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Stereoselective synthesis of azetidine-derived glutamate and aspartate analogues from chiral azetidin-3-ones

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ABSTRACT

The stereoselective syntheses of cis conformationally constrained glutamate and aspartate analogues, containing an azetidine framework were accomplished from (*S*)-*N*-tosyl-2-phenylglycine in moderate overall yields. The key steps in these syntheses involved an efficient Wittig olefination of an azetidin-3-one, followed by a highly stereoselective rhodium catalyzed hydrogenation. The route could also be applied to the synthesis of a *trans* glutamate analogue, since epimerization of cis to trans isomer could be performed using DBU in toluene at reflux.

1. Introduction

Glutamate and aspartate are the predominant excitatory amino acid (EAA) neurotransmitters in the mammalian central nervous system.[1] These excitatory amino acids activate a family of ligand-gated ion channels, called ionotropic receptors (AMPA, KA, and NMDA), and a family of receptors coupled to GTP-binding proteins (metabotropic receptors) implicated in a variety of intracellular signaling processes.[2] EAA receptors participate in fast excitatory transmission as well as in more complex signaling processes, such as those required for synaptic plasticity and higher cognitive functions.[3] In contrast to these normal signaling pathways, excessive activation of the ionotropic EAA receptors can trigger a cascade of events that eventually leads to neuronal death. This process, referred to as excitotoxicity, is thought to be the underlying pathological mechanism in a wide variety of neurological insults and degenerative disorders, such as ischemia, trauma, hypoglycemia, epilepsy, Huntington's, and Parkinson's diseases.[4] To better understand the role of glutamate and aspartate in these diseases, many research groups have investigated the interactions between synthetic amino acids and the proteins to which glutamate and aspartate bind. Conformationally restricted glutamate and aspartate analogues are molecular probes, which have proved highly valuable in providing information about the structural requirements for binding to the EAA receptors.

Although the majority of the glutamate and aspartate analogues synthesized so far display a pyrrolidine ring,[5] the use of azetidine rings as conformational constraining elements has been attracting considerable attention lately, especially for their increased rigidity and the interesting physiological activities exhibited by some azetidine amino acids. Figure 1 shows some illustrative examples of azetidine containing amino acids displaying important biological activities.[6a–d]

Glutamate **1** has been shown to act as an activator of the metabotropic receptors, whereas analogue **2** appears to be a potent agonist of the kainate receptor. Compounds **2** and **3** also inhibit sodium-dependent glutamate uptake.

2. Results and discussion

In spite of several interesting examples in the literature dealing with the synthesis of azetidine amino acids,[6] the synthesis of glutamate and aspartate analogues has been accomplished in most cases with some limitations such as low stereoselectivity, racemic synthesis, or restriction to the synthesis of the trans analogues.

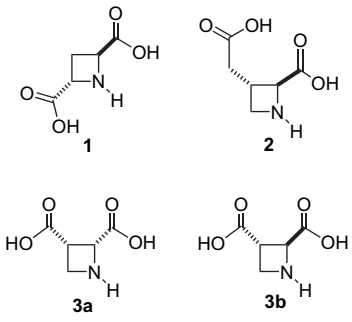

Figure 1. Some azetidine-derived glutamate and aspartate analogues displaying pharmacological activities.

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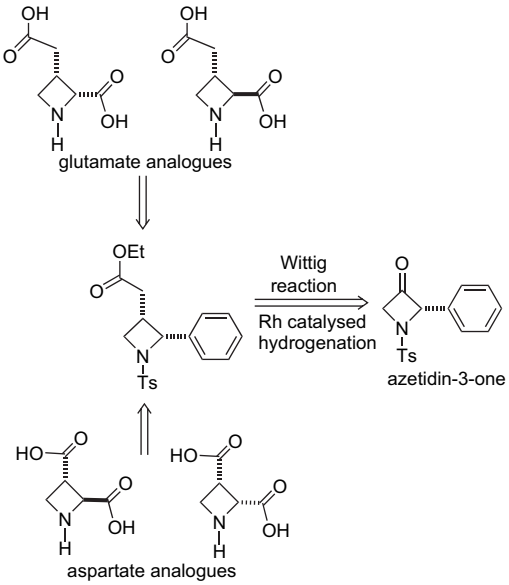
Recently, we have published a communication reporting the synthesis of the (2*R*,3*S*)-2-carboxyazetidine-3-acetic acid, a new *cis* glutamate analogue.[7a] Herein, as an extension of our studies involving the chemistry of azetidin-3-ones,[7] we wish to report in detail a straightforward route, which permits the preparation of both *cis* and *trans* azetidine-containing aspartate and glutamate analogues from a common intermediate, as depicted in Scheme 1. Some alternative routes investigated by us failed to furnish these rigidified amino acids, but provided pertinent information about the behavior of four-membered rings.



Scheme 1. Strategy for the synthesis of azetidine-derived glutamate and aspartate analogues from azetidin-3-ones.

We began our study with the synthesis of the glutamate analogues. The synthesis of glutamate analogues featured a very efficient Wittig olefination of an azetidin-3-one[8] (azetidine-3-ones can be readily prepared from commercially available amino acids), followed by a highly stereoselective rhodium catalyzed hydrogenation. For this purpose, azetidin-3-one **5**[9] was readily prepared in two steps from (*S*)-*N*-tosyl-2-phenylglycine in good overall yield (Scheme 2). The protocol involved the conversion of *N*-protected phenylglycine to the diazoketone **4** in 64%, followed by the reaction of **4** with copper(II) acetate in benzene at reflux to promote the N–H insertion reaction in 70% yield.[7,10] Next, azetidin-3-one **5** was converted to the enoate **6** in quantitative yield by a Wittig olefination reaction[11] using the stabilized ylide carboethoxyethylidene-triphenylphosphorane. Catalytic hydrogenation of enoate **6** was initially carried out using Pd/C in MeOH under H_2 atmosphere. Under these conditions, only 19% of the desired ester **7** was obtained, together with 81% of the hydrogenolysis derived product **8** (Scheme 2).

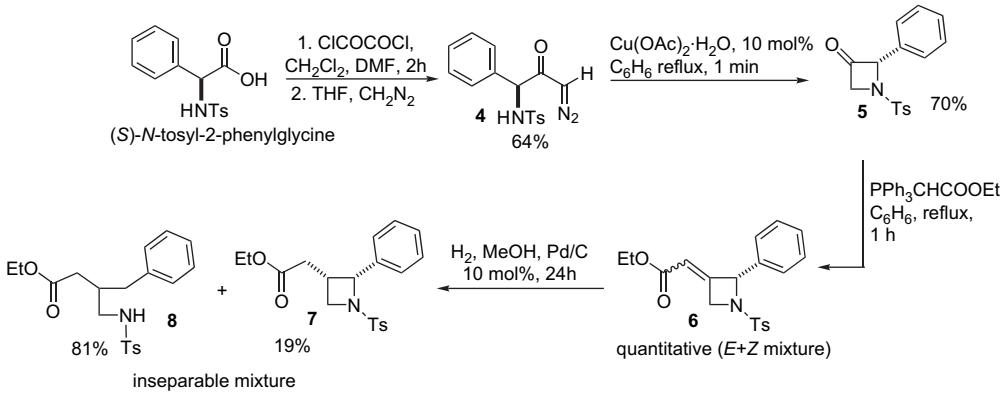
Compound **8** was the result of a hydrogenolysis reaction of the N–C2 bond of **6** and was totally suppressed when hydrogenation was performed using Rh/C as catalyst or Et_3SiH in the presence of Wilkinson's catalyst.[12] Under these conditions the *cis* ester **7**[13] was obtained in good yields (90% and 80%, respectively) with good diastereoselectivities (92:08 and 88:12, cis/trans ratio, respectively) (Scheme 3).

After finding the best conditions to perform the reduction of enoate **6**, we then proceeded in the synthesis of the glutamate analogue by oxidizing the phenyl ring of **7** to a carboxylic acid function. The ester **7** was then treated with $RuCl_3$ and $NaIO_4$[14] followed by the addition of diazomethane to furnish the *cis* diester **9**[15] in yields ranging from 40 to 54% (Scheme 3). Next, hydrolysis of the diester **9** with LiOH[16] gave the *N*-protected glutamate acid derivative **10** as a white solid (90% yield) with no detectable epimerization at C2. Although the major *cis* compounds **7**, **9**, and **10** could not be separated from their respective trans isomers (at C3) by column chromatography, a careful recrystallization (ethanol/hexane) of diacid **10** provided this key compound in an almost pure form (dr>98:02 after a single recrystallization). Completion of the synthesis of the novel conformational restricted *cis* azetidine glutamate **11** was carried out as previously reported[7a] (N-deprotection of diacid **10** with Na/naphthalene[17] in quantitative yield, after purification on ion-exchange resin).

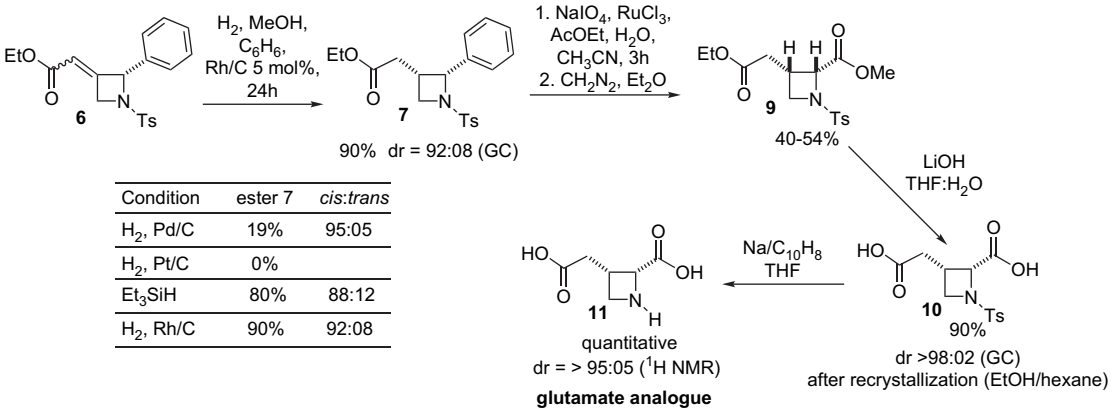
After completion of the synthesis of the *cis* glutamate analogue **11** and just to check the expandability of the present strategy, we examined the epimerization of the *cis* diester **12** (prepared from diacid **10** with trimethylsilyl-diazomethane) to its trans stereoisomer. The use of bases such as LHMDS, KHMDS, *t*-BuOK, proton sponge, Me_2NH, and pyridine led to no epimerization[18] at C2 or to decomposition of the diester **12**. However, reaction of diester **12** with DBU (10 equiv) in toluene at reflux for 7 h provided a diastereomeric mixture of diester **12** and its trans isomer (inseparable mixture) in a 20:80 (GC)[19] ratio as described in Table 1, entry 12.

After the synthesis of glutamate analogue **11**, we focused on the synthesis of the aspartate analogues. The same strategy employing a Wittig olefination reaction, followed by hydroboration and oxidation, was investigated starting from azetidin-3-one **16**[7c] (Scheme 4).

We began this study by preparing azetidin-3-one **16** in a similar way to that described for azetidin-3-one **5**, employing an N–H insertion reaction of diazoketones. Under these conditions, compound **16** could be prepared in 52% yield after three steps from *N*-Ts-L-serine **13** (Scheme 5). Next, azetidin-3-one **16** was submitted to a Wittig olefination[11] in the presence of the non-stabilized ylide $PPh_3{=}CH_2$. However, formation of olefin **17** could not be detected



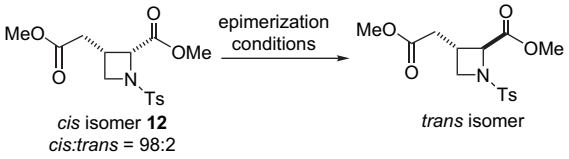
Scheme 2. Synthesis of ester **7** from azetidin-3-one.



Condition	ester 7	*cis*:*trans*
H_2, Pd/C	19%	95:05
H_2, Pt/C	0%	
Et_3SiH	80%	88:12
H_2, Rh/C	90%	92:08

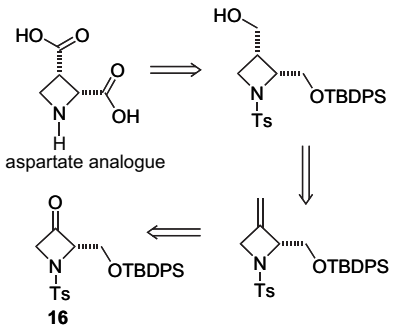
Scheme 3. Synthesis of the glutamate analogue **11** from ester **7**.

Table 1
Epimerization studies with *cis* diester **12**



Entry	Epimerization conditions	Result	*cis* Ester (%) (GC)	*trans* Ester (%) (GC)
1	Me_2NH, C_6H_6/H_2O, FTC	No epimerization	98	02
2	Pyridine, CH_2Cl_2	No epimerization	98	02
3	Et_3N, CH_2Cl_2	No epimerization	98	02
4	KHMDS, THF, −78 and 0 °C, 30′	Decomposition of 12		
5	LiHMDS, THF, −78 and 0 °C, 30′	Decomposition of 12		
6	*t*-BuO$^-$K$^+$, *t*-BuOH, 1 h	Decomposition of 12		
7	Proton sponge, CH_2Cl_2	No epimerization	98	02
8	DBU, CH_2Cl_2	Epimerization	51	49
9	DBU, C_6H_6	No epimerization	98	02
10	DBU, C_6H_6, 60–70 °C	Epimerization	55	45
11	DBU, C_6H_6, reflux, 24 h	Epimerization	20	80
12	DBU, PhMe, reflux, 7 h	Epimerization	20	80
13	DBU, xylene, reflux	Epimerization and decomposition	20	80
14	KOH, H_2O:THF	No epimerization (hydrolysis)	98	02

even after varying the experimental conditions such as the use of different solvents, temperatures, and bases. It is likely that the non-stabilized ylide act as a base removing the hydrogen at C4 thus preventing the desired Wittig olefination. Although the isolation of



Scheme 4. Strategy for the synthesis of azetidine-derived aspartate analogues from azetidin-3-one **16**.

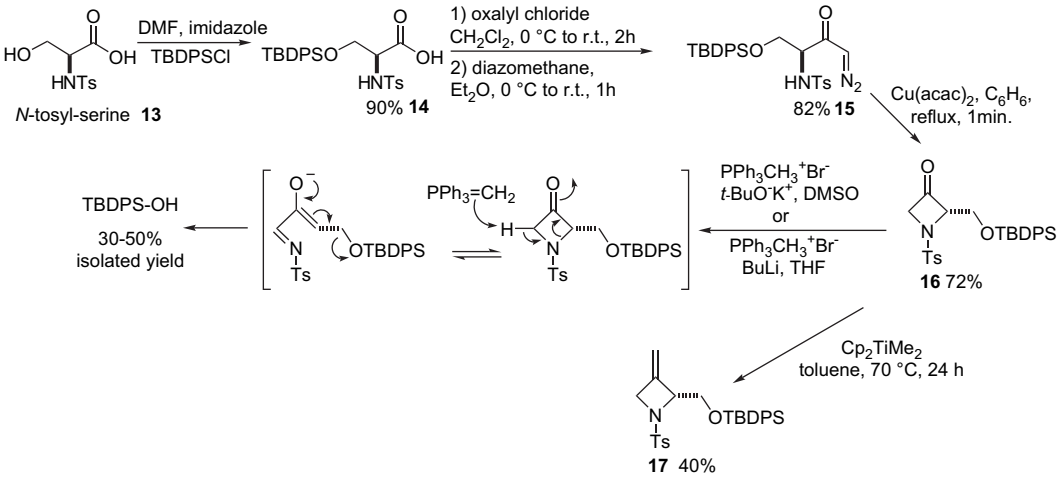
30–50% of the *tert*-butyldiphenylsilyl alcohol supports this hypothesis, this proposal is still speculative (Scheme 5). Nevertheless, this problem was circumvented by the use of the Petasis reagent[20] as the olefination source. In this case, olefin **17** could be prepared in a moderate yield of 40%.

We next investigated the hydroboration reaction of olefin **17** in the presence of $BH_3 \cdot SMe_2$ complex. Surprisingly, we obtained the expected primary alcohol **18** together with its regioisomer (tertiary alcohol **19**) in 50% yield as a 3:1 separable mixture (Scheme 6).

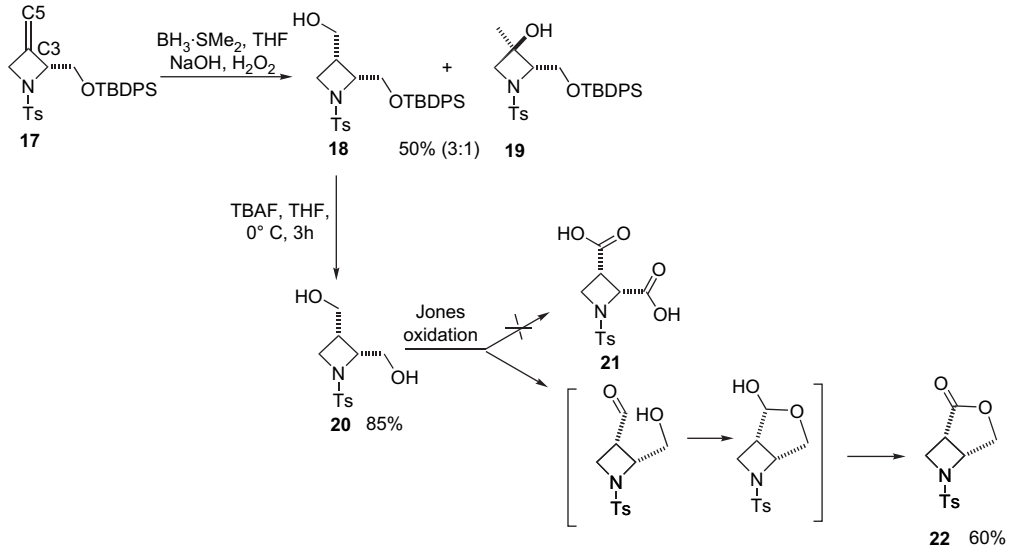
The unexpected formation of alcohol **19**, considering the hydroboration preferences, could be understood after carrying out some semi-empirical (PM3) and ab initio (B3LYP/6-31G*) calculations. In these calculations, we found out that the HOMO coefficients of the two olefinic carbons (C3 and C5) of compound **17** are almost identical. Also unexpected, the non-terminal C3 has a higher electron density than the terminal C5. Although steric effects are predominating during the hydroboration reaction, furnishing primary alcohol **18** as the major isomer, these two results with the theoretical calculations support the isolation of the tertiary alcohol in an unexpected proportion. The use of bulky borane reagents was also employed, but was fruitless regarding yields and selectivities. Aiming at the synthesis of the azetidine-derived aspartate analogue, primary alcohol **18** was then converted to diol **20** and submitted to Jones oxidation conditions. Unfortunately this protocol led to the formation of lactone **22** in 60% yield instead of the desired diacid **21** (however, the formation of **22** is a chemical proof of the cis relationship of compound **20**). This transformation involves a selective oxidation of the hydroxymethyl group at C3 to an intermediate aldehyde, cyclization to a lactol followed by oxidation.

In view of the results described above and with the objective of circumventing the formation of lactone **22**, we applied the same sequence of reactions described in Schemes 5 and 6 on azetidin-3-one **5**. Once again, Petasis olefination followed by hydroboration furnished only moderate yields of the desired products. Curiously, hydroboration in this case provided the desired primary alcohol in an even lower ratio when compared to the one described in Scheme 6. These results led us to look for alternative routes to the synthesis of the aspartate analogues.

One of these alternatives was the cyanation of 3-mesyloxy azetidines to construct the carboxylic acid function instead of the Wittig reaction, as depicted in Scheme 7. In order to test this cyanation route, azetidin-3-one **23**, previously prepared by Hanessian and co-workers,[11a,21] was reduced to the 3-azetidinol **24** in 93% yield as a single cis isomer (Scheme 8). Azetidin-3-ol **24** was then converted in a quantitative yield to mesylate **25** and submitted



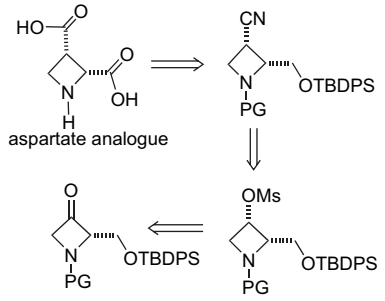
Scheme 5. Preparation of azetidin-3-one **16** and olefin **17**.



Scheme 6. Attempts in the synthesis of diacid **21** from olefin **17**.

to cyanation using KCN. Surprisingly, all attempts to form nitrile **26** failed, even under drastic conditions (DMSO, 80 °C, KCN, 7 days). The starting mesylate **25** is recovered in almost quantitative yields from these reactions.

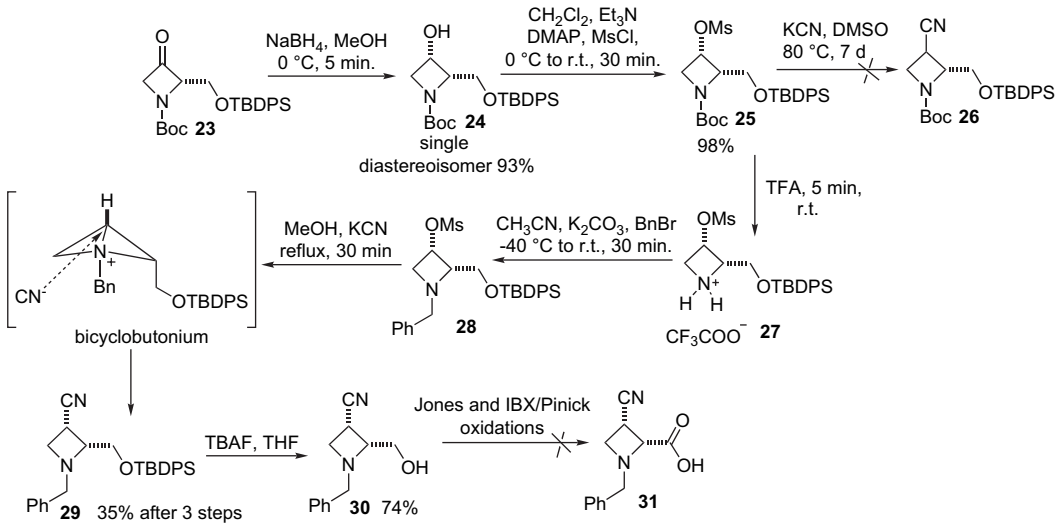
Based on the works of Masuda[22] and Marchand,[23] we realized that the formation of a bicyclobutonium is a very important step in the process and constitutes a driving-force for successful substitutions on this type of system. As the carbamate protecting group in compound **25** makes the formation of the bicyclobutonium difficult, we decided to exchange the Boc for a benzyl group and reexamine the cyanation reaction. The Boc group of mesylate **25** was then removed with trifluoroacetic acid and the resulting trifluoroacetate salt **27** was alkylated with benzyl bromide. Next, the crude *N*-benzyl-mesylate **28** was reacted with KCN in MeOH under reflux for 30 min[22] furnishing the desired nitrile **29** in 35% yield after three steps with complete retention of configuration. Although nitrile **29** could be synthesized in satisfactory yields under these conditions, removal of the TBDPS group with TBAF (74% yield), followed by the oxidation to the carboxylic acid[24] failed to provide acid **31** (Scheme 8).



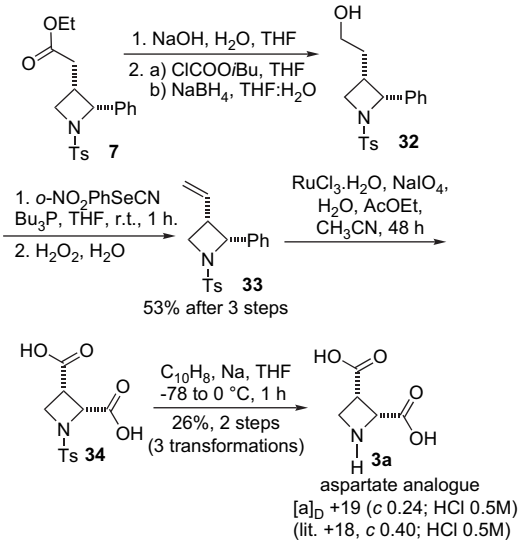
Scheme 7. Strategy for the synthesis of azetidine-derived aspartate analogues from cyanation of 3-mesyloxy azetidines.

Finally, after the above setbacks we found out that the synthesis of the azetidine-derived aspartate analogue could be performed by the reduction of the ester function in compound **7** (previously used in the synthesis of the glutamate analogues) and elimination of the primary alcohol, followed by the oxidative cleavage of the double bond (Scheme 9).

Therefore, based on a protocol described by Jiang and coworkers,[25] ester **7** was first hydrolyzed with lithium hydroxide,



Scheme 8. Attempted synthesis of azetidine-derived aspartates by cyanation of 3-mesiloxy azetidines.



Scheme 9. Synthesis of aspartate analogue **3a** from azetidine ester.

converted to a mixed anhydride and reduced in the presence of sodium borohydride. Next, the crude alcohol **32** was submitted to elimination with 2-nitrophenylselenecyanate and hydrogen peroxide to furnish olefin **33** in 53% yield after three steps (cis/trans, 92:08). After a single recrystallization from benzene/hexanes the *cis* olefin was enriched in more than 98%. The completion of the synthesis was realized after treatment of olefin **33** with $RuCl_3$ hydrate and $NaIO_4$,[14] followed by tosyl group removal with Na/naphthalene in THF.[17] After these three transformations (cleavage of terminal double bond, cleavage of phenyl ring and Ts removal) the azetidine-derived aspartate analogue **3a** was synthesized in 16% overall yield from azetidine **7**. The spectroscopic data and the optical rotation value of **3a** are in accordance with the ones described by Chamberlin and co-workers.[26]

3. Conclusions

In summary, we have accomplished the stereoselective synthesis of some glutamate and aspartate analogues, containing an azetidine nucleus, employing common intermediates from chiral (*S*)-*N*-tosyl-phenylglycine. The key steps in the synthesis involved a copper catalyzed N–H insertion of diazoketones to construct the four-membered rings, a very efficient Wittig olefination of an azetidin-3-one, followed by a highly stereoselective rhodium catalyzed hydrogenation. Epimerization of the *cis* glutamate analogue **12** with DBU allows the reported route to be extended to the synthesis of the trans analogues with good diastereoselectivity.

4. Experimental section

4.1. General procedures

Reagents and solvents are commercial grade and were used as supplied, except when specified in the experimental procedure. In the cases where dry solvents were employed, Et_3N, CH_3CN, DMF, and CH_2Cl_2 were distilled from calcium hydride and THF, Et_2O, toluene, and benzene were distilled from Na. Diazomethane was prepared from diazald®. Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous Na_2SO_4, filtered through paper filter and concentrated under reduced pressure with the aid of a rotary evaporator. *Flash* chromatography was carried out by using Merck 60 (230–400 mesh) silica gel. Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). ^1H NMR and ^{13}C NMR data were recorded on a Varian Gemini 2000 (7.0 T) or Varian Inova (11.7 T) spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane and *J* values are expressed in hertz. Spectra recorded in D_2O were referenced at 4.84 ppm. Gas chromatography analyses were carried out in a HP-6890 with a capillar column HP-5. Electron spray mass spectra were measured in an AP QTrap-LC/MS instrument. High resolution mass spectra (HRMS) were measured on a VG Autospec-Micromass spectrometer. IR spectra were obtained on a Thermo-Nicolet IR-200 spectrometer. Optical rotations were measured at 24 °C with a Perkin–Elmer 241. Melting points were measured with a Unimelt-Capilar from Thomas Hoover and were not corrected.

4.2. (*S*)-*N*-(3-Diazo-2-oxo-1-phenylpropyl)-4-methylbenzenesulfonamide (4)

To a solution of the (*S*)-*N*-Ts-2-phenylglycine (1.57 g, 5.0 mmol) in 25.0 mL of dry CH_2Cl_2 at 0 °C was added 6.0 mmol of oxalyl

chloride, followed by two drops of DMF. After 2 h of stirring at room temperature, the solvent was evaporated in vacuum and 25.0 mL of dry THF was added to the pale yellow oil. The resulting solution was cooled to 0 °C and a freshly prepared solution of the diazoalkane in ether was added (2 equiv or more). After stirring for 1 h at 0 °C, the excess of CH_2N_2 was removed (bubbling argon to the reaction flask), the solution was then concentrated in vacuum and the crude product purified by flash column chromatography (30% EtOAc/hexanes) to furnish 1.06 g (64%) of the diazoketone **4** (the compound can also be purified by recrystallization in benzene/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.36 (s, 3H), 4.87 (br s, 1H), 5.13 (s, 1H), 6.16 (d, J=5.1 Hz, 1H), 7.10–7.30 (m, 7H), 7.53 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 55.0, 63.5, 126.9, 127.6, 128.5, 128.8, 129.2, 135.6, 136.8, 143.1, 188.8; IR (neat, cm^{-1}): 3265, 3091, 2124, 1627, 1365, 1341, 1166, 725; ESI-MS: 330 (M+1), 302, 260, 184, 155, 131, 103, 91; HRMS m/z calcd for $C_{16}H_{15}N_3O_3S$: 329.0834. Found: 329.07301; TLC: R_f=0.28, 30% EtOAc/hexanes; $[\alpha]_D^{24}$ +219.5 (c 2.58, $CHCl_3$); mp: 136–137 °C.

4.3. (*S*)-2-Phenyl-1-tosylazetidin-3-one (5)

Diazoketone **4** (1.65 g, 5.0 mmol) was dissolved in 100 mL of benzene and the yellow solution heated under reflux with a heat gun with stirring. After that, 10 mol % of $Cu(OAc)_2\cdot H_2O$ was added in portions, turning the reaction mixture brown immediately and liberating nitrogen. *CAUTION: liberation of nitrogen is quite violent and large scale reactions (more than 10 mmol) should be done in big reaction recipients to permit nitrogen liberation*. After 1 min, the reaction was cooled, the solvent evaporated and the crude product purified by *flash* column chromatography (50% CH_2Cl_2/hexanes) to furnish 1.05 g (70%) of azetidin-3-one **5** (the compound can also be purified by recrystallization in benzene/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.45 (s, 3H), 4.61 (dd, J=16.1, 4.4 Hz, 1H), 4.77 (d, J=16.1 Hz, 1H), 5.74 (d, J=4.4 Hz, 1H), 7.00–7.30 (m, 7H), 7.78 (d, J=8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6, 70.2, 86.6, 126.0, 128.3, 128.7, 129.9, 131.7, 132.1, 145.0, 193.1; IR (neat, cm^{-1}): 3060, 2974, 1814, 1336, 1152, 1091, 1001; ESI-MS: 302 (M+1), 274, 184, 155, 119, 91; HRMS m/z calcd for $C_{16}H_{15}NO_3S$: 301.0773. Found: 301.0799; TLC: R_f=0.46, $CHCl_3$; mp: 163–164 °C; $[\alpha]_D^{24}$ +272.0 (c 1.05, $CHCl_3$).

4.4. (*S*)-Ethyl 2-(2-phenyl-1-tosylazetidin-3-ylidene) acetate (6)

Azetidin-3-one **5** (1.82 g, 6.05 mmol) was dissolved in 120 mL of benzene. Next, 2.32 g (6.65 mmol, 1.1 equiv) of the stabilized ylide was added to this solution, which was stirred for 1 h under reflux. After this time, the solution was cooled to room temperature and the solvent evaporated. The resulted oil was then dissolved in a 1:1 mixture of ethyl acetate and hexanes and the suspension filtered in *flash* column chromatography silica (to remove triphenyl phosphine oxide). After this purification, 2.21 g (99% yield) of enoate **6** was obtained as *E* and *Z* mixture of isomers (oil becomes solid with time). ^{1}H NMR (300 MHz, $CDCl_3$), major isomer: δ=1.23 (t, J=7.3 Hz, 3H), 2.43 (s, 3H), 4.11 (q, J=7.3 Hz, 2H), 4.71 (dt, J=16.1, 2.9 Hz, 1H), 4.84 (ddd, J=16.1, 4.4, 2.9 Hz, 1H), 5.52–5.59 (m, 2H), 7.30–7.42 (m, 7H), 7.73 (d, J=8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), major isomer: δ=14.2, 21.6, 58.7, 60.6, 73.3, 114.6, 126.7, 128.2, 128.6, 129.7, 132.0, 136.4, 144.2, 154.0, 164.7; IR (neat, cm^{-1}): 3059, 3033, 2976, 1720, 1705, 1346, 1199, 1158, 1086; HRMS m/z calcd for $C_{20}H_{21}NO_4S$: 371.1191. Found: 371.1177; TLC, major isomer: R_f=0.50, 30% EtOAc/hexanes.

4.5. Ethyl 2-((2*R*,3*S*)-2-phenyl-1-tosylazetidin-3-yl) acetate (7)

Enoate **6** (*E*+*Z*) (620.0 mg, 1.67 mmol) was dissolved in a minimum amount of benzene. Then, 55 mL of MeOH and 172.0 mg of 5% Rh/C were added and the solution was saturated with H_2 for 20 min. After that, the reaction was stirred with a H_2 atmosphere (balloon filled with H_2) until the total consumption of the enoate (2 h). After this period the solution was filtered and the solvent evaporated, furnishing 90% of *cis* ester **7** as an inseparable 92:08 isomeric mixture (single homogeneous spot in TLC). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.08 (t, J=7.3 Hz, 3H), 2.09 (dd, J=16.8, 6.6 Hz, 1H), 2.31 (dd, J=16.8, 9.5 Hz, 1H), 2.47 (s, 3H), 2.90 (m, 1H), 3.52 (dd, J=8.1, 3.7 Hz, 1H), 3.82–4.02 (m, 3H), 5.05 (d, J=8.8 Hz, 1H), 7.22–7.42 (m, 7H), 7.69 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2, 21.7, 30.8, 34.8, 52.8, 60.5, 66.9, 126.8, 128.1, 128.3, 129.6, 131.4, 135.8, 144.0, 171.2; IR (neat, cm^{-1}): 3027, 2982, 2925, 1732, 1593, 1343, 1156, 1095, 1025; HRMS m/z calcd for $C_{20}H_{23}NO_4S$: 373.1348. Found: 373.1276; TLC: R_f=0.42, 30% EtOAc/hexanes.

4.6. (2*R*,3*S*)-Methyl 3-(2-ethoxy-2-oxoethyl)-1-tosylazetidine-2-carboxylate (9)

Ester **7** (570.0 mg, 1.50 mmol) was dissolved in a 10 mL 1:1 mixture of acetonitrile and ethyl acetate. After that, 10.0 g of sodium periodate, dissolved in 40 mL of water, followed by 55.0 mg of $RuCl_3$ hydrate (35%) was added to the organic solution. The new solution was then strongly stirred at room temperature for 3 h. After this period, 40 mL of ethyl acetate was added and the mixture containing a white precipitate filtered in Celite. The organic and aqueous phases were separated and the aqueous one extracted with ethyl acetate (3×20 mL). The resulted organic phases were then dried with Na_2SO_4, filtered, and evaporated. To the resulted oil were added 10 mL of Et_2O, followed by an ethereal solution of diazomethane until the solution becomes yellow. Next, the solvent was concentrate and the oil purified by *flash* column chromatography (30% EtOAc/hexanes), furnishing 245.4 mg of diester **9** (45%) as a viscous oil (inseparable mixture of cis and trans isomers, 92:08). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (t, J=7.3 Hz, 3H), 2.45 (s, 3H), 2.59 (dd, J=16.8, 9.5 Hz, 1H), 2.65 (dd, J=16.8, 6.6 Hz, 1H), 3.47 (dd, J=8.1, 4.4 Hz, 1H), 3.00 (m, 1H), 3.73 (s, 3H), 4.00 (t, J=8.1 Hz, 1H), 4.09 (q, J=7.3 Hz, 2H), 4.71 (d, J=9.5 Hz, 1H), 7.35 (d, J=8.1 Hz, 2H), 7.77 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2, 21.6, 27.9, 34.4, 52.3, 53.0, 60.9, 62.5, 128.1, 129.7, 144.1, 168.3, 170.5; IR (neat, cm^{-1}): 2984, 2950, 2894, 1732, 1441, 1161, 1093, 1037; HRMS m/z calcd for $C_{14}H_{16}NO_5S$ (M−EtO): 310.0749. Found: 310.1006; TLC: R_f=0.25, 30% EtOAc/hexanes; trans isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (t, J=7.3 Hz, 3H), 2.39 (dd, J=16.1, 6.6 Hz, 1H), 2.45 (s, 3H), 2.51 (dd, J=16.1, 6.6 Hz, 1H), 3.02 (sext, J=7.3 Hz, 1H), 3.59 (t, J=7.3 Hz, 1H), 3.71 (s, 3H), 3.91 (t, J=7.3 Hz, 1H), 4.08 (q, J=7.3 Hz, 2H), 4.30 (d, J=7.3 Hz, 1H), 7.34 (d, J=8.8 Hz, 2H), 7.77 (d, J=8.8 Hz, 2H); TLC: R_f=0.25, 30% EtOAc/hexanes.

4.7. (2*R*,3*S*)-3-(Carboxymethyl)-1-tosylazetidine-2-carboxylic acid (10)

Diester **9** (227.5 mg, 0.64 mmol) was dissolved in 7.0 mL of THF. Next, 7.0 mL of a 2 M aqueous solution of LiOH was added and the solution stirred for 12 h at room temperature. After this period, a 2 M aqueous HCl solution was added to the reaction solution (until pH 1) and the aqueous phase extracted with ethyl acetate (3×20 mL). The organic phase was then dried with Na_2SO_4, filtered, and evaporated, furnishing 178 mg of diacid **10** (90% yield) as a white solid (mixture of isomers, 92:08). Next, diacid **10** was dissolved in a minimum amount of EtOH, followed by a slow addition of hexanes and slow freezing. After this recrystallization procedure, *cis* diacid was enriched in more than 98%. ^{1}H NMR (300 MHz, acetone-d_6): δ=2.46 (s, 3H), 2.67 (d, J=8.1 Hz, 2H), 2.97 (m, 1H), 3.50 (dd, J=8.1, 4.4 Hz, 1H), 3.90 (t, J=8.1 Hz, 1H), 4.62 (d, J=9.5 Hz, 1H), 7.49 (d, J=8.8 Hz, 2H), 7.79 (d, J=8.8 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6): δ=21.6, 28.4, 34.5, 54.2, 63.8, 129.0, 130.8, 134.1, 145.1,

169.6, 172.5; IR (neat, cm^{-1}): 3300–2500, 1698, 1437, 1346, 1229, 1161, 943; HRMS *m*/*z* calcd for $C_{13}H_{15}NO_6S$: 313.0620. Found: 313.0590; mp: 201–202 °C (dec); $[\alpha]_D^{24}$ +1.6 (*c* 2.44, THF), +3.9 (*c* 1.28, acetone).

4.8. (2*R*,3*S*)-3-(Carboxymethyl)azetidine-2-carboxylic acid (11)

Diacid **10** (30.0 mg, 0.096 mmol) was dissolved in 2.0 mL of dry THF and the suspension cooled to −78 °C. Next, a 0.8 M solution of Na/naphthalene radical anion in THF (2.5 mL, 20 equiv) was added to the reaction. The dark green solution was then stirred at 0 °C for 2 h and, after this period, H_2O was added until the disappearance of the dark green color. Next, the aqueous phase was washed with Et_2O (2×10 mL), acidified with a 2.0 M HCl aqueous solution and evaporated. The residue was then purified by ion-exchange resin (Dowex H^+ 50) and the obtained solid redissolved in H_2O. After filtration, the aqueous solution was evaporated to furnish 14.7 mg (97%) of the desired amino acid as a opaque colorless solid. ^1H NMR (300 MHz, D_2O): δ=2.44 (dd, *J*=16.1, 11.7 Hz, 1H), 2.60 (dd, *J*=16.1, 5.1 Hz, 1H), 3.40 (m, 1H), 3.77 (dd, *J*=10.9, 6.6 Hz, 1H), 4.30 (dd, *J*=10.9, 8.8 Hz, 1H), 4.90 (d, *J*=9.5 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ=30.5, 34.5, 48.5, 61.8, 170.6, 176.0; IR (cm^{-1}): 3077, 1679, 1625, 1574, 1421, 1184, 1129, 974, 801, 723; ESI-MS: 160 (M+1), 114, 97, 96, 84, 78, 68; HRMS *m*/*z* calcd for $C_6H_9NO_4$: 159.0532. Found: 159.0618; $[\alpha]_D^{24}$ −4.8 (*c* 0.30, H_2O) (optical rotatory dispersion, ORD).

4.9. (2*R*,3*S*)-Methyl-3-((methoxycarbonyl)methyl)-1-tosylazetidine-2-carboxylate (12)

Diacid **10** (10.0 mg, 0.032 mmol) was dissolved in 1.0 mL of a 2:1 mixture of benzene/methanol at room temperature. Next, a 2.0 M solution of $TMSCHN_2$ in hexanes was added dropwise until a yellow color persisted. After stirring for 30 min the solution was quenched by dropwise addition of acetic acid and evaporated, to furnish diester **12** in quantitative yield. ^1H NMR (250 MHz, $CDCl_3$): δ=2.44 (s, 3H), 2.61–2.65 (m, 2H), 2.98 (m, 1H), 3.46 (dd, *J*=8.0, 4.0 Hz, 1H), 3.63 (s, 1H), 3.72 (s, 1H), 3.99 (t, *J*=8.3 Hz, 1H), 4.69 (d, *J*=9.0 Hz, 1H), 7.35 (d, *J*=8.0 Hz, 2H), 7.77 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=21.6, 27.8, 34.1, 51.9, 52.3, 52.9, 62.5, 128.3, 129.8, 132.9, 144.4, 168.6, 171.3; IR (neat, cm^{-1}): 3033, 2993, 2954, 2895, 1734, 1597, 1441, 1340, 1209, 1157, 1099; ESI-HRMS *m*/*z* calcd for $C_{15}H_{19}NO_6SH^+$: 342.1011. Found: 342.1018; $[\alpha]_D^{24}$ +20.0 (*c* 1.25, $CHCl_3$).

4.10. (*R*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methylene-1-tosylazetidine (17)

Azetidine-3-one **16** (65.2 mg, 0.13 mmol) (see Ref. 7c for experimental details) was dissolved in 0.9 mL of a 0.5 M solution of Petasis reagent (Cp_2TiMe_2) in toluene (0.45 mmol) and the new solution stirred and heated at 70–80 °C for 24 h in the absence of light. After this period, hexane was added in the reaction flask and the mixture filtered in a short pad of silica. The solvent was then evaporated and the crude material purified by *flash* column chromatography (20% Et_2O/hexanes) to provide 25.1 mg (40%) of olefin **17**. ^1H NMR (300 MHz, $CDCl_3$): δ=1.05 (s, 9H), 2.41 (s, 3H), 3.90 (d, *J*=5.4 Hz, 2H), 4.24 (dq, *J*=12.6, 2.7 Hz, 1H), 4.34 (dq, *J*=12.6, 2.7 Hz, 1H), 4.50 (m, 1H), 4.93 (m, 1H), 5.08 (m, 1H), 7.20–7.75 (Ar, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.4, 21.7, 26.9, 57.8, 65.3, 71.7, 108.2, 127.6, 128.1, 129.6 (2C), 133.0, 133.2, 135.5, 138.2, 143.8; IR (neat, cm^{-1}): 3072, 3043, 2930, 2657, 1601, 1428, 1348, 1163, 1111, 1092, 703; ESI-MS: 492 (M+1), 414, 337, 236, 155, 75; HRMS *m*/*z* calcd for $C_{28}H_{33}NO_3SSi$: 491.1950. Found: 491.2043; TLC: R_f=0.38, 20% EtOAc/hexanes; $[\alpha]_D^{24}$ +68.1 (*c* 1.35, $CHCl_3$).

4.11. ((2*R*,3*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-1-tosylazetidin-3-yl)methanol (18)

Olefin **17** (281.0 mg, 0.57 mmol) was dissolved in 5.7 mL of dry THF and the solution cooled to 0 °C. Next, 65 μL of $BH_3 \cdot SMe$ complex was added and the reaction stirred for 2 h at room temperature. The solution was then cooled to 0 °C, followed by the addition of 0.4 mL of a 3 M aqueous NaOH solution and 0.4 mL of 30% aqueous H_2O_2 solution. After stirring for 1 h at room temperature, H_2O was added to the reaction flask and the product extracted with EtOAc (3×20 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated to furnish the crude alcohol **18**, which was purified by *flash* column chromatography (50% EtOAc/hexanes) to provide 150.0 mg (50%) of a separable mixture of the two regioisomers **18** and **19** in a 3:1 ratio. Compound **18**: ^1H NMR (300 MHz, $CDCl_3$): δ=1.05 (s, 9H), 2.41 (s, 3H), 2.60 (m, 1H), 3.36 (dd, *J*=8.4, 4.2 Hz, 1H), 3.54 (t, *J*=8.4 Hz, 1H), 3.63 (dd, *J*=11.7, 4.2 Hz, 1H), 3.76–3.87 (m, 1H), 3.92 (dd, *J*=11.1, 4.8 Hz, 1H), 4.17 (2t, *J*=11.1 Hz, 2H), 7.20–7.75 (14H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.0, 21.6, 26.7, 33.6, 60.9, 62.2, 63.0, 127.5, 127.7, 129.4, 129.9, 135.2, 135.3, 143.8; IR (neat, cm^{-1}): 3481, 3086, 2955, 2928, 2856, 1597, 1428, 1347, 1160, 1106, 820, 742, 704; ESI-MS: 510 (M+1), 432, 354, 254, 236, 155, 83; HRMS *m*/*z* calcd for $C_{24}H_{26}NO_4SSi$ (M−*t*-Bu): 452.1351. Found: 452.1464; TLC: R_f=0.46, 50% EtOAc/hexanes; $[\alpha]_D^{24}$ +102.9 (*c* 0.95, $CHCl_3$). Compound **19**: ^1H NMR (300 MHz, $CDCl_3$): δ=1.05 (s, 9H), 1.53 (s, 3H), 2.43 (s, 3H), 3.32 (d, *J*=7.8 Hz, 1H), 3.53 (d, *J*=7.8 Hz, 1H), 3.57 (dd, *J*=9.3, 4.8 Hz, 1H), 3.86 (dd, *J*=10.5, 9.3 Hz, 1H), 3.95 (dd, *J*=10.5, 4.8 Hz, 1H), 7.20–7.80 (14H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.3, 21.6, 21.7, 26.9, 62.5, 62.6, 69.8, 73.4, 127.7, 128.3, 129.6, 129.7, 132.8, 133.0, 135.4, 143.9; IR (neat, cm^{-1}): 3518, 3072, 2933, 2915, 2857, 1593, 1428, 1341, 1327, 1151, 1107, 1086, 704; ESI-MS: 510 (M+1), 432, 279, 275, 149; HRMS *m*/*z* calcd for $C_{24}H_{26}NO_4SSi$ (M−*t*-Bu): 452.1351. Found: 452.1374; TLC: R_f=0.49, 50% EtOAc/hexanes; $[\alpha]_D^{24}$ +86.8 (*c* 2.13, $CHCl_3$).

4.12. ((2*R*,3*S*)-1-Tosylazetidine-2,3-diyl)dimethanol (20)

Alcohol **18** (100.0 mg, 0.2 mmol) was dissolved in 2.0 mL of THF and the solution cooled to 0 °C. Next, 0.3 mL (0.3 mmol) of a 1 M solution of TBAF was added and the reaction stirred for 3 h at room temperature. After that, the solvent was evaporated and the residue purified by *flash* column chromatography (60% EtOAc/hexanes), to furnish 45.0 mg of diol **20** (85%). ^1H NMR (300 MHz, $CDCl_3$): δ=2.47 (s, 3H), 2.50 (m, 1H), 3.50 (dd, *J*=8.4, 4.0 Hz, 1H), 3.57 (t, *J*=8.4 Hz, 1H), 3.76 (dd, *J*=11.7, 5.1 Hz, 1H), 3.83–4.08 (m, 4H), 7.39 (d, *J*=7.8 Hz, 2H), 7.72 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6, 33.3, 49.8, 60.7, 61.2, 65.1, 128.1, 129.6, 130.6, 144.1; IR (neat, cm^{-1}): 3387, 3068, 2954, 2929, 2856, 1467, 1429, 1338, 1159, 1111, 1043, 854, 820, 704; ESI-HRMS *m*/*z* calcd for $C_{12}H_{17}NO_4SH^+$: 272.0957. Found: 272.0961; $[\alpha]_D^{24}$ +25.0 (*c* 0.30, $CHCl_3$).

4.13. (1*S*,5*R*)-6-Tosyl-3-oxa-6-azabicyclo[3.2.0]heptan-2-one (22)

Diol **20** (22.0 mg, 0.08 mmol) was dissolved in 2.0 mL of acetone and the solution cooled to 0 °C. A solution of Jones' reagent was then added to the cooled solution dropwise, until the brown color persisted. After that, the bath was removed and the reaction stirred for 30 min. Isopropanol was added to the flask, the mixture filtered in a short pad of Celite, the solvent dried over Na_2SO_4, filtered, and evaporated. *Flash* column purification of the crude material in 60% EtOAc/hexanes provided 12.8 mg (60%) of the lactone **22**. ^1H NMR (300 MHz, $CDCl_3$): δ=2.47 (s, 3H), 3.07 (ddd, *J*=9.0, 6.6, 2.6 Hz, 1H), 3.80 (dd, *J*=9.0, 2.6 Hz, 1H), 3.98 (t, *J*=9.0 Hz, 1H), 4.33 (dd, *J*=11.6, 3.9 Hz, 1H), 4.54 (d, *J*=11.6 Hz, 1H), 4.78 (dd, *J*=6.5, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.7, 33.1, 52.3, 63.2, 73.0, 127.9, 128.0,

129.7, 130.0, 144.8, 176.0; IR (neat, cm^{-1}): 2958, 2918, 2844, 1777, 1597, 1343, 1160, 1104, 1054, 972; ESI-MS: 268 (M+1), 184, 155, 119, 91; HRMS *m*/*z* calcd for $C_{12}H_{13}NO_4S$: 267.0565. Found: 267.0580; TLC: R_f=0.38, 60% EtOAc/hexanes; $[\alpha]_D^{24}$ +100.0 (*c* 0.32, $CHCl_3$).

4.14. (2*S*,3*S*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)-methyl)-3-hydroxyazetidine-1-carboxylate (24)

To a solution of 887.4 mg (2.02 mmol) of 3-azetidinone **23** in 20.0 mL of methanol at 0 °C was added 94.0 mg (2.53 mmol) of $NaBH_4$ and the reaction stirred at this temperature for 5 min. After this period, a 10% aqueous solution of citric acid was added to the reaction (until pH 3.0), which was stirred for 5 min. The methanol was then removed and the aqueous phase extracted with CH_2Cl_2 (3×30 mL). After drying over Na_2SO_4, the organic phase was filtered and evaporated to provide 823.7 mg (93%) of the alcohol **24** as a single cis diastereoisomer. ^1H NMR (300 MHz, C_6D_6, 70 °C): δ=1.10 (s, 9H), 1.40 (s, 9H), 3.60 (m, 1H), 3.80–3.90 (m, 2H), 3.95–4.10 (m, 2H), 4.30 (m, 2H), 7.20 (m, 6H), 7.75 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6, 70 °C): δ=19.4, 27.1, 28.6, 60.0, 62.9, 65.1, 67.2, 78.8, 127.5, 127.8, 127.9, 128.0, 129.9, 132.8, 133.3, 135.6, 135.9, 155.1; IR (neat, cm^{-1}): 3469, 3077, 3052, 2962, 2931, 2852, 1700, 1678, 1427, 1107, 702; ESI-MS: 442 (M+1), 342, 308, 264, 186; HRMS *m*/*z* calcd for $C_{21}H_{26}NO_3Si$ (M−*t*-BuO): 368.1682. Found: 368.1592; TLC: R_f=0.36, 30% EtOAc/hexanes; $[\alpha]_D^{24}$ +34.0 (*c* 1.16, $CHCl_3$).

4.15. (2*S*,3*S*)-*tert*-Butyl-2-((*tert*-butyldiphenylsilyloxy)-methyl)-3-(methylsulfonyloxy)azetidine-1-carboxylate (25)

Alcohol **24** (794.0 mg, 1.80 mmol) was dissolved in 18 mL dry CH_2Cl_2, followed by the addition of 1.30 mL (9.00 mmol, 5 equiv) of triethylamine and catalytic DMAP (some crystals). The solution was then cooled to 0 °C and 0.21 mL (2.70 mmol, 1.5 equiv) of distilled mesyl chloride (MsCl) added dropwise. The bath was removed and the reaction stirred at room temperature for 1 h. In the work up, 25 mL of CH_2Cl_2 was added and the mixture filtered over silica gel. The silica was washed with 50% EtOAc/CH_2Cl_2 and the two organic phases grouped. Evaporation furnished 916.0 mg of the pure mesylate **25** as a colorless oil (98%). ^1H NMR (300 MHz, $CDCl_3$): δ=1.08 (s, 9H), 1.39 (s, 9H), 2.90 (s, 3H), 3.94 (dd, *J*=10.8, 2.4 Hz, 1H), 4.04–4.33 (m, 3H), 4.50 (td, *J*=6.6, 2.1 Hz, 1H), 5.37 (dt, *J*=7.0, 5.1 Hz, 1H), 7.30–7.53 (m, 6H), 7.64–7.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.3, 26.9, 28.4, 38.2, 56.2, 59.9, 66.7, 68.3, 80.2, 127.6 (2C), 129.6, 129.7, 132.9, 133.0, 135.4, 155.0; IR (neat, cm^{-1}): 3072, 3048, 2933, 2889, 2858, 1702, 1365, 1179, 1180, 1112, 964, 860, 703; ESI-MS: 520 (M+1), 420, 386, 342, 246, 197; HRMS *m*/*z* calcd for $C_{22}H_{28}NO_5SSi$ (M−*t*-BuO): 446.1458. Found: 446.1511; TLC: R_f=0.40, 30% EtOAc/hexanes; $[\alpha]_D^{24}$ +25.1 (*c* 0.49, $CHCl_3$).

4.16. (2*R*,3*S*)-1-Benzyl-2-((*tert*-butyldiphenylsilyloxy)-methyl)azetidine-3-carbonitrile (29)

Mesylate **25** (914.6 mg, 1.76 mmol) was dissolved in 1.80 mL of trifluoroacetic acid and the solution stirred for 5 min at room temperature. After that, all the solvent was evaporated and the dry salt **27** [^1H NMR (300 MHz, $CDCl_3$): δ=1.08 (s, 9H), 2.93 (s, 3H), 4.04 (dd, *J*=10.0, 5.0 Hz, 1H), 4.15 (dd, *J*=10.0, 5.0 Hz, 1H), 4.34 (m, 2H), 4.70 (m, 1H), 4.56 (m, 1H), 7.3–7.8 (m, 10H)] dissolved in dry acetonitrile. The solution was then cooled to −40 °C, followed by the addition of anhydrous K_2CO_3 (730 mg) and benzyl bromide (0.23 mL, 1.94 mmol). After stirring for 30 min at room temperature, the mixture was filtered (removal of K_2CO_3) and the organic phase evaporated. To the resulting crude benzylated azetidine **28** in 18.0 mL of methanol was added 400.0 mg (6.16 mmol) of KCN and the reaction stirred under reflux for 30 min. After that, the solvent was evaporated to dryness and the residue dissolved in 60 mL of Et_2O. The organic phase was then washed with H_2O (2×30 mL), dried over Na_2SO_4, filtered, and evaporated. *Flash* column chromatography purification (30% EtOAc/hexanes) furnished 259.3 mg of nitrile **32** (34% after three steps). ^1H NMR (300 MHz, $CDCl_3$): δ=1.07 (s, 9H), 3.07 (t, *J*=7.7 Hz, 1H), 3.24 (td, *J*=7.7, 3.1 Hz 1H), 3.42–3.52 (m, 3H), 3.68 (dd, *J*=11.0, 6.2 Hz, 1H), 3.74 (d, *J*=12.4 Hz, 1H), 3.85 (dd, *J*=11.0, 6.2 Hz, 1H), 7.20 (m, 5H), 7.40 (m, 6H), 7.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=19.1, 23.3, 26.7, 53.6, 61.6, 64.8, 65.9, 119.6, 127.3, 127.7, 128.3, 128.6, 129.8, 133.2, 135.6, 136.8; IR (neat, cm^{-1}): 3077, 2930, 2856, 2239, 1471, 1427, 1110, 823, 740, 701; ESI-MS: 441 (M+1), 363, 310, 185, 91; HRMS *m*/*z* calcd for $C_{28}H_{32}N_2OSi$: 440.2284. Found: 440.2301; TLC: R_f=0.34, 20% EtOAc/hexanes; $[\alpha]_D^{24}$ +28.0 (*c* 1.28, $CHCl_3$).

4.17. (2*R*,3*S*)-1-Benzyl-2-(hydroxymethyl)azetidine-3-carbonitrile (30)

Nitrile **29** (212.0 mg, 0.48 mmol) was dissolved in 5.0 mL of THF and the solution cooled to 0 °C 0.63 mL (0.63 mmol) of a 1 M solution of TBAF was added and the reaction stirred for 30 min at room temperature. Next, the solvent was evaporated and the residue purified by *flash* column chromatography (60% EtOAc/hexanes), to furnish 74% of alcohol **30**. ^1H NMR (300 MHz, $CDCl_3$): δ=3.22 (dd, *J*=8.7, 7.5 Hz, 1H), 3.27–3.38 (m, 1H), 3.52–3.72 (m, 6H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.8, 53.7, 61.5, 62.5, 65.9, 119.4, 127.6, 128.5 (2C), 128.7, 136.6; IR (neat, cm^{-1}): 3408, 3066, 2954, 2933, 2858, 2247, 1466, 1427, 1363, 1111, 1039, 850, 821; ESI-MS: 203 (M+1), 91; ESI-HRMS *m*/*z* calcd for $C_{12}H_{14}N_2OH^+$: 203.1184. Found: 203.1188; $[\alpha]_D^{24}$ +9.0 (*c* 1.55, $CHCl_3$).

4.18. (2*R*,3*S*)-2-Phenyl-1-tosyl-3-vinylazetidine (33)

Ester **7** (448.6 mg, 1.2 mmol) was dissolved in 12.0 mL of THF. Followed by the addition of 12.0 mL of an aqueous LiOH 2 M solution, the mixture was kept under stirring for 12 h and, after that, the aqueous phase was washed with Et_2O. The organic phase was then acidified with $NaHSO_4$ (until pH 2.0) and extracted with EtOAc (3×30 mL). After evaporation of the organic phase, the crude oil was dried and dissolved in 6.0 mL of dry THF. To this new solution, at −21 °C, were added 230 μL of triethylamine (1.4 equiv) and 190 μL of isobutyl cloroformate (1.2 equiv). After stirring for 30 min, the solution was filtered quickly (removal of the ammonium hydrochloride), added to a solution of $NaBH_4$ (180 mg) in H_2O (3.0 mL) and stirred for 16 h. After this time, the solution was extracted with Et_2O (4×20 mL), dried with Na_2SO_4, and evaporated. The crude primary alcohol **32** was then dried in vacuum and used in the elimination step directly. For this step, the crude alcohol **32** was dissolved in 6.0 mL of dry THF, followed by the addition of 545.0 mg (2.0 equiv) of *o*-NO_2-PhSeCN. Next, the solution was cooled to 0 °C and 0.5 mL of Bu_3P added. After stirring for 1 h at room temperature, 3.0 mL of a 30% aqueous solution of H_2O_2 was added and the mixture stirred for more 3 h. The suspension was then extracted with CH_2Cl_2 and the organic phase dried with Na_2SO_4, filtered, and evaporated to furnish a yellow solid, which was purified by *flash* column chromatography (50% $CHCl_3$/hexanes). After this purification, 197.8 mg of the terminal olefin was furnished (53% after three steps) as a inseparable 90:10 cis/trans isomeric mixture (a single recrystallization in benzene/hexanes raised the proportion of the cis isomer in more than 98%). ^1H NMR (300 MHz, $CDCl_3$): δ=2.45 (s, 3H), 3.10 (dddd, *J*=8.4, 8.7, 9.0, 4.2 Hz, 1H), 3.66 (dd, *J*=8.4, 4.2 Hz, 1H), 3.96 (t, *J*=8.4 Hz, 1H), 4.89 (d, *J*=16.2 Hz, 1H), 4.91 (d, *J*=11.4 Hz, 1H), 5.08 (d, *J*=8.7 Hz, 1H), 5.55 (ddd, *J*=16.2, 11.4, 9.0 Hz, 1H), 7.20–7.80 (9H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 38.5, 52.4, 68.4, 117.8, 126.8, 127.6, 128.1, 128.4, 129.7, 131.9, 135.4, 136.6, 144.0; IR (neat, cm^{-1}): 3085, 2974, 2880, 1601, 1340, 1156, 1091, 911, 751;

HRMS *m/z* calcd for $C_{18}H_{19}NO_2S$: 313.1137. Found: 313.1170; TLC: R_f=0.45, 30% EtOAc/hexanes; $[\alpha]_D^{24}$ +262.6 (*c* 1.74, CH_2Cl_2).

4.19. (2*R*,3*S*)-Azetidine-2,3-dicarboxylic acid (3a)

To a solution of 85.0 mg (0.27 mmol) of olefin **36** in 6.0 mL of a 1:1 mixture of ethyl acetate and acetonitrile was added 10.0 mL of an aqueous solution of $NaIO_4$ (1.75 g). After that, 10.0 mg of 35% $RuCl_3$ hydrate was added and the mixture was vigorously stirred for 1 h. A gray salt was precipitated after this period and a TLC analysis revealed the complete disappearance of the terminal olefin and the formation of two new compounds (mono and diacid). After this analysis, more 4.0 mL of H_2O and 5.0 mg of the ruthenium catalyst were added every 12 h of reaction, until the total conversion of the monoacid to the diacid **34** was observed (48 h by TLC). EtOAc (20 mL) was then added to the reaction vessel and the mixture filtered in Celite. The two phases were separated and the aqueous phase extracted 3× with EtOAc. All the organic phases were grouped, dried with Na_2SO_4, and evaporated to furnish the crude diacid **34**. Next, to the crude diacid in 2.0 mL of dry THF at −78 °C (suspension), a solution of Na/naphthalene radical anion in THF was added until the dark green color persisted in the reaction. The solution was then stirred at 0 °C for 1 h and, after this period, H_2O was added until the disappearance of the dark green color. Next, the aqueous phase was acidified with a 2.0 M HCl aqueous solution and washed with Et_2O for naphthalene removal. The aqueous phase was evaporated to dryness and the residue purified by ion-exchange resin (Dowex H^+ 50) and recrystallized with ethanol. The azetidine amino acid **3a** was obtained in 26% (10.0 mg) after the three transformations, as an opaque solid. ^{1}H NMR (300 MHz, D_2O): δ=3.74 (m, 1H), 4.06 (dd, *J*=10.5, 5.4 Hz, 1H), 4.25 (dd, *J*=10.5, 9.0 Hz, 1H), 5.02 (d, *J*=10.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ=41.1, 45.7, 60.7, 171.5, 175.8; IR (neat, cm^{-1}): 3037, 1575, 1402, 1311; $[\alpha]_D^{24}$ +19.3 (*c* 0.24, HCl 0.5 M in H_2O) (lit: +18 (*c* 0.40, HCl 0.5 M in H_2O)).

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Supplementary data

^{1}H NMR, ^{13}C NMR, and IR spectra for all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.001.

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