2005**, *7*, 2547–2550.
11. For recent reviews, see: (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283; (b) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037; (c) Evans, P.; Kavanagh, Y. In *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.
12. (a) Honda, T.; Kaneda, K. *J. Org. Chem.* **2007**, *72*, 6541–6547; (b) Kaneda, K.; Honda, T. *Tetrahedron* **2008**, *64*, 11589–11593.
13. Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745–6754.
14. (a) Shambayti, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289–5292; (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204–206.
15. X-ray deposition number for **9a** CCDC 670403: Formula: $C_{17}H_{21}NO_3S$: Unit cell parameters: *a* 5.5026(5); *b* 9.1774(8); *c* 16.7670(16); *β* 96.814(2); space group *P*21.
16. Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915.
17. Adrio, J.; Rodríguez Rivero, M.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 2906–2908; Adrio, J.; Rodríguez Rivero, M.; Carretero, J. C. *Synlett* **2005**, 26–41.
18. (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99; (b) Evans, P.; Johnson, P.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2006**, 1740–1754.
19. Günter, M.; Gais, H.-J. *J. Org. Chem.* **2003**, *68*, 8037–8041.
20. For a recent *exo*-selective intramolecular PKR of a vinyl sulfone see: Krafft, M. E.; Kyne, G. M.; Hirosawa, C.; Schmidt, P.; Abboud, K. A.; L'Helias, N. *Tetrahedron* **2006**, *62*, 11782–11792.
21. Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049–1052.
22. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
23. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370; (b) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.
24. (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661; (b) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072–1073.
25. Kavanagh, Y.; Chaney, C. M.; Muldoon, J.; Evans, P. *J. Org. Chem.* **2008**, *73*, 8601–8604.
26. House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800–2810.
27. van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558–2563.
28. Blumenkopf, T. A. *Synth. Commun.* **1986**, *16*, 139–147.