Pergamon

Tetrahedron 58 (2002) 9621–9628

TETRAHEDRON

Reversal of diastereofacial selectivity in the nucleophilic addition reaction to chiral *N*-sulfinimine and application to the synthesis of indrizidine 223AB

Yuji Koriyama, Akihiro Nozawa, Ryuuichirou Hayakawa and Makoto Shimizu*

Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan

Received 15 August 2002; accepted 26 September 2002

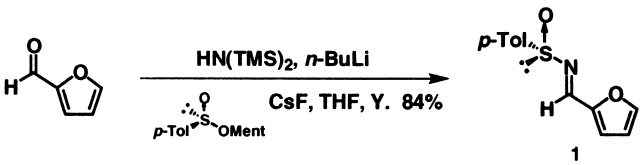
Abstract—Diastereoselective addition reaction of ester enolates and Grignard reagents to optically active *N*-sulfinimines was examined. Reversal of the diastereofacial selectivity was realized by using appropriate metal species, solvents and additives, and the β-amino esters (up to >98% de) and the homoallylic amines (up to >98% de) were obtained in good yields. β-Amino esters thus obtained were converted to the useful β-amino acids involving (*R*)-homoserine. Application to the synthesis of indrizidine alkaloids was also described. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Recently, we reported a reversal of diastereofacial selectivity in the condensation reaction using an optically active *N*-sulfinimine as a chiral source.[1] Both diastereomers of the β-amino esters were synthesized selectively from a single chiral *N*-sulfinimine in good yields and diastereomeric excesses by changing the enolate metal species. The obtained β-amino esters were converted to 3-unsubstituted β-lactams, which are useful intermediates for the synthesis of β-lactam antibiotics. Chiral sulfinimines are easily prepared from commercially available reagents.[2] This type of chiral sulfinimines is one of the attractive building blocks which have been recently employed in the asymmetric synthesis of amines,[3] β-amino acids, their ester derivatives,[4] β-aminophosphonic acids,[5] the taxol® side chain,[6] its fluorinated analog, isoquinoline derivatives,[7] *N*-sulfinyl-*cis*-aziridine-2-carboxylate,[8] β-hydroxy-α-amino acids,[9] and 2*H*-aziridinecarboxylates.[10] Use of sulfoxides as chiral synthons in asymmetric synthesis is now a well-established and reliable strategy, and has been the subject of several excellent reviews.[11] In this paper, we describe the nucleophilic addition reaction to a chiral *N*-sulfinimine and application to the synthesis of indrizidine 223AB.

2. Results and discussion

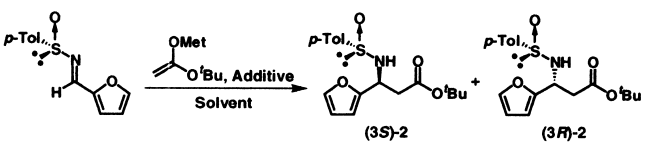
We have already reported a reversal of diastereofacial selectivity in the condensation reaction using an optically active *N*-sulfinimine as a chiral source.[1] We applied this methodology to a diastereoselective addition reaction to the chiral *N*-sulfinimine **1** possessing a furan ring. The starting *N*-sulfinimine was prepared according to the literature procedure (Scheme 1).[12]



Scheme 1.

2.1. Synthesis of β-amino ester

The asymmetric addition was carried out in the following manner (Scheme 2): deprotonation of *tert*-butyl acetate with LDA was followed by addition of *N*-sulfinimine **1** at −78°C. In the case of transmetallation, metal halides such as $ClTi(O^iPr)_3$ and $ClAlEt_2$ were added to the lithium enolate, and the resulting enolate was stirred for 30 min followed by addition of the sulfinimine **1**. The resulting reaction mixture was stirred for several hours at −78 to 0°C and quenched by an addition of phosphate buffer solution. The crude addition



Scheme 2.

Keywords: diastereoselective; sulfinimin; asymmetric addition; β-aminoester; homoallyl amine; alkaloid.

* Corresponding author. Tel./fax: +81-59-231-9413; e-mail: mshimizu@chem.mie-u.ac.jp

0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(02)01250-4

Table 1. Diastereoselective addition to *N*-sulfinimine **1**

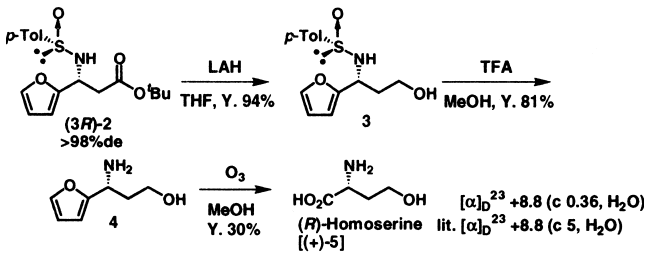
Metal	Additive (equiv.)	Solvent	Time	Yield (%)	3*S*:3*R*[a]
Li	–	THF	6 h	96	14:86
$AlEt_2$		THF	4 h	31	6:94
$Ti(O^iPr)_3$		THF	3 h	80	4:96
$Ti(O^iPr)_3$	–	Et_2O	2 h	98	<1:99[b]
K	HMPA (30)	THF	5 min	88	86:14[c]

[a] Determined by HPLC analysis.
[b] The reaction was quenched at −78°C.
[c] The reaction was carried out at −100°C.

product was purified on preparative silica gel TLC which was pre-treated with phosphate buffer. As shown in Table 1, addition products **2** were obtained in good yield and excellent selectivity. The diastereomeric ratio of the β-amino ester obtained was determined by HPLC analysis.

The titanium enolate gave significantly good results over the aluminum enolate. When the reaction was conducted in Et_2O, the best result was observed (98% yield, 3*S*:3*R*=<1:99). We also observed the reversal of the diastereofacial selectivity using the potassium enolate in the presence of HMPA (88% yield, 3*S*:3*R*=86:14).

The determination of the absolute configuration of the addition product was carried out as follows (Scheme 3). The β-aminoester **2** was reduced to the corresponding alcohol **3**, and removal of the chiral sulfinyl group was conducted with TFA to give the amino alcohol **4**, and the following ozonolysis of the furan ring afforded (*R*)-homoserine.[13] The spectral data and optical rotation of the obtained (*R*)-homoserine were identical with the literature data.[13]



Scheme 3. Synthesis of (*R*)-homoserine.

The sense of diastereoselectivity is predictable by non-chelation and chelation-control model. In the case of the potassium enolate with HMPA in THF, asymmetric addition would proceed through a non-chelation transition state which is similar to the case with *N*-sulfinimine possessing a 1,3-dioxorane ring[1] to give the (3*S*)-β-amino ester. On the other hand, in the case of the lithium, aluminum, and titanium enolates, a six-membered chair-like transition state containing a four-membered metallacycle, and/or a seven-membered counterpart may be involved, which is responsible for the formation of (3*R*)-isomer (Fig. 1). In each case, the enolate approaches from the direction opposite to the sterically congested *p*-tolyl group, forming the carbon–carbon bond with high diastereoselectivity.

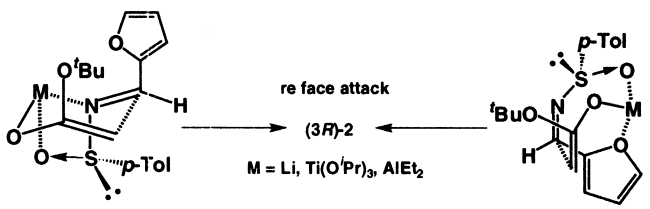
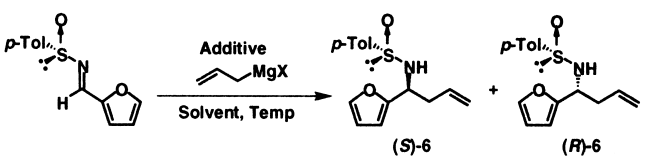


Figure 1. Possible transition states.

2.2. Asymmetric allylation

Next, we applied this methodology to an asymmetric allylation using allyl Grignard and allyl borane reagents (Scheme 4). In the case of allyl Grignard reagent, the combination of allyl magnesium bromide in CH_2Cl_2 gave the best result (Table 2, 98% yield, *S*:*R*=9:91). We also succeeded in the reversal of the diastereofacial selectivity by using allyl borane reagent. The allyl borane reagent was prepared in situ, and the best result was obtained using allylmagnesium chloride and $BF_3{\cdot}OEt_2$ in Et_2O (83% yield, *S*:*R*=>99:1).



Scheme 4. Asymmetric allylation.

Table 2. Diastereoselective allylation to *N*-sulfinimine **1**

X	Additive	Solvent	Temperature (°C)	Time	Yield (%)	*S*:*R*[a]
Br	–	Et_2O	−78–rt	12 h	94	15:85
	–	CH_2Cl_2	−78–0	4 h	98	9:91
	$BF_3{\cdot}OEt_2$	Et_2O	−78	5 min	31	92:8
Cl	–	Et_2O	−78–0	5 h	99	14:86
	–	CH_2Cl_2	−78–0	4 h	98	12:88
	$BF_3{\cdot}OEt_2$	Et_2O	−78–−40	2 h	83	>99:1

[a] Determined by HPLC analysis.

The present diastereoselectivity is also predictable by chelation-control model (Fig. 2). In the case of the allyl Grignard reagent, a four and six-membered metallacycle, and/or a seven-membered counterpart may be involved, which is responsible for the formation of (*R*)-isomer. In the case of allyl borane reagent, a six-membered chair-like transition state without chelation between the oxygen of sulfinyl group and the borane atom may be involved. In each case, the enolate approaches from the direction opposite to the bulky *p*-tolyl group, forming the carbon–carbon bond with high diastereoselectivity.

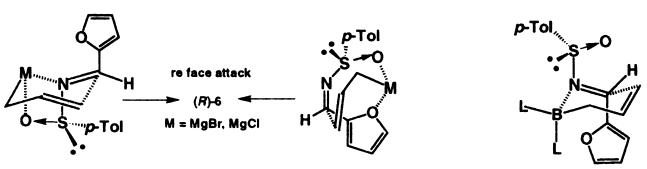
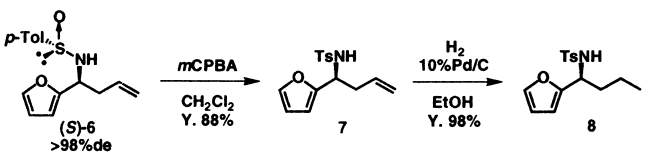


Figure 2. Possible transition states.

The absolute configuration of the obtained homoallylamine **6** was determined in the following manner (Scheme 5). The obtained homoallylamine **6** was oxidized with *m*CPBA to give an *N*-tosyl derivative **7** and then the terminal olefin was hydrogenated to the known *N*-tosyl amine **8**. Comparison of

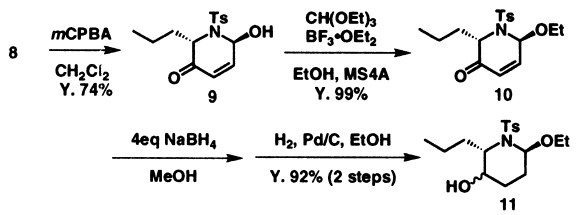


Scheme 5. Determination of the absolute configuration.

the spectral data and optical rotation of the synthesized compound to those in the literature established the stereochemistry.[14]

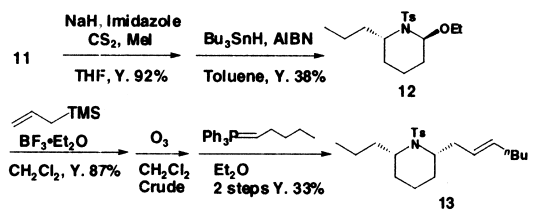
3. Synthesis of indrizidine 223AB

Alkaloids containing the indolizidine skelton have a wide and varied distribution within nature and demonstrate a broad range of pharmacological activity, representing a structural class of non-competitive blockers of neuromuscular transmission. Indrizidine 223AB[15] is one of these alkaloids isolated in minute quantity from the skin extracts of the neo-tropical poison-dart frog (genus *Dendrobates*) and has been the target of many synthetic efforts. Application to the synthesis of indrizidine 223AB was carried out as follows. *N*-tosyl amine **8** was cyclized to dihydropyridinone **9** using *m*CPBA (Scheme 6). After ethyl etherification of the alcohol moiety using triethyl orthoformate and $BF_3{\cdot}OEt_2$, the reduction of the enone **10** was carried out with $NaBH_4$ to afford a mixture of a saturated alcohol and its unsaturated counterpart. The subsequent hydrogenation of the mixture gave **11**.



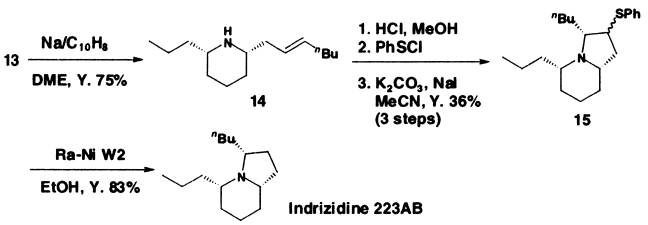
Scheme 6.

The hydroxy group of **11** was removed using the Barton reaction[16] to afford the 2,6-disubstituted piperidine **12**. An allyl group was introduced stereoselectively via tosyl iminium salt,[17] and the subsequent ozonolysis of the terminal olefin and Wittig olefination gave the compound **13** which has a side chain necessary for the construction of five-membered ring (Scheme 7).



Scheme 7.

The tosyl group of **13** was deprotected using sodium naphthalenide[18] to give a piperidine **14**. After conversion to the HCl salt, phenyl sulfenyl chloride was added to the olefin moiety. The obtained crude addition product was treated with potassium carbonate and sodium iodide in acetonitrile to give a cyclized compound **15** as an 87:13 mixture of epimers (Scheme 8). The sulfenyl group was removed by Ra-Ni (W2) to afford the indrizidine 223AB. The spectral data of the synthesized compound were identical with those reported.[19]



Scheme 8.

4. Conclusions

We investigated diastereoselective addition reaction of ester enolates, allyl Grignard, and allyl borane reagents to an optically active *N*-sulfinimine, and we were able to accomplish the reversal of the diastereofacial selectivity by using the appropriate metal species, solvents, and additives. Since the homoallyl amines and β-amino acids obtained stereoselectively are useful precursors for the synthesis of several bioactive compounds, this methodology offers a convenient approach to such a useful class of compounds.

5. Experimental

5.1. General aspects

Infrared spectra were determined on a JASCO IR-810 spectrometer. ^{1}H NMR spectra were recorded with a JEOL EX-270 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken on a Waters micromass ZQ. High performance liquid chromatography (HPLC) was carried out using a Hitachi L-4000 detector and a Hitachi L-6000 pump with a Merck Hibar column. Purification of products was performed by column chromatography on silica gel (Merck Silica Gel-60), and/or preparative TLC on silica gel (Merck Kisel Gel PF254). Reagents and solvents were used after purification or as purchased.

5.2. Synthesis of β-amino ester

5.2.1. 4-Methylbenzenesulfinic acid furan-2-yl-methyleneamide (1).[12] To a solution of lithium bis(trimethylsilyl)amide at −78°C, which was freshly prepared from 1,1,1,3,3,3-hexamethyldisilazane (3.23 mL, 15.3 mmol) and *n*-butyllithium (1.44 M, 10.6 mL, 15.3 mmol), in 5 mL of THF was added a solution of (*S*)-(−)-menthyl-*p*-toluenesulfinate (3 g, 10.2 mmol) in 15 mL of THF. The reaction was warmed gradually and, then stirred for 2 h at room temperature. The reaction mixture was cooled to 0°C, and to it was added a freshly distilled furfural (1.27 mL, 15.3 mmol) and cesium fluoride (2.3 g, 15.3 mmol), and the whole was stirred overnight. The reaction mixture was quenched by an addition of a phosphate buffer solution at 0°C, extracted with AcOEt,

dried over Na_2SO_4, and then evaporated in vacuo. The crude product was purified by silica gel column chromatography (pre-treated with 5% Et_3N in hexane) eluenting with hexane–ether=1:1 to give the title imine as a light yellow crystalline. Yield 1.99 g (8.5 mmol, 84%). The spectral data are in accordance with those in the literature.[12]

^{1}H NMR (270 MHz, $CDCl_3$) δ 2.40 (s, 3H), 6.47 (dd, 1H, J=2.0, 2.0 Hz), 6.98 (d, 1H, J=4.0 Hz), 7.23 (d, 2H, J=8.2 Hz), 7.57 (d, 1H, J=2.0 Hz), 7.58 (d, 2H, J=8.2 Hz), 8.50 (s, 1H); IR (neat) 1610, 1540, 1470, 1170, 790, 550 cm^{-1}; $[\alpha]_D^{23}$=+82.0 (c 0.93, $CHCl_3$).

5.2.2. 3-Furan-2-yl-3-(toluene-4-sulfinylamino)-propionic acid *tert*-butyl ester (3*R*-2, with the Li enolate). To a solution of freshly prepared lithium diisopropylamide (0.23 mmol) in 3 mL of THF was added a solution of *t*-butyl acetate (26.1 mg, 0.23 mmol) in 3 mL of THF dropwise at −78°C under an argon atmosphere, and the mixture was stirred for 30 min. To the reaction mixture was added a solution of 4-methylbenzenesulfinic acid furan-2-ylmethyleneamide (35 mg, 0.15 mmol) in 3 mL of THF, and the mixture was allowed to warm to 0°C during 6 h with stirring. The reaction was quenched by an addition of a phosphate buffer solution, extracted with AcOEt, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative silica gel TLC (pre-treated with phosphate buffer) to afford the β-amino ester as a colorless oil (diastereomeric mixture). Yield 50.1 mg (0.14 mmol, 96%); 3*S*:3*R*=14:86.

3*R*: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.41 (s, 3H), 2.75 (ddd, 2H, J=6.0, 9.9, 2.6 Hz), 4.86 (dd, 1H, J=6.1, 7.6 Hz), 4.99 (d, 1H, J=7.6 Hz), 6.33 (d, 2H, J=1.7 Hz), 7.25–7.39 (m, 3H), 7.60 (d, 2H, J=8.3 Hz), IR (neat) 3175, 2975, 1730, 1360, 1170, 1060, 810, 740 cm^{-1}; MS (exact mass calcd for $C_{18}H_{23}NO_4S$, *m/e* 349.1348, found *m/e* 349.1393).

5.2.3. 3-Furan-2-yl-3-(toluene-4-sulfinylamino)-propionic acid *tert*-butyl ester (3*R*-2, with the Ti enolate). To a solution of freshly prepared lithium diisopropylamide (0.46 mmol) in 3 mL of Et_2O was added a solution of *t*-butyl acetate (52.3 mg, 0.45 mmol) in 3 mL of THF dropwise at −78°C under an argon atmosphere, and the mixture was stirred for 30 min. A solution of 1 M chlorotitanium triisopropoxide in hexane (0.46 mL, 0.46 mmol) was added to the reaction mixture, which was stirred for 30 min. To the reaction mixture was added a solution of 4-methylbenzenesulfinic acid furan-2-ylmethyleneamide (35 mg, 0.15 mmol) in 3 mL of THF, and the whole was allowed to warm to −45°C during 2 h with stirring. The reaction was quenched by an addition of a phosphate buffer solution, extracted with AcOEt, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer) to afford the β-amino ester as a colorless oil (diastereomeric mixture). Yield 51.3 mg (0.14 mmol, 98%); 3*S*:3*R*=<1:99.

5.2.4. 4-Methylbenzenesulfinic acid (1-furan-2-yl-3-hydroxypropyl)amide (3). To a suspension of LAH (82 mg, 2.16 mmol) in 3 mL of THF cooled in an ice water bath was added a solution of 3-furan-2-yl-3-(toluene-4-sulfinylamino)propionic acid *t*-butyl ester (625.5 mg, 1.8 mmol, >98% de) in 15 mL of THF dropwise, and the whole was stirred for 1 h at 0°C. The reaction was quenched by an addition of sat. Na_2SO_4 aq. The insoluble materials were removed by filtration through a celite® pad and the filtrate was evaporated in vacuo. The crude product was purified by silica gel column chromatography (pre-treated with 5% Et_3N in hexane, hexane–AcOEt=1:2) to give the title compound as a colorless oil. Yield 471.5 mg (1.69 mmol, 94%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.92–2.15 (m, 2H), 2.35 (s, 3H), 3.59–3.68 (m, 2H), 3.95 (brs, 1H), 4.70 (dd, 1H, J=6.4, 7.3 Hz), 5.27 (d, 1H, J=6.6 Hz), 6.30, (m, 2H), 7.20 (d, 2H, J=8.3 Hz), 7.36 (d, 1H, J=1.0 Hz), 7.49 (d, 2H, J=7.9 Hz); IR ($CHCl_3$) 3200, 2850, 1920, 1660, 1350, 970, 900, 540 cm^{-1}; MS (exact mass calcd for $C_{14}H_{17}NO_3S$, *m/e* 279.0929, found *m/e* 279.0893).

5.2.5. 3-Amino-3-furan-2-ylpropan-1-ol (4). To a solution of 4-methylbenzenesulfinic acid (1-furan-2-yl-3-hydroxypropyl)amide (335.4 mg, 1.2 mmol) in MeOH cooled in an ice water bath was added trifluoroacetic acid (273.7 mg, 2.4 mmol), and the whole was stirred for 4 h at 0°C. The reaction mixture was evaporated in vacuo to remove the solvent and excess TFA. To the residue was added water, and the mixture was basified with 1N NH_3 aq (pH 9–10) and extracted with AcOEt. The combined extracts were dried over $MgSO_4$ followed by solvent evaporation. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, AcOEt–MeOH=5:1×3) to give the title amino alcohol as a colorless oil. Yield 136.6 mg (0.97 mmol, 81%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.85–2.04 (m, 2H), 3.27 (brs, 3H), 3.85 (t, 2H, J=5.3 Hz), 4.14 (dd, 1H, J=5.1, 3.3 Hz), 6.12 (d, 1H, J=3.3 Hz), 6.31 (dd, 1H, J=2.0, 1.3 Hz), 7.34 (dd, 1H, J=0.7, 1.0 Hz). Despite several attempts, a satisfactory mass analysis data could not be obtained, and therefore, this material was used for the next step without further characterization.

5.2.6. 3-Amino-5-hydroxypentanoic acid ((+)-5, homoserine).[13] Ozone was bubbled into a solution of 3-amino-3-furan-2-ylpropan-1-ol (73.6 mg, 1.52 mmol) in 5 mL of MeOH at −78°C. The reaction was monitored by TLC. After the starting material was consumed, argon gas was bubbled into the reaction mixture, which was warmed gradually to room temperature. Dimethyl sulfide (3 mL) was added to the resulting mixture, which was stirred for 3 h at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was partitioned between hexane and water. After evaporation of water, the residue was purified by ion exchange resin (Dowex® 50×2 100(H^+), distilled water then 1N NH_3 aq) to give (*R*)-homoserine as a white solid. Yield 18.8 mg (0.16 mmol, 30%). The spectral data are in accordance with those in the literature.[13]

^{1}H NMR (270 MHz, D_2O) δ 1.88–2.07 (m, 2H), 3.70–3.83 (m, 3H); $[\alpha]_D^{23}$=+8.8 (c 0.36, H_2O); lit. $[\alpha]_D^{23}$=+8.8 (c 5, H_2O).

5.3. Asymmetric allylation

5.3.1. 4-Methyl-benzenesulfinic acid (1-furan-2-ylbut-3-enyl)amide (*R*-6, with allylmagnesium bromide). To a solution of 4-methylbenzenesulfinic acid furan-2-ylmethyleneamide (35 mg, 0.15 mmol) in 5 mL of ether was added dropwise a solution of 0.52 M allyl magnesium bromide in ether (0.81 mL, 0.42 mmol), and the whole was stirred overnight during which it was allowed to warm to room temperature. After cooling to 0°C, the reaction mixture was quenched by an addition of sat. NH_4Cl aq, extracted with AcOEt, dried over Na_2SO_4, and evaporated. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, hexane–ether=1:1×3) to give the title homoallyl amine as a colorless oil. Yield 38.8 mg (0.14 mmol, 94%); *S*:*R*=15:85 (determined by HPLC).

R: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.55–2.60 (m, 2H), 4.34 (d, 1H, *J*=5.9 Hz), 4.59 (q, 1H, *J*=6.5 Hz), 5.04–5.19 (m, 2H), 5.50–5.64 (m,1H), 6.33 (m, 2H), 7.29 (d, 2H, *J*=8.1 Hz), 7.40 (m, 1H), 7.59 (d, 2H, *J*=8.1 Hz); IR (neat) 3200, 1190, 1160, 920, 810, 740 cm^{-1}; MS (exact mass calcd for $C_{15}H_{17}NO_2S$, *m*/*e* 275.0980, found *m*/*e* 275.1051).

5.3.2. 4-Methylbenzenesulfinic acid (1-furan-2-ylbut-3-enyl)amide (*S*-6, with allylmagnesium chloride+BF_3·OEt_2). To a solution of BF_3·OEt_2 (0.037 mL, 0.30 mmol) in 3 mL of ether cooled in an ice water bath was added 0.52 M allylmagnesium chloride (1.73 m, 0.90 mmol) in ether dropwise, and the whole was refluxed for 1 h. After cooling to −78°C, a solution of 4-methylbenzenesulfinic acid furan-2-ylmethyleneamide (35 mg, 0.15 mmol) was added dropwise to the resulting mixture with stirring for 5 min. Work-up and purification were done as in the above case. Yield 34.4 mg (0.12 mmol, 83%), a colorless oil, *S*:*R*=>99:1.

S: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.63–2.80 (m, 2H), 4.42 (d, 1H, *J*=6.9 Hz), 4.53 (q, 1H, *J*=6.6 Hz), 5.05–5.20 (m, 2H), 5.63–5.78 (m, 1H), 6.12 (m, 1H), 7.26 (m, 3H), 7.63 (d, 2H, *J*=8.3 Hz); MS (exact mass calcd for $C_{15}H_{17}NO_2S$, *m*/*e* 275.0980, found *m*/*e* 275.1050).

5.3.3. *N*-(1-Furan-2-ylbut-3-enyl)-4-methylbenzene sulfonamide (7). To a suspension of 80% *m*CPBA (99 mg, 0.57 mmol) in 5 mL of CH_2Cl_2 was added a solution of 4-methylbenzenesulfinic acid (1-furan-2-ylbut-3-enyl)-amide (123 mg, 0.44 mmol, >98% de) in 5 mL of CH_2Cl_2 at −30°C, and the whole was stirred until the temperature reached 0°C. The reaction was quenched by an addition of sat. $NaHCO_3$ aq, extracted with CH_2Cl_2, dried over Na_2SO_4, and then evaporated. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, hexane–ether=3:2×3) to give the title compound as a white crystalline solid. Yield 112.7 mg (0.39 mmol, 88%). The spectral data are in accordance with those in the literature.[14]

^{1}H NMR (60 MHz, CCl_4) δ 2.38 (s, 3H), 2.57 (d, 2H, *J*=6.2 Hz), 4.45 (q, 1H, *J*=7.1 Hz), 4.80–6.16 (m, 6H), 7.03–7.28 (m, 3H), 7.67 (d, 2H, *J*=8.0 Hz); IR ($CHCl_3$) 3250, 1500, 1450, 1320, 1160, 920, 660 cm^{-1}, $[\alpha]_D^{23}$=−74.8 (*c* 0.78, $CHCl_3$); MS (Found: M^+, 291).

5.3.4. *N*-(1-Furan-2-ylbutyl)-4-methylbenzene sulfonamide (8).[14] A mixture of 10% Pd/C (3.6 mg) and *N*-(1-furan-2-ylbut-3-enyl)-4-methylbenzenesulfonamide (140 mg, 0.48 mmol) in EtOH was stirred for 6 h under a H_2 atmosphere (balloon). After the reaction was completed, the catalyst was removed by filtration through a celite® pad, and the whole was concentrated by evaporation followed by purification on preparative silica gel TLC (pre-treated with phosphate buffer, hexane–ether=3:2×3) to give the title compound as a white crystalline solid. Yield 141 mg (0.48 mmol, 99%). The spectral data are in accordance with those in the literature.[14]

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84 (t, 3H, *J*=7.3 Hz), 1.06–1.37 (m, 2H), 1.74 (q, 2H, *J*=7.6 Hz), 2.36 (s, 3H), 4.40 (q, 1H, *J*=7.8 Hz), 5.44 (d, 1H, *J*=8.6 Hz), 5.89 (d, 1H, *J*=3.3 Hz), 6.07 (dd, 1H, *J*=1.8, 3.1 Hz), 7.10–7.18 (m, 3H), 7.62 (d, 2H, *J*=8.6 Hz); IR ($CHCl_3$) 2850, 1590, 1460, 1340, 1320, 980 cm^{-1}; $[\alpha]_D^{23}$=−57.5 (*c* 2.8, EtOH); MS (Found: M^+, 293).

5.4. Synthesis of indrizidine 223AB

5.4.1. 6-Hydroxy-2-propyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (9). To a solution of *N*-(1-furan-2-ylbutyl)-4-methylbenzenesulfonamide (45 mg, 0.15 mmol) in 2 mL of CH_2Cl_2 was added a solution of 80% *m*CPBA (39.6 mg, 0.18 mmol) in 3 mL of CH_2Cl_2 at 0°C, and the whole was stirred for 3 h, during which time the mixture was allowed to warm to room temperature. The reaction was quenched by an addition of sat. $NaHCO_3$ aq at 0°C, extracted with CH_2Cl_2, dried over Na_2SO_4, and then evaporated. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, hexane–ether=3:2×3) to give the title compound as a white crystalline solid. Yield 34.3 mg (0.11 mmol, 74%). The spectral data are in accordance with those in the literature.[14]

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J*=7.3 Hz), 1.29–2.04 (m, 4H), 2.39 (s, 3H), 4.31 (dd, 1H, *J*=6.8, 8.4 Hz), 5.84–5.92 (m, 2H), 6.77 (dd, 1H, *J*=4.5, 10.4 Hz), 7.26 (d, 2H, *J*=8.3 Hz), 7.60 (d, 2H, *J*=8.3 Hz); IR ($CHCl_3$) 2650, 1730, 1580, 1360, 1000, 900 cm^{-1}; $[\alpha]_D^{23}$=+116.6 (*c* 0.69, EtOH).

5.4.2. 6-Ethoxy-2-propyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (10). To a solution of 6-hydroxy-2-propyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (417.5 mg, 1.35 mmol) in 25 mL of ether cooled in an ice water bath was added triethyl orthoformate (1.1 g, 7.46 mmol) in the presence of MS4Å (5 g), and then to it was added seven drops of BF_3·OEt_2. The whole was allowed to warm to room temperature during 3 h with stirring. The reaction was quenched by an addition of Et_3N (excess to BF_3·OEt_2). MS4Å was removed by filtration through a celite® pad, and the whole were washed with AcOEt. The organic layer was washed with sat. NaCl aq, dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified on preparative silica gel TLC (pre-treated with buffer solution, hexane–ether=3:2×3) to give the title ethyl ether as a white crystalline solid. Yield 455 mg (1.34 mmol, 99%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (t, 3H, J=7.3 Hz), 1.26 (t, 3H, J=6.9 Hz), 1.45–2.04 (m, 4H), 2.38 (s, 3H), 3.66–3.78 (m, 1H), 4.01–4.12 (m, 1H), 4.25 (dd, 1H, J=4.8, 10.1 Hz), 5.59–5.75 (m, 1H), 6.69 (dd, 1H, J=4.5, 10.4 Hz), 7.23 (d, 2H, J=8.1 Hz), 7.54 (d, 2H, J=8.1 Hz); IR ($CHCl_3$) 2950, 1680, 1340, 1170, 1020, 580 cm^{-1}; $[\alpha]_D^{23}$=+39.2 (*c* 0.59, EtOH); MS (exact mass calcd for $C_{22}H_{35}NO_2S$–OEt, *m/e* 292.1007, found *m/e* 292.1035).

5.4.3. 6-Ethoxy-2-propyl-1-(toluene-4-sulfonyl)-piperidin-3-ol (11). To a solution of 6-ethoxy-2-propyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (610 mg, 1.8 mmol) in 25 mL of MeOH was added $NaBH_4$, keeping the temperature below −30°C. The reaction was monitored by TLC. After the starting material was consumed, the reaction was quenched by an addition of acetone (12.2 mL). The solvent was removed under reduced pressure, and to the residue was added AcOEt. The whole was washed with sat. NaCl aq, dried over Na_2SO_4, and then concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane–ether=1:1) to give a mixture of saturated and unsaturated alcohols (570 mg). The mixture was hydrogenated for 27 h under an atmosphere (balloon) of hydrogen in EtOH in the presence of 10% Pd/C (73 mg). After filtration through a celite® pad, the crude product was purified by silica gel column chromatography (hexane–ether=1:1) to give the title compound as a colorless crystalline. Yield 564.7 mg (1.65 mmol, 92%, 2 steps).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.1 Hz), 1.19 (t, 3H, J=7.4 Hz), 1.23–1.90 (m, 9H), 2.42 (s, 3H), 3.25 (brs, 1H), 3.49–3.92 (m, 3H), 5.12 (d, 1H, J=7.4 Hz), 7.29 (d, 2H, J=8.1 Hz), 7.67 (d, 2H, J=8.1 Hz); IR ($CHCl_3$) 3500, 2950, 2860, 1340, 1160, 1000 cm^{-1}); MS (exact mass calcd for $C_{17}H_{27}NO_4S$, *m/e* 341.1661, found *m/e* 341.1900).

5.4.4. Dithiocarbonic acid *O*-[6-ethoxy-2-propyl-1-(toluene-4-sulfonyl)piperidin-3-yl]ester *S*-methyl ester. To a stirred solution of NaH (337 mg, 9.84 mmol, 60% oil dispersion) in THF was added a solution of 6-ethoxy-2-propyl-1-(toluene-4-sulfonyl)piperidin-3-ol (560 mg, 1.64 mmol) in THF (40 mL), and the mixture was refluxed for 1.5 h. After cooling to 0°C, carbondisulfide (0.49 mL, 8.2 mmol) was added to the reaction mixture, which was refluxed for 0.5 h. Methyl iodide (0.53 mL, 8.5 mmol) was added dropwise to the resulting reaction mixture at 0°C, and it was refluxed for 0.5 h. The reaction was quenched by an addition of sat. NaCl aq at 0°C, extracted with AcOEt, dried over Na_2SO_4, and evaporated. The crude product was passed through a short silica gel column chromatography (hexane–ether=4:1) to give the title dithiocarbonate as a pale yellow oil. Yield 691 mg (1.6 mmol, 98%). This material was uded for the next step without further purification.

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=5.8 Hz), 1.20 (t, 3H, J=7.1 Hz), 1.34–2.19 (m, 8H), 2.42 (s, 3H), 2.54 (s, 3H), 3.54–3.60 (m, 1H), 3.83–3.89 (m, 1H), 4.38–4.42 (m, 1H), 5.02–5.11 (m, 1H), 5.15 (d, 1H, J=3.3 Hz), 7.31 (d, 2H, J=8.3 Hz), 7.76 (d, 2H, J=8.3 Hz); IR ($CHCl_3$) 2950, 1340, 1200, 1160, 1060, 960, 750 cm^{-1}. Despite several attempts, a satisfactory mass spectral analysis data could not be obtained, and therefore, this material was used for the next step without further characterization.

5.4.5. 2-Ethoxy-6-propyl-1-(toluene-4-sulfonyl)-piperidine (12). A mixture of tributyltin hydride (0.34 mmol), AIBN (cat. amt.), and dithiocarbonic acid *O*-[6-ethoxy-2-propyl-1-(toluene-4-sulfonyl)piperidin-3-yl]ester *S*-methyl ester (45 mg, 0.1 mmol) in toluene (3 mL) was refluxed for 5 h. After cooling to 0°C, the reaction was quenched by an addition of sat. NaCl aq, extracted with AcOEt, dried over Na_2SO_4, and then evaporated in vacuo. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, hexane–ether=12:1, multiple development) to give the title compound as a white crystalline solid. Yield 12.9 mg (0.04 mmol, 38%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, 3H, J=7.3 Hz), 1.20 (t, 3H, J=7.1 Hz), 1.24–1.91 (m, 10H), 2.42 (s, 3H), 3.47–3.59 (m, 1H), 3.71–3.87 (m, 2H), 5.23 (d, 2H, J=2.3 Hz), 7.29 (d, 2H, J=8.1 Hz), 7.70 (d, 2H, J=8.1 Hz); IR ($CHCl_3$) 2950, 1340, 1160, 920, 750, 660 cm^{-1}; MS (exact mass calcd for $C_{17}H_{27}NO_3S$, *m/e* 325.1712, found *m/e* 325.2100).

5.4.6. 2-Allyl-6-propyl-1-(toluene-4-sulfonyl)piperidine. To a solution of 2-ethoxy-6-propyl-1-(toluene-4-sulfonyl)-piperidine (250 mg, 0.76 mmol) in CH_2Cl_2 (20 mL) was added a solution of allyltrimethylsilane (183 mg, 1.61 mmol) in CH_2Cl_2 (15 mL), and the mixture was cooled to −78°C. To the resulting mixture was added a solution of $BF_3{\cdot}OEt_2$ (229 mg, 1.61 mmol) in CH_2Cl_2 (12.5 mL) dropwise, and it was allowed to warm to −20°C during 3.5 h with stirring. The reaction was quenched by an addition of sat. Na_2CO_3 aq, extracted with ether, dried over Na_2SO_4, and then evaporated. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, hexane–ether=4:1×5) to give the title compound as a colorless oil. Yield 211.9 mg (6.6 mmol, 87%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, 3H, J=7.3 Hz), 1.10–1.77 (m, 10H), 2.33–2.54 (m, 2H), 2.41 (s, 3H), 3.93–4.02 (m, 2H), 5.03–5.09 (m, 2H), 5.72–5.85 (m, 1H), 7.27 (d, 2H, J=8.1 Hz), 7.71 (d, 2H, J=8.1 Hz); IR (neat) 2950, 2870, 1640, 1600, 1450, 1330, 1160, 660 cm^{-1}; $[\alpha]_D^{23}$=−7.5 (*c* 0.16, AcOEt); MS (exact mass calcd for $C_{18}H_{27}NO_2S$, *m/e* 321.1762, found *m/e* 321.2300).

5.4.7. 2-Hex-2-enyl-6-propyl-1-(toluene-4-sulfonyl)-piperidine (13). Ozone was bubbled into a solution of 2-allyl-6-propyl-1-(toluene-4-sulfonyl)piperidine (100 mg, 0.31 mmol) in CH_2Cl_2 (8 mL) at −78°C until the starting material was consumed. The reaction was quenched by an addition of dimethylsulfide (0.057 mL, 0.78 mmol), and then warmed to room temperature. The resulting mixture was evaporated in vacuo to remove the excess dimethylsulfide. [6-Propyl-1-(toluene-4-sulfonyl)piperidin-2-yl]-acetaldehyde was obtained as a crude product (136 mg), and used for the next reaction without further purification. To a suspension of pentyltriphenylphosphonium bromide (384 mg, 0.93 mmol) in Et_2O (4 mL) was added *n*-butyl lithium (1.52N, 0.61 mL) dropwise, and the whole was refluxed for 2 h. To the resulting mixture was added a solution of the aldehyde in Et_2O (4 mL) at 0°C, and the

whole was refluxed overnight. The reaction mixture was cooled to 0°C, quenched by an addition of water, extracted with Et_2O, dried over $MgSO_4$, and then evaporated. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer solution, hexane–Et_2O=8:1) to give the title olefin as a colorless oil. Yield 70.3 mg (0.18 mmol, 60%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86–0.96 (m, 6H), 1.05–1.73 (m, 14H), 1.98–2.05 (m, 2H), 2.36–2.49 (m, 2H), 2.41 (s, 3H) 3.99–3.86 (m, 2H), 5.31–5.48 (m, 2H), 7.26 (d, 2H, J=8.3 Hz), 7.71 (d, 2H, J=8.3 Hz); IR (neat) 2920, 1720, 1450, 1340, 1160, 750, 660 cm^{-1}; $[\alpha]_D^{23}=-20.1$ (c 0.37, $CHCl_3$); MS (exact mass calcd for $C_{22}H_{35}NO_2S$, m/e 377.2388, found m/e 377.2306).

5.4.8. 2-Hept-2-enyl-6-propylpiperidine (14). To a solution of 2-hex-2-enyl-6-propyl-1-(toluene-4-sulfonyl)piperidine (65 mg, 0.17 mmol) in 1,2-dimethoxy ethane (DME) was added a solution of sodium naphthalenide in DME, freshly prepared from sodium and naphthalene, until the color of the reaction mixture turned to light brown. The resulting mixture was warmed to 0°C, quenched by an addition of sat. $NaHCO_3$ aq, extracted with AcOEt, dried over K_2CO_3, and then evaporated. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, CH_2Cl_2–MeOH–Et_3N=10:1:0.2) to give the title compound as a colorless oil. Yield 29 mg (0.13 mmol, 75%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.67–0.98 (m, 6H), 0.99–1.11 (m, 2H), 1.23–1.40 (m, 9H), 1.61–1.75 (m, 2H), 1.80–1.81 (m, 2H) 1.93–2.17 (m, 4H), 2.41–2.53 (m, 2H), 5.28–5.39 (m, 1H), 5.44–5.57 (m, 1H); IR (neat) 2920, 1450, 1370, 1330, 1120, 970 cm^{-1}; $[\alpha]_D^{23}=-12.1$ (c 0.12, $CHCl_3$); MS (exact mass calcd for $C_{15}H_{29}N$, m/e 223.2300, found m/e 223.2245).

5.4.9. 2-(3-Chloro-2-phenylsulfenylheptyl)-6-propylpiperidine; hydrochloride. 2-Hept-2-enyl-6-propylpiperidine (29 mg, 0.13 mmol) was treated with HCl in MeOH. After evaporation, CH_2Cl_2 was added to the residue, which was cooled to 0°C. To the above suspension was added a solution of an excess phenylsulfenyl chloride (188 mg, 0.13 mmol) in CH_2Cl_2 and it was stirred for 10 min. The reaction mixture was evaporated in vacuo to give a crude product as a yellow solid. The stereochemistry and regioselectivity of the obtained compound were not determined at this stage, and it was used for the next reaction without further purification. Yield 32.1 mg (crude).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.81–0.98 (m, 6H), 1.01–2.15 (m, 19H), 2.35–3.01 (m, 2H), 3.30–3.54 (m, 1H), 3.98–4.16 (m, 1H), 7.20–7.48 (m, 5H); MS (exact mass calcd for $C_{21}H_{34}ClNS$, m/e 367.2100, found m/e 367.2003).

5.4.10. 3-Butyl-2-phenylsulfenyl-5-propyloctahydroindolizine (15). To a solution of 2-(3-chloro-2-phenylsulfenylheptyl)-6-propylpiperidine hydrochloride (30.1 mg, 0.075 mmol) in MeCN was added K_2CO_3 (83.5 mg, 0.34 mmol) and sodium iodide (80.5 mg, 0.3 mmol), and the whole was heated at reflux for 5 h. The insoluble material was removed by filtration and the filtrate was concentrated in vacuo. To the residue was added sat. NaCl aq, and the whole was extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$ and evaporated. The crude product was purified on preparative silica gel TLC (pre-treated with phosphate buffer, hexane–AcOEt=10:1) to give the title compound (an 87:13 mixture of epimers) as a colorless oil. Yield 9.0 mg (0.027 mmol, 36%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83–0.98 (m, 6H), 1.03–1.45 (m, 10H), 1.53–1.82 (m, 8H), 2.18–2.28 (m, 1H), 2.54–2.69 (m, 2H) 3.33 (brs, 1H), 7.15–7.37 (m, 5H); MS (exact mass calcd for $C_{21}H_{33}NS$, m/e 331.2334, found m/e 331.2266).

5.4.11. 3-Butyl-5-propyloctahydroindolizine; indrizidine 223AB.[19] To a solution of 3-butyl-2-phenylsulfanyl-5-propyloctahydroindolizine (9 mg, 0.027 mmol) in EtOH was added Ra-Ni (W2) (200 mg suspended in EtOH), and the whole was refluxed for 20 min. After cooling to room temperature, the catalyst was removed by filtration through a celite® pad. The filtrate was concentrated in vacuo to give the title compound as a colorless oil. Yield 5 mg (0.022 mmol, 83%). The spectral data are in accordance with those in the literature.[19]

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86–1.00 (m, 6H), 1.15–1.88 (m, 20H), 2.11–2.28 (m, 2H), 2.50–2.70 (m, 1H), 5.44–5.57 (m, 1H); IR (neat) 2950, 2850, 1780, 1466, 1120 cm^{-1}; MS (Found: M^+, 223).

Acknowledgements

We thank Professor D. H. Hua of Kansas State University for very helpful discussions.

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