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Synthesis of 4-alkyl-pyrrolidine-3-carboxylic acid stereoisomers

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Abstract—All four possible stereoisomers of the 3-carboxyl-4-isopropyl-pyrrolidine (**4**) were prepared and their stereochemistry was assigned unambiguously.

Pregabalin (**1**) and gabapentin (**2**) are active in preclinical models of epilepsy, and neuropathic pain.[1–3] Both compounds have high affinity for the α2δ component of voltage gated ion channels.[4] Previous studies have found that a β-pyrrolidine analog of gabapentin, compound **3**, also showed appreciable binding affinity for the α2δ subunit of calcium channels.[5] In order to investigate the binding properties of a series of constrained analogs of pregabalin, stereocontrolled routes to the four possible stereoisomers of pyrrolidines **4** were needed. In this paper we describe the stereocontrolled synthesis and characterization of the four possible stereoisomers of these 3-carboxy-4-isopropylpyrrolidines (Fig. 1).

The development of stereoselective synthetic routes to pyrrolidine 3-carboxylic acids is an important problem because these compounds, also known as β-proline derivatives, play an important role in medicinal chemistry. They form the heterocyclic nucleus of a variety of biologically active compounds. Some recent examples include endothelin antagonists **5**,[6] PLG receptor agonists **6**,[7] and factor Xa inhibitors such as **7**[7] (Fig. 2).

The field of enantioselective pyrrolidine synthesis has been reviewed recently.[8] Several strategies have emerged for the stereocontrolled synthesis of 3-pyrroldine carboxylic acids.[9–15]

A radical cyclization strategy has been used to prepare such pyrrolidine rings as exemplified in Scheme 1.[9] Cyclization of the radical derived from phenyl selenide **9** gave pyrrolidines **10** with the phenyl and carboxylate groups in a *trans* orientation. *cis* Stereochemistry predominated across the 3–4 positions of the pyrrolidine ring. This reaction is noteworthy in that, it sets the relative stereochemistry of three contiguous centers with good overall selectivity.

Aspartic acid has been used recently as the source of chirality for the synthesis of 4-benzyl-3-carboxyl pyrrolidine derivatives as summarized in Scheme 2.[16] The bis benzyl

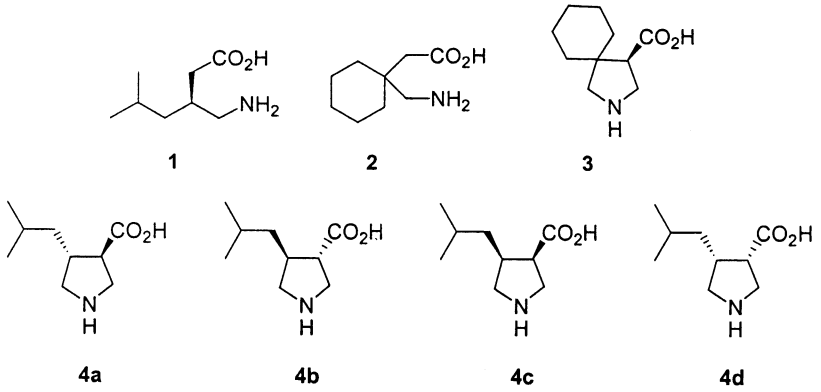

Figure 1. Pregabalin, gabapentin and pyrrolidine derivatives.

Keywords: 1-3 dipolar cycloaddition; chiral oxazolidinone; β-proline.

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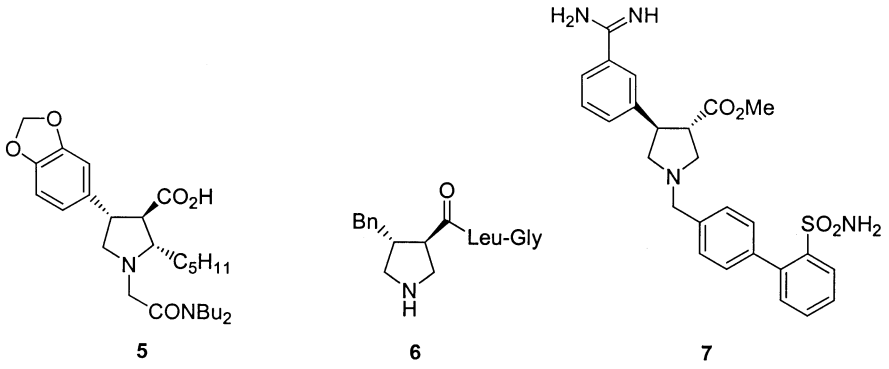
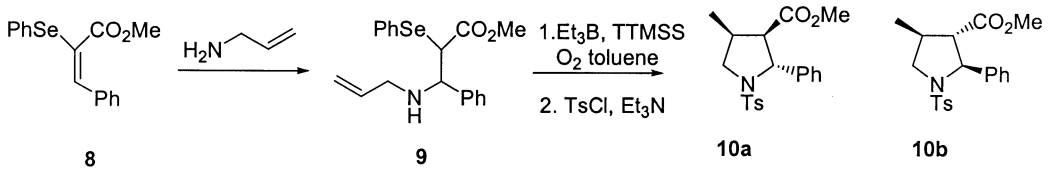


5 6 7

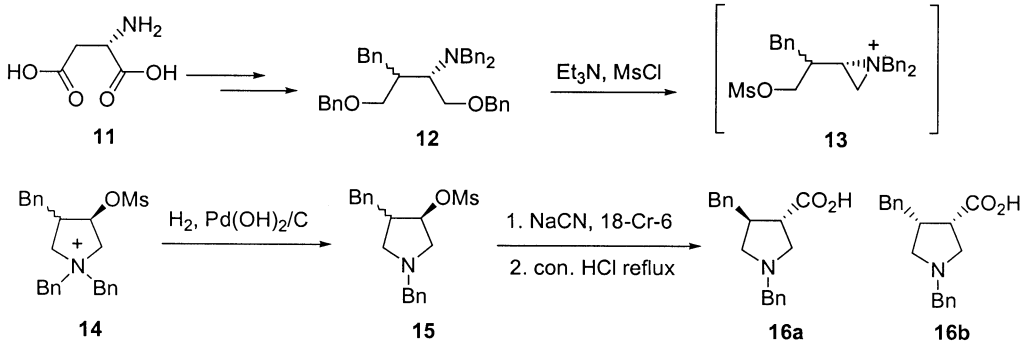
Figure 2. Examples of biologically active pyrrolidine-3-carboxylic acid derivatives.



8 9 10a 10b

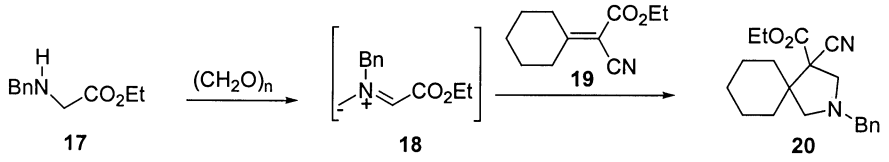
10a:10b 88:12

Scheme 1. Radical cyclization strategy.



11 12 13 14 15 16a 16b

Scheme 2. Chiral pyrrolidine carboxylates derived from aspartate.



17 18 19 20

Scheme 3. Azomethine ylide approach.

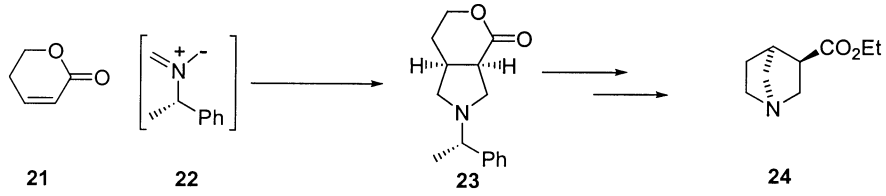
derivative **12** was caused to undergo rearrangement and cyclization to the pyrrolidinium quaternary salt **14** which was subsequently converted to the desired β-proline derivatives **16a** and **16b**.

1,3-Dipolar cycloaddition reactions between unsaturated esters and azomethine ylides have been recognized as an efficient way to construct pyrrolidines in general[17] and 3-carboxy pyrrolidine ring systems in particular.[18–20] This strategy was recently employed in the synthesis of an intermediate for pyrrolidine **3** (Scheme 3).[5] Reaction of formaldehyde with *N*-benzyl glycine derivative **17** results in the in situ formation of azomethine ylide **18** which reacts with Knoevenagle product **19** giving the pyrrolidine ester **20**.

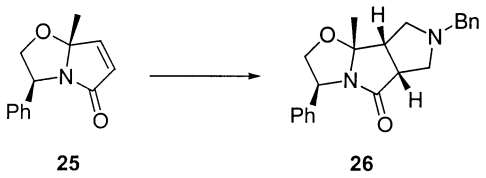
Azomethine ylide **22** having a chiral group appended to the nitrogen underwent a 1,3-dipolarcycloaddition that proceeded with synthetically useful levels of stereo control. Reaction of the unsaturated lactone **21** with azomethine ylide **22** gave the bicyclic derivative **23** with good stereoselectivity which was ultimately converted to the azabicycloheptane system **24** (Scheme 4).[21]

More often the chirality induced by this type of 3+2 cycloaddition reaction has been controlled by the stereochemistry of the dipolarophile as in the synthesis of tricyclic lactam **26** (Scheme 5).[13]

Cycloaddition of azomethine ylides (derived in situ from



Scheme 4. Dipolar cycloaddition reaction controlled by chiral azomethine ylide.



Scheme 5. Dipolarophile controlled cycloaddition reaction.

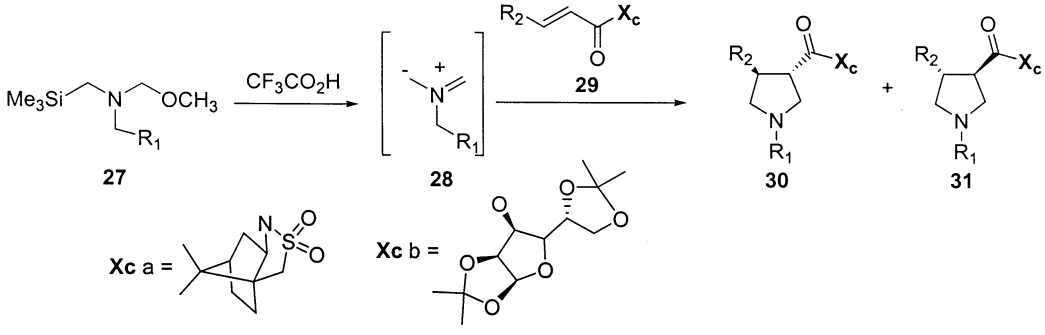
N-benzyl-*N*-methoxymethyl-*N*-trimethylsilylmethyl amine) with simple enoate ester chiral auxiliary derivatives offer an alternative strategy for the concise stereoselective construction of pyrrolidine-3-carboxylic acid derivatives. A number of chiral auxiliaries have been investigated some of which are shown below (Scheme 6).

The reaction of camphorsultam derived cinamates (Scheme 6, entries 1–3) proceeded in good yield. Good to moderate diastereoselectivity was observed depending on the phenyl group substitution.[10–12] The stereoselectivity of the reaction appeared to be affected by substitution on the cinamate phenyl group. The diastereoselectivity observed using the furanose derived chiral auxiliary was lower than that observed with the camphorsultam (Scheme 6, entry 4).[11]

Oxazolidinones have also been successfully used as chiral auxiliaries in a number of synthetic processes.[22] Recently they have been shown to influence the dipolar cycloaddtion of azomethine ylides to form 3-pyrrolidine carboxylic acid templates (Scheme 7).[10,14]

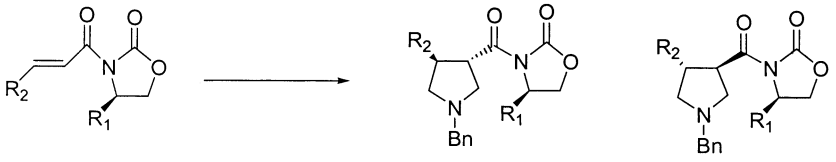
The initial screening of various four substituted oxazolidinones revealed that the 4-phenyl derivative gave the best stereoselectivity (entries 1–3). This same auxiliary has previously been shown to be most effective in directing 1,4-conjugate additions.[23] Increasing the size of the alkyl substituent in the β position of the enoate also led to a modest increase in the stereoselectivity. A slightly greater degree of stereoselectivity was observed when the 1,3-dipolar cycloaddition reaction was carried out in toluene than when dichloromethane was used as the solvent.[14] In a subsequent study it was determined that the 4-*t*-butyl oxazolidinone induced the opposite sense of relative diastereocontrol albeit with moderate selectivity (Scheme 8).[10]

This reversal in stereoselectivity has been explained by differences in the preferred reacting conformation of the dipolarophile. Reaction of the phenyl substituted oxazolidinone derivative **31f** was postulated to proceed mainly through the *U* conformer as depicted in Scheme 9. For the *t*-butyl oxazolidinone **34**, the *Z* conformation of the dipolarophile, as shown in Scheme 9, is thought to be the modestly preferred conformation for reaction.[10]



Entry	R1	R2	Xc	30 : 31
1	Phenyl	3-Trifluoromethylphenyl	a	7 : 1
2	Phenyl	Phenyl	a	3 : 1
3	4-Bromophenyl	3-Cyanophenyl	a	2.5 : 1
4	Phenyl	Phenyl	b	3 : 2

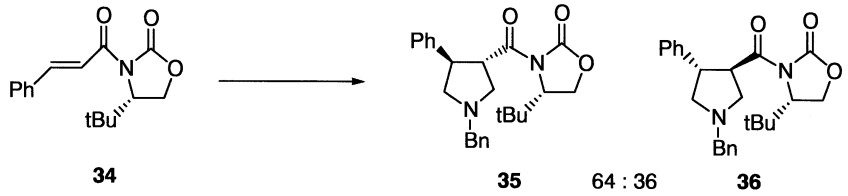
Scheme 6. Chiral auxiliary controlled 1,3 dipolar cycloaddition reactions.



31 32 33

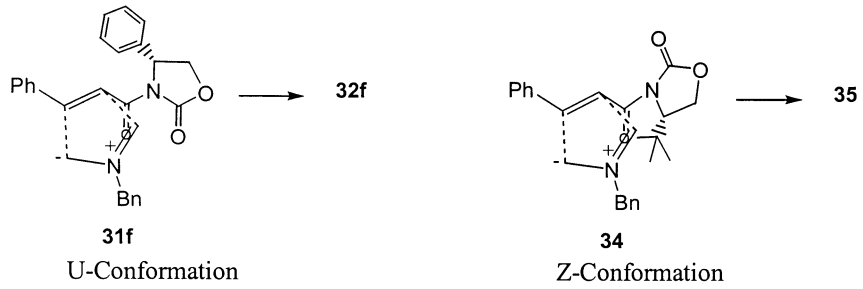
Entry	R_1	R_2	32 : 33
1	iPr	Me	60 : 40
2	Bn	Me	58 : 42
3	Ph	Me	73 : 27
4	Ph	Et	77 : 33
5	Ph	cPr	80 : 20
6	Ph	Ph	67 : 33

Scheme 7. Oxazolidinone chiral auxiliaries.



34 35 64 : 36 36

Scheme 8.



31f 32f 34 35

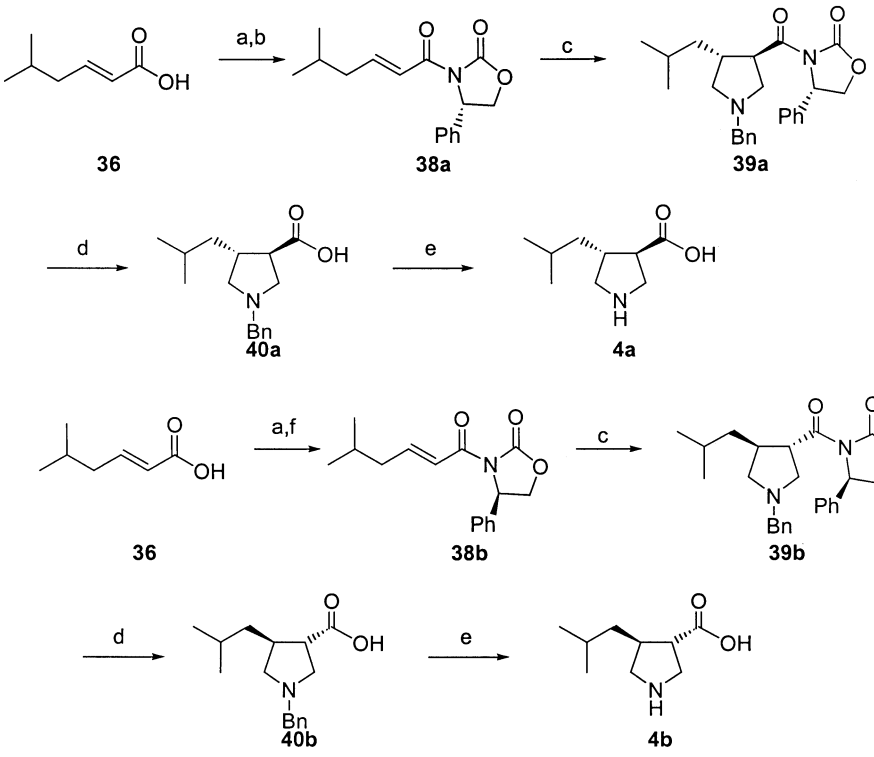
U-Conformation Z-Conformation

Scheme 9. 1,3 Cycloaddition transition states through the *U* and *Z* conformations.

This dependence on dipolarophile conformation in determining the relative (and therefore absolute) stereochemical outcome of this process explains why both the oxazolidinone and to a lesser extent the olefin substituent play a role in determining diastereoselectivity.

With these considerations in mind we undertook the synthesis of **4a** and **4b** using the 4-phenyl oxazolidinone chiral auxiliary controlled 1,3-dipolar cycloaddition as the key pyrrolidine forming reaction (Scheme 10). The dipolarophile **38a** was easily prepared by coupling (*E*)-enoic acid **36** and (*S*)-4-phenyl oxazolidinone (**37a**). Dipolar cycloaddition of **38a** with the azomethine ylide derived from *N*-benzyl-*N*-(methoxymethyl)-trimethylsilylmethylamine in the presence of trifluoroacetic acid, provided pyrrolidine **39a** as a single diastereomer. In contrast to previous cases, no minor stereoisomer was observed by proton and ^{13}C NMR of the crude reaction mixture. The relative and therefore absolute stereochemistry of **39a** was unambiguously determined to be 3*R*4*R* by single crystal X-ray diffraction (Fig. 3). In this case the reaction proceeds exclusively through the extended U-conformer of oxazolidinone **38a** as shown in Scheme 11. It is possible that the greater selectivity seen in this reaction results from a greater energetic preference for this conformer due to the more bulky isopropyl group.

Hydrolysis of **39a** with lithium hydroperoxide[24] resulted in



Scheme 10. Synthesis of enantiomers **4a** and **4b**. (a) Oxalyl chloride, DMF, Toluene, rt; (b) NaH, (*S*)-4-phenyl-2-oxazolidinone (**37a**), THF, 0°C, 98% (two steps); (c) $Me_3SiCH_2N(Bn)CH_2OMe$, TFA, Toluene, 0°C, 62%; (d) LiOH, H_2O_2, THF–H_2O, rt, 78%; (e) H_2, 20%Pd/C, EtOH, 70%. (f) NaH, (*S*)-4-phenyl-2-oxazolidinone (**37b**), THF, 0°C, 98% (two steps).

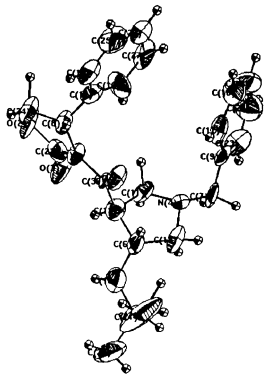
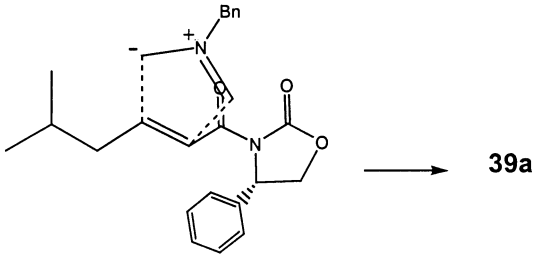


Figure 3. ORTEP plot of **39a**.

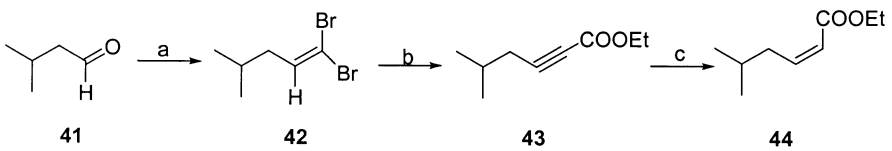


Scheme 11. Transition state of the reaction of **38a** with an azomethine ylide.

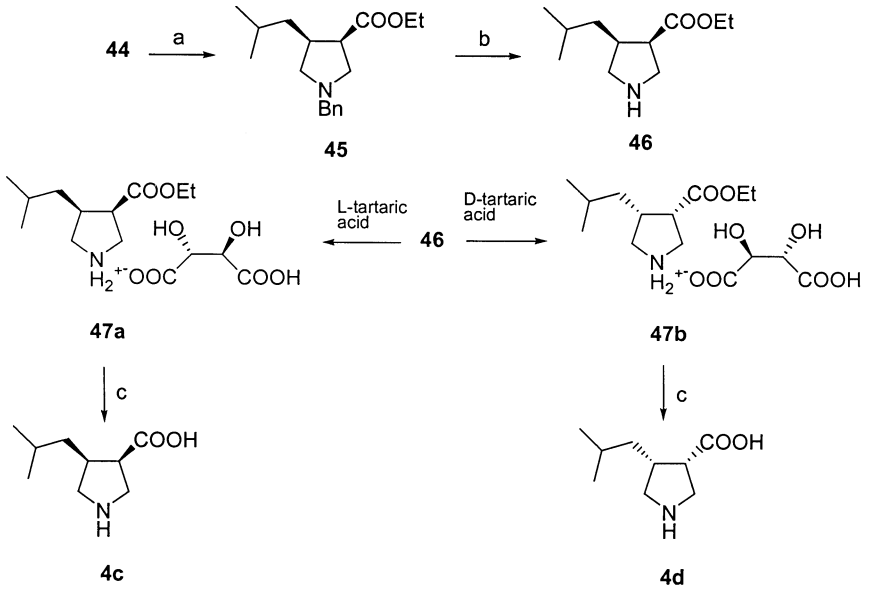
formation of β-aminoacid **40a** and the recovery of the chiral auxiliary in nearly quantitative yields. Finally the benzyl group was removed under reductive conditions providing the *R*,*R* pyrrolidine **4a** in 70% yield. Similarly, the *S*,*S* enantiomer **4b** was obtained by use of (*R*)-4-phenyl oxazolidinone (**37b**) as the chiral auxiliary.

In order to prepare the stereoisomers **4c** and **4d** via the cycloaddition strategy, the *Z*-enoate **44** was required. Synthesis of **44** has been reported previously in the literature,[25,26] however, we adopted a convenient three-step procedure shown in Scheme 12. Subjecting 3-methyl butyraldehyde (**41**) to Corey–Fuchs conditions[27] gave the dibromoolefin **42** which was converted to the acetylene carboxylate **43**. Lindlar hydrogenation of this substrate gave the desired *Z*-enoate **44** in good overall yield. All attempts to append the phenyloxazolidinone chiral auxiliary to **44** or the corresponding acid resulted in significant double bond isomerization.

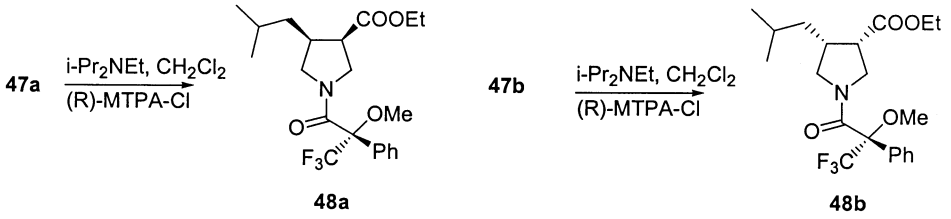
Instead, the eneoate **44** was reacted directly with *N*-benzyl-*N*-(methoxymethyl)-trimethylsilylmethylamine in the presence of trifluoroacetic acid to give the *cis* di-substituted pyrrolidine **45** in racemic form (Scheme 13). The benzylic group was removed by hydrogenation. Resolution of the



Scheme 12. Synthesis of *cis* eneoate. (a) Ph_3P,CBr_4, CH_2Cl_2, −10°C, 78%; (b) *n*-BuLi, EtOCOCl, THF, 92%; (c) H_2, Lindlar cat., THF, 86%.



Scheme 13. Synthesis of *cis* pyrroldine enantiomers **4c** and **4d**. (a) $Me_3SiCH_2N(Bn)CH_2OMe$, TFA, Toluene, 0°C, 62%; (b) H_2, 20%Pd/C, EtOH, 70%; (c) 2N NaOH then 6N HCl.



Scheme 14. Synthesis of MPTA derivatives.

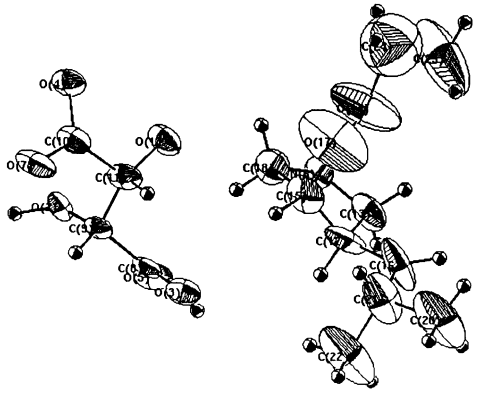


Figure 4. ORTEP plot of **47a**.

pyrrolidines **46** was accomplished by fractional crystallization of its tartaric acid salts **47a** (L-tartaric acid) and **47b** (D-tartaric acid) from methanol. The enantiomeric excesses of amines **47a** and **47b** were determined by GC analysis of the MTPA derivatives **48a** and **48b** (Scheme 14). Both **47a** and **47b** were recrystallized to greater than 98% stereochemcial purity. The absolute configuration of the of the pyrrolidine portion of **47a** was determined to be 3*R*4*S* by single crystal X-ray crystallography (Fig. 4). The tartaric acid salt **47a** and **47b** were converted to the corresponding free amino esters, which were subjected to hydrolysis and ion exchange column chromatography to provide **4c** and **4d**, respectively.

Using complementary methodology all four stereoisomers of constrained pregabalin analogs were prepared with known relative and absolute stereochemistry. The *trans* isomers **4a** and **4b** were obtained via a highly stereoselective 1,3-dipolar cycloaddition azomethine ylide reaction. However, this methodology was not readily applicable to the preparation of *cis* isomers **4c** and **4d**. These compounds were obtained through resolution with diastereomeric salts of cycloaddition intermediates. These compounds represent possible conformations of pregabalin and their enantiomers which can be used in better understanding the molecular interaction of pregabalin with its site of action.

1. Experimental

1.1. General

The structure of all the compounds were confirmed by ^1H NMR and in most cases ^{13}C NMR on a Varian Unity 400 MHz spectrometer. Chemical ionization mass spectra were obtained on a Micromass Trio 2A spectrometer. Elemental analysis was performed in the Robertson labs. Where analyses are indicated by the symbols of elements,

the results are within ±0.4% of the theoretical values. Analytical thin layer chromatography (TLC) was performed on 0.25 mm Merck silica gel F254 glass plates. Flash column chromatography was performed on silica gel (E, Merck, grade 60, 230–300 mesh). Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20°C. $[\alpha]_D$ values were given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected.

1.1.1. 3-[(*E*)-3-Isobutylpropenoyl]-4-(*S*)-phenyl-2-oxazolidinone (38a). To a solution of (*E*)-5-methyl-hex-2-enoic acid (**36**) (3.2 g, 25 mmol) in toluene (20 mL) was added oxalyl chloride (4.4 mL, 50 mmol) slowly at 0°C under N_2 followed by one drop of DMF. The mixture was stirred at 22°C for 1 h. The volatiles were removed under reduced pressure to give the desired acid chloride which was used without further purification. To a solution of NaH (0.84 g, 21 mmol) in THF (30 mL) was added a solution of (*S*)-(−)-4-phenyl-2-oxazolidinone (**37a**) (3.4 g, 21 mmol) in THF (10 mL) at 0°C. The mixture was stirred at 22°C for 1 h. The crude acid chloride was then introduced while maintaining the temperature at 0°C. The mixture was stirred at 0°C for 1 h and then at 22°C for an additional 12 h. The reaction was quenched with 1N HCl aqueous solution, extracted with $CHCl_3$, then dried over Na_2SO_4. After the solvent was evaporated at reduced pressure the crude product was subjected to column chromatography (silica gel, hexanes–ether=2:1) to give 6.25 g (100% yield) of **38a** as a white solid. mp 84–85°C; ^{1}H NMR ($CDCl_3$): δ 0.81 (d, J=6.8 Hz, 6H, CH(CH_3)$_2$), 1.68–1.78 (m, 1H, CH$_2$CH(CH$_3$)$_2$), 2.11–2.14 (m, 2H, CH_2CH(CH$_3$)$_2$), 4.24–4.27 (m, 1H, oxazolidinone ring), 4.65–4.72 (t, J=8.8 Hz, 1H, oxazolidinone ring), 5.44–5.48 (m, 1H, oxazolidinone ring), 7.02–7.09 (m, 1H, vinyl), 7.23–7.28 (m, 1H, vinyl), 7.31–7.38 (m, 5H, aromatic); ^{13}C NMR ($CDCl_3$): δ 22.35, 22.39, 27.88, 41.82, 57.77, 69.92, 121.11, 125.95, 128.63, 129.16, 139.14, 151.10, 153.70, 164.56; MS (CI) m/z 274 (M+1)$^+$. Anal. ($C_{16}H_{19}NO_3$) C, H, N. Exp. 70.02, 7.00, 5.26; Theor. 70.31, 7.01, 5.12.

1.1.2. 1-Benzyl-4-(*R*)-isobutyl-3-(*R*)-[4′-(*S*)-phenyl-2′-oxazolidinon-3′-yl]carbonyl pyrrolidine (39a). To a stirred solution of 3-[(*E*)-3-isobutylpropenoyl]-4-(*S*)-phenyl-2-oxazolidinone (**38a**) (1.50 g, 5.50 mmol) in toluene (20 mL) was added *N*-benzyl-*N*-(methoxymethyl) trimethylsilylmethylamine (1.56 g, 6.60 mmol) at 0°C under N_2. After 20 min, a solution of TFA (1 M in CH_2Cl_2, 0.55 mmol) was added slowly at 0°C. The mixture was stirred at 0°C for 30 min and then at 22°C for an additional 12 h. The reaction was quenched with H_2O, extracted with $CHCl_3$, then dried over $MgSO_4$. The solvent was evaporated to dryness, and the oily residue was subjected to column chromatography (silica gel, hexanes–ether=2:1) to give 1.37 g (62% yield) of **39a** as a white solid which was subjected to recrystallization in ether–hexanes to provided crystalline needled. Mp 34–35°C; ^{1}H NMR ($CDCl_3$): δ 0.84–0.86 (m, 6H, CH(CH_3)$_2$), 1.26–1.29 (m, 2H, CH_2CH(CH$_3$)$_2$), 1.42–1.47 (m, 1H, CH$_2$CH(CH$_3$)$_2$), 2.08 (t, J=7.3 Hz, 1H, pyrrolidine ring), 2.62 (dd, J=9.8 Hz, 4.6 Hz, 1H, pyrrolidine ring), 2.83–2.94 (m, 3H, pyrrolidine ring), 3.37–3.67 (ABq, J=13.0 Hz, 2H, CH_2Ph), 3.68–3.72 (m, 1H, pyrrolidine ring), 4.16–4.19 (m, 1H, oxazolidinone ring), 4.63 (t, J=9.0 Hz, 1H, oxazolidinone ring), 5.40 (m, 1H, oxazolidinone ring), 7.18–7.36 (m, 5H, aromatic); ^{13}C NMR ($CDCl_3$): δ 22.46, 23.05, 26.72, 37.00, 44.07, 49.41, 57.48, 57.85, 59.84, 60.54, 69.87, 125.67, 126.80, 128.21, 128.48, 128.65, 129.25, 139.01, 139.05, 153.55, 173.71; MS (CI) m/z 407 (M+1)$^+$. Anal. ($C_{25}H_{30}N_2O_3$) C, H, N. Exp. 73.75, 7.44, 6.74; Theor. 73.86, 7.44, 6.86.

1.1.3. *trans*-4-(*R*)-Isobutylpyrrolidine-3-(*R*)-carboxylic acid (4a). To a solution of 1-benzyl-4-(*R*)-isobutyl-3-(*R*)-[4′-(*S*)-phenyl-2′-oxazolidinon-3′-yl)carbonyl]pyrrolidine **39a** (1.37 g, 3.37 mmol) in THF (30 mL) was added a solution of LiOH (1 M in H_2O, 8.44 mmol) and H_2O_2 (30%, 6.75 mmol) in H_2O (10 mL) at 0°C slowly. The reaction mixture was stirred at 0°C for 1 h, then diluted with water (40 mL). Sodium sulfite (0.85 g, 6.75 mmol) was added and the mixture was extracted with ethyl acetate. The aqueous phase was adjusted to pH 5.0 with KH_2PO_4 (1.51 g, 11.1 mmol) and 10% HCl. This solution was extracted with isopropyl alcohol–methylene chloride (1:3), which was dried over Na_2SO_4 and concentrated to afford 0.88 g of 1-benzyl-4-(*R*)-isobutylpyrrolidine-3-(*R*)-carboxylic acid (**40a**) which was used without further purification. To a solution of this carboxylic acid (0.72 g) in ethanol (55 mL) was added 20% Pd/C (0.11 g) and hydrogenated at 50 psi for 11 h. The reaction mixture was filtered through a pad of Celite. After the solvent was evaporated at reduced pressure the crude product was subjected to ion exchange column (Dowex 50) and recrystallized from methanol–ether to give 0.33 g (71% yield) of **4a** as a white solid. $[\alpha]_D$=+44.8°; mp 236–239°C; ^{1}H NMR (CD_3OD): δ 0.89 (m, 6H, CH_3), 1.26 (m, 1H, CH$_2$CH(CH$_3$)$_2$), 1.51 (m, 1H, CH_2CH(CH$_3$)$_2$), 1.60 (m, 1H, CH_2CH(CH$_3$)$_2$), 2.52 (m, 2H, pyrrolidine ring), 2.78 (m, 1H, pyrrolidine ring), 3.37 (m, 2H, pyrrolidine ring), 3.44 (m, 1H, pyrrolidine ring); ^{13}C NMR (CD_3OD): δ 21.07, 22.07, 26.29, 40.81, 41.83, 48.39, 50.11, 51.78, 177.47; MS (CI) m/z 172 (M+1)$^+$. Anal. ($C_9H_{17}NO_2$) C, H, N. Exp. 62.85, 10.20, 8.09; Theor. 63.13, 10.01, 8.18.

1.1.4. 3-[(*E*)-3-Isobutylpropenoyl]-4-(*R*)-phenyl-2-oxazolidinone (38b). To a solution of (*E*)-5-methyl-hex-2-enoic acid (**36**) (1.77 g, 13.8 mmol) in toluene (20 mL) was added oxalyl chloride (2.4 mL, 27.6 mmol) slowly at 0°C under N_2 followed by one drop of DMF. The mixture was stirred at 22°C for 1 h. The volatiles were removed under reduced pressure to give the desired acid chloride which was used without further purification. To a solution of NaH (0.37 g, 9.2 mmol) in THF (30 mL) was added a solution of (*R*)-(−)-4-phenyl-2-oxazolidinone (**37b**) (1.5 g, 9.2 mmol) in THF (10 mL) at 0°C. The mixture was stirred at 22°C for 1 h. The crude acid chloride was then introduced while maintaining the temperature at 0°C. The mixture was stirred at 0°C for 1 h and then at 22°C for an additional 12 h. The reaction was quenched with 1N HCl aqueous solution, extracted with $CHCl_3$, then dried over Na_2SO_4. After the solvent was evaporated at reduced pressure the crude product was subjected to column chromatography (silica gel, hexanes–acetone=3:1) to give 2.5 g (100% yield) of **38b** as a white solid. mp 84–85°C; ^{1}H NMR ($CDCl_3$): δ 0.81 (d, J=6.8 Hz, 6H, CH(CH_3)$_2$), 1.68–1.78 (m, 1H, CH$_2$CH(CH$_3$)$_2$), 2.11–2.14 (m, 2H,CH_2CH(CH$_3$)$_2$), 4.24–4.27 (m, 1H, oxazolidinone ring), 4.65–4.72 (t, J=8.8 Hz, 1H, oxazolidinone

ring), 5.44–5.48 (m, 1H, oxazolidinone ring), 7.02–7.09 (m, 1H, vinyl), 7.23–7.28 (m, 1H, vinyl), 7.31–7.38 (m, 5H, aromatic); ^{13}C NMR ($CDCl_3$): δ 22.35, 22.39, 27.88, 41.82, 57.77, 69.92, 121.11, 125.95, 128.63, 129.16, 139.14, 151.10, 153.70, 164.56; MS (CI) *m/z* 274 $(M+1)^+$. Anal. ($C_{16}H_{19}NO_3$) C, H, N. Exp. 70.20, 7.05, 5.15; Theor. 70.31, 7.01, 5.12.

1.1.5. 1-Benzyl-4-(*S*)-isobutyl-3-(*S*)-[4′-(*R*)-phenyl-2′-oxazolidinon-3′-yl]carbonyl pyrrolidine (39b). To a stirred solution of 3-[(*E*)-3-isobutylpropenoyl]-4-(*R*)-phenyl-2-oxazolidinone (**38b**) (1.50 g, 5.50 mmol) in toluene (20 mL) was added *N*-benzyl-*N*-(methoxymethyl) trimethylsilylmethylamine (1.56 g, 6.60 mmol) at 0°C under N_2. After 20 min, a solution of TFA (1 M in CH_2Cl_2, 0.55 mmol) was added slowly at 0°C. The mixture was stirred at 0°C for 30 min and then at 22°C for an additional 12 h. The reaction was quenched with H_2O, extracted with $CHCl_3$, then dried over $MgSO_4$. The solvent was evaporated to dryness, and the oily residue was subjected to column chromatography (silica gel, hexanes–ether=2:1) to give 1.45 g (65% yield) of **39b** as a white solid. mp 33–35°C; ^{1}H NMR ($CDCl_3$): δ 0.84–0.86 (m, 6H, $CH(CH_3)_2$), 1.26–1.29 (m, 2H, $CH_2CH(CH_3)_2$), 1.42–1.47 (m, 1H, $CH_2CH(CH_3)_2$), 2.08 (t, *J*=7.3 Hz, 1H, pyrrolidine ring), 2.62 (dd, *J*=9.8 Hz, 4.6 Hz, 1H, pyrrolidine ring), 2.83–2.94 (m, 3H, pyrrolidine ring), 3.37–3.67 (ABq, *J*=13.0 Hz, 2H, CH_2Ph), 3.68–3.72 (m, 1H, pyrrolidine ring), 4.16–4.19 (m, 1H, oxazolidinone ring), 4.63 (t, *J*=9.0 Hz, 1H, oxazolidinone ring), 5.40 (m, 1H, oxazolidinone ring), 7.18–7.36 (m, 5H, aromatic); ^{13}C NMR ($CDCl_3$): δ 22.46, 23.05, 26.72, 37.00, 44.07, 49.41, 57.48, 57.85, 59.84, 60.54, 69.87, 125.67, 126.80, 128.21, 128.48, 128.65, 129.25, 139.01, 139.05, 153.55, 173.71; MS (CI) *m/z* 407 $(M+1)^+$. Anal. ($C_{25}H_{30}N_2O_3$) C, H, N. Exp. 73.60, 7.41, 6.69; Theor. 73.86, 7.44, 6.86.

1.1.6. *trans*-4-(*S*)-Isobutylpyrrolidine-3-(*S*)-carboxylic acid (4b). To a solution of 1-benzyl-4-(*S*)-isobutyl-3-(*S*)-[4′-(*R*)-phenyl-2′-oxazolidinon-3′-yl)carbonyl]pyrrolidine (**39b**) (1.44 g, 3.56 mmol) in THF (30 mL) was added a solution of LiOH (1 M in H_2O, 8.89 mmol) and H_2O_2 (30%, 7.11 mmol) in H_2O (10 mL) at 0°C slowly. The reaction mixture was stirred at 0°C for 1 h, then diluted with water (40 mL). Sodium sulfite (0.89 g, 7.11 mmol) was added and the mixture was extracted with ethyl acetate. The aqueous phase was adjusted to pH 5.0 with KH_2PO_4 (1.59 g, 11.7 mmol) and 10% HCl. This solution was extracted with isopropyl alcohol–methylene chloride (1:3), which was dried over Na_2SO_4 and concentrated to afford 0.93 g of 1-benzyl-4-(*S*)-isobutylpyrrolidine-3-(*S*)-carboxylic acid (**40b**) which was used without further purification. To a solution of this carboxylic acid (0.94 g) in ethanol (55 mL) was added 20% Pd/C (0.21 g) and hydrogenated at 50 psi for 11 h. The reaction mixture was filtered through a pad of Celite. After the solvent was evaporated at reduced pressure the crude product was subjected to ion exchange column (Dowex 50) and recrystallized from methanol–ether to give 0.43 g (70% yield) of **4b** as a white solid. $[\alpha]_D=-45.8°$; mp 251–254°C; ^{1}H NMR (CD_3OD): δ 0.89 (m, 6H, CH_3), 1.26 (m, 1H, $CH_2CH(CH_3)_2$), 1.51 (m, 1H, $CH_2CH(CH_3)_2$), 1.60 (m, 1H, $CH_2CH(CH_3)_2$), 2.52 (m, 2H, pyrrolidine ring), 2.78 (m, 1H, pyrrolidine ring), 3.37 (m, 2H, pyrrolidine ring), 3.44 (m, 1H, pyrrolidine ring); ^{13}C NMR (CD_3OD): δ 21.07, 22.07, 26.29, 40.81, 41.83, 48.39, 50.11, 51.78, 177.47; MS (CI) *m/z* 172 $(M+1)^+$. Anal. ($C_9H_{17}NO_2$) C, H, N. Exp. 62.96, 9.89, 7.98; Theor. 63.13, 10.01, 8.18.

1.1.7. 1,1-Dibromo-4-methyl-1-pentene (42). To a stirred solution of carbon tetrabromide (30 g, 90.93 mmol) in dichloromethane (400 mL) at −10°C was added triphenylphosphine (60 g, 229 mmol) in portions. The internal temperature of the reaction vessel was kept below 5°C during the addition, and it was stirred for an additional 30 min at this temperature after the addition was completed. To this mixture was slowly added a solution of isovaleraldehyde (**41**) (9.4 mL, 87.6 mmol) in methylene chloride (40 mL). The reaction was stirred for 3 h during which time the temperature did not rise above 5°C. After the solvent was removed on a rotary evaporator, pentane (600 mL) was added to the residue. The solid which separated was removed by filtration. Evaporation of the solvent from the filtrate gave a light oil which was chromatographed on a silica gel column. The pure compound was eluted with pet ether to afford 1,1-dibromo-4methyl-pent-1-ene (**42**) as an oil (16.5 g, 78%). ^{1}H NMR ($CDCl_3$): δ 0.89 (d, 6H), 1.70 (m, 1H), 1.95 (triplet, 2H), 6.38 (triplet, 1H).

1.1.8. 5-Methyl-hex-2-ynoic acid ethyl ester (43). 1,1-Dibromo-4-methyl-pent-1-ene (**42**) (40 g 165.9 mmol) was dissolved in dry THF (120 mL) and the solution was cooled to −78°C. To the stirred solution was added *n*-butyllithium (1.6 M sol., in hexanes, 190 mL, 305 mmol) in a dropwise manner. After 1 h, ethyl chloroformate (15 mL, 154.5 mmol) was added and the reaction was stirred at ambient temperature overnight. The reaction was carefully poured into water and extracted with ether (3×250 mL), dried over magnesium sulfate and the solvents were evaporated under reduced pressure. The resulting light oil was flash chromatographed on silica gel using 10% ether in pet ether as the eluant to afford 5-methyl-hex-2-ynoic acid ethyl ester (**43**) (23.6 g, 92%). ^{1}H NMR ($CDCl_3$): δ 0.94 (d, 6H), 1.24 (t, 3H), 1.85 (m, 1H), 2.16 (d, 2H), 4.14 (m, 2H).

1.1.9. (*Z*)-5-Methyl-hex-2-enoic acid ethyl ester (44). 5-Methyl-hex-2-ynoic acid ethyl ester (**43**) (20.97 g, 136.08 mmol), in a solution of THF (540 mL) and pyridine (60 mL) was hydrogenated in the presence of 5% PD/$BaSO_4$ (1.10 g) for 3.25 h. The solvent was evaporated and the light oil was chromatographed over silica gel using 5% ether in pet. ether as the eluant. An initial fraction of unreacted acetylene was collected prior to isolation of the pure (*Z*)-5-methyl-hex-2-enoic acid ethyl ester (**44**) (12.0 g, 56%)

1.1.10. *cis*-1-Benzyl-4-isobutylpyrrolidine-3-carboxylic acid ethyl ester (45). To a stirred solution of α,β-unsaturated carboxylic acid ethyl ester **44** (1.82 g 11.70 mmol) in toluene (20 mL) was added *N*-benzyl-*N*-(methoxymethyl) trimethylsilylmethylamine (3.33 g, 14.10 mmol) at 0°C under N_2. After 20 min, a solution of TFA (1 M in CH_2Cl_2, 1.17 mmol) was added slowly at 0°C. The mixture was stirred at 0°C for 30 min and then at 22°C for an additional 12 h. The reaction was quenched with H_2O, extracted with $CHCl_3$, then dried over $MgSO_4$. The solvent was evaporated to dryness, and the oily residue was subjected to column chromatography (silica gel, hexanes–ether=6:1)

to give *cis*-1-benzyl-4-isobutylpyrrolidine-3-carboxylic acid ethyl ester (**45**) (1.38 g, 41% yield;) ^{1}H NMR ($CDCl_3$): δ 0.83–0.87 (m, 6H, $CH(CH_3)_2$), 1.18–1.29 (m, 5H, CH_2CH_3 and $CH_2CH(CH_3)_2$), 1.46–1.49 (m, 1H, $CH_2CH(CH_3)_2$), 2.07 (t, J=9.5 Hz, 1H, pyrrolidine ring), 2.56–2.66 (m, 2H, pyrrolidine ring), 3.00–3.13 (m, 2H, pyrrolidine ring), 3.65 (s, 2H, CH_2Ph), 4.10–4.18 (m, 2H, CH_2CH_3), 7.25–7.32 (m, 5H, aromatic ring); ^{13}C NMR ($CDCl_3$): δ 15.59, 23.07, 24.83, 27.64, 40.14, 40.23, 47.41, 57.73, 60.69, 61.47, 61.80, 128.19, 129.51, 130.05, 140.44, 175.41; MS (CI) *m/z* 290 $(M+1)^+$. Anal. ($C_{18}H_{27}NO_2$) C, H, N. Exp. 74.82, 9.48, 4.90; Theor. 74.70, 9.40, 4.84.

1.1.11. *cis*-4-(*S*)-Isobutylprrolidine-3-(*R*)-carboxylic acid, ethyl ester (46). *cis*-1-Benzyl-4-isobutylpyrrolidine-3-carboxylic acid ethyl ester (**45**) (2.25 g, 7.78 mmol) in ethanol (75 mL) and 20% Pd/C (210 mg) was placed under 50 psi of hydrogen and the reaction proceeded for 5.5 h. The reaction was filtered through a pad of celite and the filtrate evaporated to give *cis*-4-(*S*)-isobutylprrolidine-3-(*R*)-carboxylic acid, ethyl ester (**19**) as an oil which was used without further purification.

1.1.12. *cis*-4-(*S*)-Isobutylprrolidine-3-(*R*)-carboxylic acid,-ethyl ester (*R*,*R*)-tartaric acid salt (47a). A 250 mL flask was charged with (±)**46** (5.70 g, 28.64 mmol), L-tartaric acid(3.87 g, 25.77 mmol) and 15 mL of MeOH. The mixture was heated to 60°C for 10 min and cooled to 25°C for crystallization. The crystals was collected and rinsed with MeOH. Recrystallization was done in MeOH. 1.6 g of **47a** was obtained as colorless needles. $[\alpha]^{25}=-35°$ (c=0.25, MeOH); mp 173–174°C; ^{1}H NMR (CD_3OD): δ 0.91 (m, 6H, $CH(CH_3)_2$), 1.26 (m, 5H, $CH_2CH(CH_3)_2$, OCH_2CH_3), 1.65 (m, 1H, $CH_2CH(CH_3)_2$), 2.67 (m, 1H, pyrrolidine ring), 2.97 (t, J=11.0 Hz, 1H, pyrrolidine ring), 3.23 (m, 2H, pyrrolidine ring), 3.42–3.55 (m, 3H, pyrrolidine ring), 4.11–4.25 (m, 2H, OCH_2CH_3), 4.39 (s, 2H, tartaric acid); ^{13}C NMR (CD_3OD): δ 11.81, 19.99, 20.21, 20.23, 24.77, 35.81, 38.07, 44.27, 47.15, 59.53, 71.48, 171.09, 174.39; Anal. ($C_{15}H_{27}NO_8$) C, H, N. Exp. 51.71, 7.58, 3.97; Theor. 51.57, 7.79, 4.01.

1.1.13. *cis*-4-(*S*)-Isobutylpyrrolidine-3-(*R*)-carboxylic acid (4c). To a solution of **47a** (1.25 g, 3.57 mmol) in $CHCl_3$ (30 mL) was added 20 mL of NaOH (2N) aqueous solution and stirred for 10 min. The organic layer was separated and concentrated. The crude oil was added 6N HCl (20 mL). The reaction mixture was refluxed for 12 h. After the solvent was evaporated at reduced pressure the crude product was subjected to ion exchange column (Dowex 50) and recrystallized from methanol–ether to give 4-alkyl-pyrrolidine-3-carboxylic acid 0.54 g (88% yield) of **4c** as a white solid. $[\alpha]_D=-9°$ (c=0.11, MeOH); mp 224°C (dec); ^{1}H NMR (CD_3OD): δ 0.89 (m, 6H, CH_3), 1.26 (m, 1H, $CH_2CH(CH_3)_2$), 1.49 (m, 1H, $CH_2CH(CH_3)_2$), 1.64 (m, 1H, $CH_2CH(CH_3)_2$), 2.52 (m, 2H, pyrrolidine ring), 2.78 (m, 1H, pyrrolidine ring), 3.37 (m, 2H, pyrrolidine ring), 3.44 (m, 1H, pyrrolidine ring); ^{13}C NMR (D_2O): δ 21.47, 22.43, 26.01, 37.66, 38.54, 48.40, 48.98, 49.18, 179.32; MS (CI) *m/z* 172 $(M+1)^+$. Anal. ($C_9H_{17}NO_2$) C, H, N. Exp. 62.99, 10.02, 8.08; Theor. 63.13, 10.01, 8.18.

1.1.14. *cis*-4-(*R*)-Isobutylprrolidine-3-(*S*)-carboxylic acid, ethyl ester (*S*,*S*)-tartaric acid salt (47b). A 100 mL flask was charged with enantiomerically enriched **46** (2.54 g, 12.76 mmol), D-tartaric acid(1.72 g, 11.48 mmol) and 8 mL of MeOH. The mixture was heated to 60°C for 10 min and cooled to 25°C for crystallization. The crystals was collected and rinsed with MeOH. Recrystallization in MeOH afforded 0.8 g of **47b** as white needles. $[\alpha]^{25}=+37°$ (c=0.15, MeOH); mp 172–173°C; ^{1}H NMR (CD_3OD): δ 0.91 (m, 6H, $CH(CH_3)_2$), 1.27 (m, 5H, $CH_2CH(CH_3)_2$ and OCH_2CH_3), 1.65 (m, 1H, $CH_2CH(CH_3)_2$), 2.67 (m, 1H, pyrrolidine ring), 2.97 (t, J=11.2 Hz, 1H, pyrrolidine ring), 3.23 (m, 2H, pyrrolidine ring), 3.42–3.55 (m, 3H, pyrrolidine ring), 4.11–4.25 (m, 2H, OCH_2CH_3), 4.39 (s, 2H, tartaric acid); ^{13}C NMR (CD_3OD): δ 13.41, 21.58, 21.80, 21.83, 26.35, 37.39, 39.66, 45.85, 48.73, 61.12, 73.07, 172.68, 175.99; Anal. ($C_{15}H_{27}NO_8$) C, H, N. Exp. 51.47, 7.59, 3.83; Theor. 51.57, 7.79, 4.01.

1.1.15. *cis*-4-(*R*)-Isobutylpyrrolidine-3-(*S*)-carboxylic acid (4d). To a solution of **47b** (0.8 g, 2.29 mmol) in $CHCl_3$ (30 mL) was added 20 mL of NaOH (2N) aqueous solution and stirred for 10 min. The organic layer was separated and concentrated. The crude oil was added 6N HCl (20 mL). The reaction mixture was refluxed for 12 h. After the solvent was evaporated at reduced pressure the crude product was subjected to ion exchange column (Dowex 50) and recrystallized from methanol–ether to 0.32 g (81% yield) of **4d** as a white solid. $[\alpha]_D=+8°$ (c=0.10, MeOH); mp 234°C (dec); ^{1}H NMR (CD_3OD): δ 0.89 (m, 6H, CH_3), 1.26 (m, 1H, $CH_2CH(CH_3)_2$), 1.49 (m, 1H, $CH_2CH(CH_3)_2$), 1.64 (m, 1H, $CH_2CH(CH_3)_2$), 2.52 (m, 2H, pyrrolidine ring), 2.78 (m, 1H, pyrrolidine ring), 3.37 (m, 2H, pyrrolidine ring), 3.44 (m, 1H, pyrrolidine ring); ^{13}C NMR (D_2O): δ 21.47, 22.44, 26.02, 37.66, 38.53, 48.39, 48.98, 49.17, 179.29; MS (CI) *m/z* 172 $(M+1)^+$. Anal. ($C_9H_{17}NO_2$) C, H, N. Exp. 63.05, 9.93, 8.10; Theor. 63.13, 10.01, 8.18.

1.2. X-Ray structure of 40a

The compound **40a** was crystallized from ethanol solutions. The crystals are rhombohedral, space group *P*61, with unit cell dimensions $a=b=c$=18.43 Å. X-Ray diffraction data were collected at room temperature on a CAD-4 diffractometer. The structure was solved by direct methods using the MAXUS program set and refined to R=0.116. An ORTEP plot of the refined structure is shown in Fig. 3.

1.3. X-Ray structure of 47a

The compound **47a** was crystallized from ethanol solutions. The crystals are monoclinic, space group *P*21, a=7.68 (5) Å, b=7.67 Å, c=16.02 Å. X-Ray diffraction data were collected at room temperature on a CAD-4 diffractometer. The structure was solved by direct methods using the MAXUS program set and refined to R=0.118. An ORTEP plot of the refined structure is shown in Fig. 4.

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References

1. Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149–177.
2. Martin, L.; Rabasseda, X.; Leeson, P.; Castaner, J. *Drugs Future* **1999**, *24*, 862–870.
3. Field, M.; McCleary, S.; Hughes, J.; Singh, L. *Pain* **1999**, *80*, 391–398.
4. Gee, N. S.; Brown, J.; Dissanayake, V.; Offord, J.; Thurlow, R.; Woodruff, G. *J. Biol. Chem.* **1996**, *271*, 5768–5776.
5. Bryans, J. S. C. H. D.; Ratctiffe, G. S.; Receveur, J.-M.; Rubin, J. R. *J. Biorrg. Chem.* **1999**, *7*, 715–721.
6. Boyd, S. A.; Mantei, R. A.; Tasker, A. S.; Liu, G.; Sorensen, K. B.; Henry, Jr., K. J.; Von Geldern, T. W.; Winn, M.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Hutchins, C. W.; Marsh, K. C.; Nguyen, B.; Opgenorth, T. J. *Bioorg. Med. Chem.* **1999**, *7*, 991–1002.
7. Fevig, J. M.; Buriak, Jr., J.; Stouten, P. F. W.; Knabb, R. M.; Lam, G. N.; Wong, P. C.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1195–1200.
8. Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221–3235.
9. Berlin, S.; Engman, L. *Tetrahedron Lett.* **2000**, *41*, 3701–3704.
10. Karlsson, S.; Han, F.; Hogberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2606–2616.
11. Li, Q.; Wang, W.; Berst, K. B.; Claiborne, A.; Hasvold, L.; Raye, K.; Tufano, M.; Nilius, A.; Shen, L. L.; Flamm, R.; Alder, J.; Marsh, K.; Crowell, D.; Chu, D. T. W.; Plattner, J. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1953–1958.
12. Fukui, H.; Shibata, T.; Naito, T.; Nakano, J.; Maejima, T.; Senda, H.; Iwatani, W.; Tatsumi, Y.; Suda, M.; Aurika, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2833–2838.
13. Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362–3374.
14. Ma, Z.; Wang, S.; Cooper, C. S.; Fung, A. K. L.; Lynch, J. K.; Plagge, F.; Chu, D. T. W. *Tetrahedron: Asymmetry* **1997**, *8*, 883–887.
15. Stafford, J. A.; Valvano, N. L.; Feldman, P. L.; Brawley, E. S.; Cowan, D. J.; Domanico, P. L.; Leesnitzer, M. A.; Rose, D. A.; Stimpson, S. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1977–1982.
16. Thomas, C.; Ohnmacht, U.; Niger, M.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2885–2890.
17. Pearson, W. H. The synthesis of pyrrolidine-containing natural products via [3+2] cycloadditions. *Stud. Nat. Prod. Chem.* **1988**, *1*, 323–358.
18. Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 2762–2766.
19. Morimoto, T.; Nezu, Y.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 4596–4599.
20. Joucla, M.; Mortier, J. *J. Chem. Soc. Chem. Commun.* **1985**, *22*, 1566–1567.
21. Cottrell, I. F.; Hands, D.; Kennedy, D. J.; Paul, K. J.; Wright, S. H. B.; Hoogsteen, K. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1091–1097.
22. Ager, D. J.; Prakash, I.; Schaad, D. R. Chiral oxazolidinones in asymmetric synthesis. *Aldrichim. Acta* **1997**, *30*, 3–12.
23. Lin, J.; Liao, S.; Han, Y.; Qiu, W.; Hruby, V. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3213–3221.
24. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.
25. Kaori, A. *Tetrahedron Lett.* **1995**, *36*, 4105–4108.
26. Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163–167.
27. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.