Synthesis of (±)-*trans*-Hexahydropyrrolo[3,4-*d*]oxazol-2-one and Its Derivatives by Using *N*-(*tert*-Butyloxycarbonyl)-3-pyrroline as Precursor

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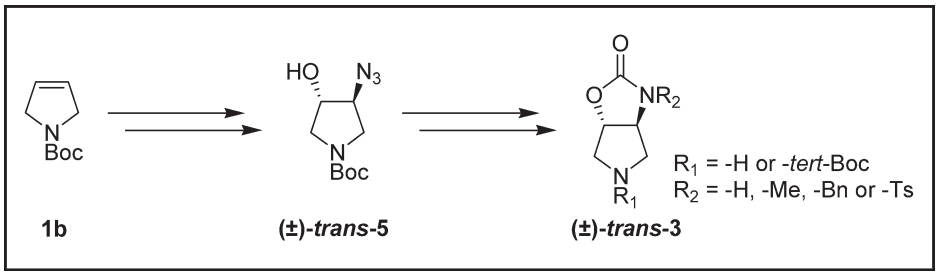

Synthetic method for the preparation of (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives has been developed. By one route, an efficient preparation of these fused heterobicyclic moieties could be achieved, which are prepared by using *N*-(*tert*-butyloxycarbonyl)-3-pyrroline as precursor. These fused heterobicyclic systems could be useful to develop a series of 2-oxazolidinone analogues.

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INTRODUCTION

Diverse biological activities are encountered in fused heterocyclic systems containing the pyrrolidine and 2-oxazolidinone moieties [1]. In continuation of our interest in this field of 2-oxazolidinones [2], it was thought worthwhile to incorporate 2-oxazolidinone (**2**) to the 3-pyrroline ring by using *N*-(*tert*-butyloxycarbonyl)-3-pyrroilne (**1b**) as a precursor for building of newly fused heterobicyclic systems, (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives (**3**) (Fig. 1).

N-Substituted-3-pyrrolines are an important class of compounds which exhibit biological activity and serve as useful synthetic intermediates [3]. The alkene moiety of 3-pyrroline can serves as a handle for various functional group transformations.

The oxazolidinone family represents one of only two new chemical classes of antibiotics disclosed in the past 40 years [4]. Linezolid (Fig. 2), the first approved oxazolidinone, demonstrates good activity against all major pathogenic Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA*a*), vancomycin-resistant *Enterococcus faecium* (VREF), and penicillin-resistant *Streptococcus pneumoniae* [5]. However, not long after the commercial release of linezolid, oxazolidinone resistant strains of MRSA and VREF began to appear in the clinic [6], underscoring the increasingly urgent need for improved antibiotics that overcome bacterial resistance mechanisms. A particularly attractive goal would be a next-generation oxazolidinone with improved spectrum and binding affinity, while retaining properties for good oral exposure and safety [7].

Several SAR studies of the 2-oxazolidinones have demonstrated a high tolerance for structural variation at the 4-position of the phenyl ring [8], while the oxazolidinone ring is essential for biological activity [9]. These fused heterobicyclic systems could be useful to develop a series of oxazolidinone analogues where the morpholine moiety of linezolid could be replaced with these heterobicyclic systems such as RWJ-416457 [10] (Fig. 2).

RESULTS AND DISCUSSION

The literature survey of the titled compound reveals the *cis* fusion of pyrrolidine and 2-oxazolidinone rings for the preparation of (±)-*cis*- and (3a*R*,6a*S*)-hexahydro-3-methylpyrrolo[3,4-*d*]oxazol-2-one only [11]. Furthermore, it is very important to find out a general methodology to synthesize (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives (**3**). The key challenge of the synthesis is the effective *trans* fusion of 2-oxazolidinone ring using alkene moiety between 3 and 4 positions of 3-pyrroline (**1a**). We required a general

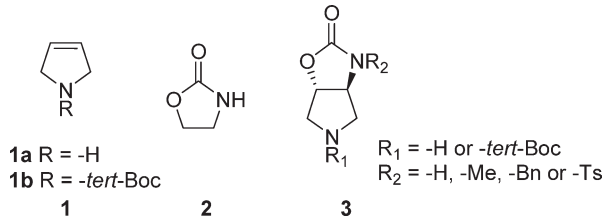
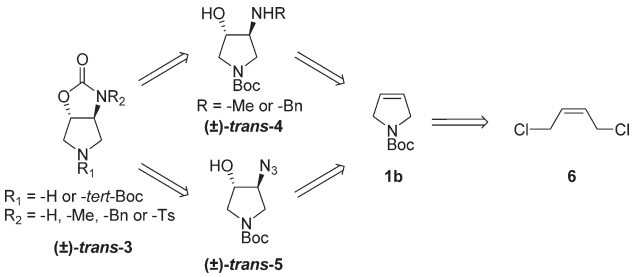


Figure 1. Chemical structures of 3-Pyrroline (**1a**), *N*-Boc-3-pyrroline (**1b**), 2-oxazolidinone (**2**), and (±)-*trans*-hexahydropyrrolo[3,4-*d*]oxazol-2-one and its derivatives (**3**).

Scheme 1. Retrosynthetic analysis to prepare (±)-*trans*-**3**



method for the preparation of these *trans* fused heterobicyclic systems (**3**) which should be the most attractive in terms of practical and economical. Based on retrosynthetic analysis, we designed two synthetic routes to **3** and are shown in Scheme 1. Each synthetic route includes a key intermediate amino alcohol (**4**) or azido alcohol (**5**) which gives the targeted moieties (**3**).

To prepare these intermediates, *N*-(tert-butyloxycarbonyl)-3-pyrroline (**1b**) or *cis*-1,4-dichloro-2-butene (**6**) are regarded as a common starting material. Recently, **1b** was prepared by us with high purity in large scale starting from *cis*-1,4-dichloro-2-butene **6** *via* Delépine reaction [12] and subsequent *in situ* cyclization in the presence of potassium carbonate (K_2CO_3) followed by *N*-Boc protection with di-*tert*-butyldicarbonate (Boc_2O) in methanol [3]. This is an efficient and commercial viable synthetic method for *N*-(*tert*-butyloxycarbonyl)-3-pyrroline.

Reaction of **1b** with *N*-bromosuccinimide (NBS) in DMSO–H_2O at room temperature afforded the racemic *trans* bromohydrin (**7**) [13]. The ^{1}H NMR spectra of the latter product revealed disappearance the triplet corresponding to alkenyl protons at δ 5.78 ppm, whereas broad singlet for hydroxyl signal appeared at δ 2.8 ppm and also the mass spectrum showed in addition to molecular ion peak, bromine isotopic peak (M^++2) at *m*/*z* 268.

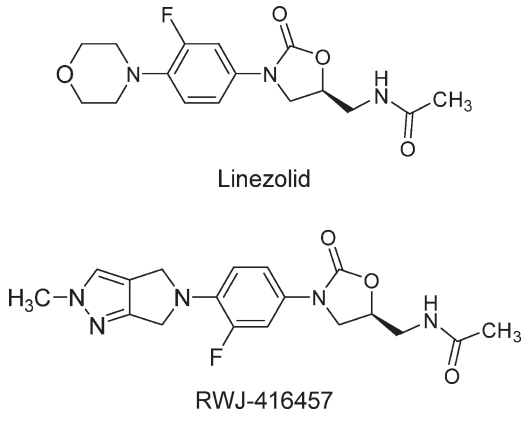


Figure 2. 2-Oxazolidinone antibacterials with different *N*-substitutents.

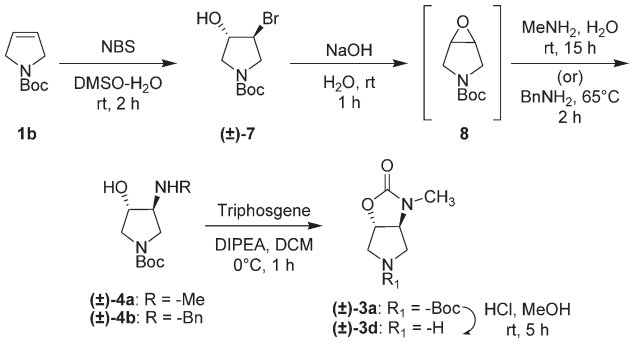
Under basic conditions (NaOH), the bromohydrin (±)-**7** was converted to the epoxide **8**, followed by treatment with methylamine or benzylamine furnished the desired intermediates **4a** or **4b**. However, the carbonyl insertion between β-amino alcohol of **4b** with various reagents, such as *N*,*N*′-carbonyldiimidazole (CDI), diethyl carbonate or triphosgene in different reaction conditions were not successful. Although in case of **4a**, after screening of several reaction conditions the required 2-oxazolidinone **3a** was obtained in low yield (36%) with triphosgene using *N*,*N*-diisopropylethylamine (DIPEA) as a base at 0°C. On treatment of **3a** with HCl in methanol, to remove the *N*-Boc protection, **3d** was obtained in good yield (Scheme 2).

On the other hand, **4b** on protection with Boc_2O gives the di-*tert*-boc protected compound which on further treatment with mesyl chloride, tosyl chloride, or thionyl chloride, the corresponding fused 2-oxazolidinone was not achieved [14]. Thus, we have studied the scope of this approach by opening of epoxy compound **8** with different amines. We were not obtained the right results on the formation of 2-oxazolidinone heterobicyclic systems using different methodologies, such as direct carbonyl insertion or *tert*-boc protection of the amines **4** followed by reaction with mesyl chloride or tosyl chloride.

Finally, our attention was altered to another approach (Scheme 3). The major difference in this strategy is ring opening of epoxy compound **8** with sodium azide instead of amines. In the previous approach, the alkyl substituent on exo cyclic amine of **4** may hinders the formation of 2-oxazolidinone ring due to steric factor. Probably, by choosing alternative strategy, 2-oxazolidinone ring formation followed by alkylation, could be succeeded due to lower steric factor. The epoxide **8** was readily opened with sodium azide in AcOH—H_2O at room temperature gave the corresponding azido alcohol, (±)-*trans*-**5**. The infra-red spectrum of **5** showed clearly a new band at $\upsilon = 2096\ cm^{-1}$ for N_3 group.

Azido alcohol (±)-**5** on further treatment with phenyl chloroformate using pyridine in dichloromethane at room temperature yielded the phenyl carbonate **9**. The ^{1}H NMR spectra of the latter product **9** divulged a

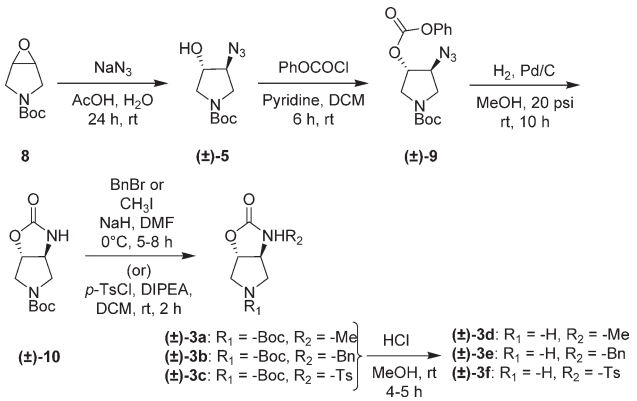
Scheme 2

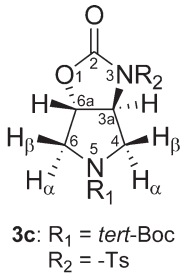


multiplet at δ 5.08–5.14 ppm due to deshielding of the C_3—H signal attached to phenyl carbonate and also two bands were appeared at ν = 1757, 1682 cm^{-1} corresponding to carbonyl (C=O) groups in the infra-red spectrum. Reduction of azide in phenyl carbonate (±)-**9** could be achieved by hydrogenation (10% Pd/C, 20 psi, methanol) gave the corresponding amine which undergoes *in situ* cyclisation produced the required basic fused heterobicyclic compound (±)-**10**. Whereas the same reaction is performed in ethyl acetate instead of methanol, *in situ* cyclisation was not occurred. The spectral analysis of the latter product **10** showed the absence of phenyl protons in the ^{1}H NMR spectrum and disappearance of azido absorption band at ν = 2122 cm^{-1} in addition, two bands were appeared at ν = 1749, 1694 cm^{-1} corresponding to carbonyl (C=O) groups in the infra-red spectrum. This heterobicyclic compound (±)-**10** was utilized to make derivatization with various substituents at 2-oxazolidinone site.

Compound (±)-**10** was alkylated with benzyl bromide or iodomethane using sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) at 0°C gave the related *tert*-butylhexahydro-3-alkyl-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate, **3a-b**. On the other hand, the alkylation of (±)-**10** with *p*-toluenesulfonyl chloride was attempted under similar conditions (NaH, DMF, 0°C), the reaction was very slow and also observed the incompletion of the reaction even at elevated temperatures. Finally, sulfonylation was achieved by the reaction of (±)-**10** with tosyl chloride using DIPEA in dichloromethane at 0°C.

Scheme 3





H-H interaction in NOE spectra (DMSO-d6)
H6a-H_β4: NOE (due to same spatial arrangement)
H6a-H_α4: no NOE (due to different spatial arrangement)
H_β4-H_α4: strong NOE (due to geminal coupling)
H_α4-H3a: strong NOE (due to same spatial arrangement)
H_β4-H3a: minimal NOE
(due to different spatial arrangement)

Figure 3. H–H interaction of compound **3c** in NOE spectra (DMSO-*d*6).

Compounds **3a-c** are well characterized by spectral data. The ^{1}H NMR spectrum of **3a-c** showed the corresponding alkylation peaks at *N*-3 site. Compound **3a-c** on *N*-*tert*-boc deprotection was achieved with HCl in methanol afforded the targeted hexahydro-3-alkylpyrrolo [3,4-*d*]oxazol-2-one **3e-f** in high yield (Scheme 3). Compounds **3d-f** have been characterized by spectral and elemental analyses.

The *trans* fusion of the two rings, pyrrolidine and 2-oxazolidinone, was assigned by using NOESY studies. To demonstrate the *trans* fusion of the synthesized compounds **3a-f**, the example chosen for NOESY experiments is **3c**. Upon irradiation of H-6a of compound **3c**, led to enhancement of the H_β-4 and no cross peak of H_α-4, which suggested that both H-6a and H_β-4 are in the same spatial arrangement in addition H-6a and H_α-4 are in different special arrangement. Whereas irradiation of H_α-4 revealed that H-3a and H_α-4 are in the same spatial arrangement (strong enhancement of H-3a signal). This indicates *trans* fusion at the ring junction, which was further confirmed by the very low NOE signal of H-3a upon irradiation of H_β-4 (Fig. 3). A similar spectral phenomenon was also observed in case of compound **9**.

As a conclusion, a simple and straightforward method was developed to synthesis (±)-*trans*-hexahydropyrrolo [3,4-*d*]oxazol-2-one and its derivatives. Further studies on the application of these compounds to prepare a series of 2-oxazolidinone analogues where the morpholine moiety of linezolid could be replaced with these

heterobicyclic systems are actively underway in our laboratories.

EXPERIMENTAL

N-(*tert*-Butyloxycarbonyl)-3-pyrroline (**1b**) was synthesized in-house (purity >99%) [3]. All reagents and solvents used were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried at 200°C, flame-dried, and flushed with dry nitrogen prior to use. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. TLC was performed on Kieselgel 60 F_{254} silica-coated aluminium plates (Merck) and visualized by UV light ($\lambda = 254$ nm) or by spraying with a solution of ninhydrin. Organic extracts were dried over anhydrous Na_2SO_4. Flash chromatography was performed using Kieselgel 60 brand silica gel (230–400 mesh). The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FTIR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C). Chemical shifts were given in ppm relative to trimethylsilane. Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

Preparation of (±)-*trans-tert*-butyl 3-bromo-4-hydroxy pyrrolidine-1-carboxylate, 7 [13]. To a stirred solution of **1b** (60 g, 0.355 mol), DMSO (420 mL) and H_2O (22 mL), NBS (75.3 g, 0.423 mol) was gradually added over 30 min at 0°C. After stirring at room temperature for 2 h, water (490 mL) was added and the mixture was extracted with AcOEt (3 × 200 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent removed under vacuum to leave a crude **7** as oil in 99.6% yield (94.0 g); ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H, *t*-butyl), 2.8 (br s, 1H, OH), 3.36–3.45 (m, 1H, C_5—H), 3.62–3.96 (m, 2H, C_5—H and C_2—H), 3.98–4.14 (m, 1H, C_2—H), 4.15–4.20 (m, 1H, C_3—H), 4.40–4.48 (m, 1H, C_4—H); APCI-MS: *m/z* (%) 266.0 (90, M^++1), 268.0 (88, M^++2), 533.1 (100, $2M^+$+3); IR (neat): ν 3387 (OH), 1655 (C=O) cm^{-1}.

Preparation of (±)-*trans-tert*-butyl 3-hydroxy-4-(methyl amino)pyrrolidine-1-carboxylate, 4a. A mixture of crude **7** (47.0 g, 0.177 mol) and aqueous NaOH (1N, 222 mL, 0.222 mol) was stirred at room temperature for 1 h. The mixture was treated with 40% methylamine-water (182 mL, 2.344 mol) and stirred at room temperature for 15 h. After evaporation of the solvent, the residue was triturated with *i*-Pr_2O to give **4a** as white crystals in 71% yield relative to **1b** (27.2 g), mp 98–100°C; ^{1}H NMR (DMSO-d_6): δ 1.40 (s, 9H, *t*-butyl), 2.38 (dd, 1H, C_2—H), 2.43 (s, 3H, CH_3), 3.1 (dd, 1H, C_5—H), 3.2 (m, 2H, C_2—H and C_5—H), 3.51 (br s, 2H, OH, and NH), 4.0 (m, 1H, C_4—H), 4.17 (m, 1H, C_3—H); ESI-MS: *m/z* (%) 161 (100), 217 (85, M^++1); IR (KBr): ν 3309 (OH), 2972, 1694 (C=O) cm^{-1}.

Preparation of (±)-*trans-tert*-butyl 3-(benzylamino)-4-hydroxypyrrolidine-1-carboxylate, 4b. A mixture of crude **7** (47.0 g, 0.177 mol) and aqueous NaOH (1N, 222 mL, 0.222 mol) was stirred at room temperature for 1 h. The mixture was treated with benzylamine (47.2 g, 0.44 mol) and stirred at 65°C for 2 h, then cooled to 0°C. The resultant precipitates were collected by filtration, washed with water and *i*-Pr_2O and dried to afford **4b** as white crystals in 60% yield relative to **1b** (31.1 g), mp 140–141°C; ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-butyl), 1.8 (br s, 2H, OH and NH) 3.10–3.30 (m, 3H, C_2—2H and C_5—H), 3.57–3.75 (m, 2H, C_3—H and C_5—H), 3.82 (d, 2H, NCH_2—Ph), 4.1 (m, 1H, C_4—H), 7.21–7.38 (m, 5H, ArH); ESI-MS: *m/z* (%) 291.2 (100, M^+−1), 293.2 (15, M^++1); IR (KBr): ν 3255 (OH), 1694 (C=O) cm^{-1}.

Preparation of (±)-*trans-tert*-butyl hexahydro-3-methyl-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate, 3a. The amino alcohol **4a** (5.0 g, 0.023 mol) was dissolved in dichloromethane (30 mL) and the solution was cooled to 0°C. Triphosgene (8.23 g, 0.028 mol) was added followed by DIPEA (9.0 g, 0.07 mol) at 0°C. After 1 h, the mixture was washed with water, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate: hexane (1:1) to give **3a** as colourless liquid in 36% yield.

Preparation of (±)-*trans-tert*-butyl 3-azido-4-hydroxy pyrrolidine-1-carboxylate, 5. To a stirred mixture of **1b** (150 g, 0.89 mol), DMSO (1050 mL) and H_2O (55 mL), NBS (188.3 g, 1.06 mol) was gradually added over 30 min at 0°C. After stirring at room temperature for 2 h, water (1225 mL) was added and the mixture was extracted with AcOEt (3 × 500 mL). The organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give crude **7** as oil. To this crude **7**, aqueous NaOH (1N, 1110 mL, 1.11 mol) was added at room temperature. After 1 h, the reaction mixture was extracted with AcOEt (3 × 500 mL). The organic layer was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give compound **8** as oil.

To a solution of sodium azide (274 g, 4.21 mol) and water (1250 mL), compound **8** was added at room temperature. To this solution, acetic acid (350 mL) was slowly added at room temperature over 40 min. After the reaction mixture was stirred at room temperature for 24 h, the mixture was extracted with AcOEt (3 × 500 mL). The organic layer was washed with saturated sodium bicarbonate followed by saturated NaCl solution, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to give **5** as pale yellow color oil (162 g). This pale yellow color oil compound was proceeded to next step without further purification; ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H, *t*-butyl), 2.75 (br s, 1H, OH), 3.23–3.54 (m, 2H, C_2—H and C_5—H), 3.56–3.80 (m, 2H, C_2—H and C_5—H), 3.90–4.01 (m, 1H, C_3—H), 4.20–4.30 (m, 1H, C_4—H); ESI-MS: *m/z* (%) 229 (100, M^++1); IR (neat): ν 3419 (OH), 2096 (N_3), 1668 (C=O) cm^{-1}.

Preparation of (±)-*trans*-1-(*tert*-butoxycarbonyl)-4-azido pyrrolidin-3-yl phenyl carbonate, 9. To a solution of **5** (50 g, 0.22 mol) in dichloromethane (500 mL), pyridine (50 mL) was added at 0°C. To this mixture, phenyl chloroformate (41 g, 0.262 mol) was slowly added at 0°C over 1 h. After the reaction mixture was stirred at room temperature for 6 h, the mixture was washed with water (250 mL) followed by saturated NaCl solution, dried over anhydrous Na_2SO_4 and then concentrated under vacuum. The residue was triturated with *n*-heptane and filtered to give **9** as a white solid in 80% yield

(61 g), mp 92–94°C; ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H, *t*-butyl), 3.42–3.80 (m, 4H, C_2—2H and C_5—2H), 4.20–4.24 (m, 1H, C_4—H), 5.08–5.14 (m, 1H, C_3—H), 7.18–7.42 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$): δ 153.9, 150.7, 129.6, 126.4, 120.8, 80.4, 79.7, 78.9, 63.1, 62.3, 49.4, 49.0, 48.9, 48.5, 28.4; ESI-MS: *m*/z (%) 349.28 (100, M^++1); IR (KBr): ν 2122 (N_3), 1757 (C=O), 1682 (C=O) cm^{-1}.

Preparation of *tert*-butyl hexahydro-2-oxopyrrolo[3,4-*d*] oxazole-5-carboxylate, 10. A solution of **9** (20 g, 0.057) in methanol (200 mL) was treated with palladium carbon (2 g, 10% palladium content) and hydrogenated at 20 psi for 10 h. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by column chromatography eluting with ethyl acetate: hexane (2:1) to give *tert*-butyl hexahydro-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate (**10**) as a colorless oil in 62% yield (8.1 g), ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H, *t*-butyl), 3.56–3.61 (m, 1H, C_4—H), 3.65–3.78 (m, 4H, C_4—H, C_6—2H and C_{3a}—H) 4.80–4.96 (m, 1H, C_{6a}—H), 8.02 (br s, 1H, NH); ESI-MS: *m*/z (%) 229.2 (100, M^++1); IR (neat): ν 2972 (NH), 1749 (C=O), 1694 (C=O) cm^{-1}.

General procedure for the preparation of *tert*-butyl hexa hydro-3-alkyl-2-oxopyrrolo[3,4-*d*]oxazole-5-carboxylate, 3a-b. To a solution of **10** (1.0 g, 0.0044 mol) in DMF (30 mL), sodium hydride (0.5 g, 60% dispersion in mineral oil) was added in one portion at room temperature. After 1 h, benzyl bromide or iodomethane (0.0044 mol) was added in a drop wise fashion. The reaction was left to stir for 5–8 h at room temperature. The reaction mixture was then poured into ice (20 mL) and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined dichloromethane layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the obtained residue was purified by column chromatography eluting with ethyl acetate: hexane (1:1) to give corresponding 2-oxazolidinone.

***tert*-Butyl hexahydro-3-methyl-2-oxopyrrolo[3,4-d]oxazole-5-carboxylate, 3a.** This compound was obtained as colorless liquid in 66% yield; ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-butyl), 3.20–3.30 (m, 1H, C_4—H), 3.4–3.7 (m, 4H, C_4—H, C_6—2H and C_{3a}—H), 3.82 (s, 3H, CH_3), 4.8 (m, 1H, C_{6a}—H); ESI-MS: *m*/z (%) 243.15 (100, M^++1); IR (neat): ν 2975, 1695 (C=O), 1423 cm^{-1}.

***tert*-Butyl hexahydro-3-benzyl-2-oxopyrrolo[3,4-d]oxazole-5-carboxylate, 3b.** This compound was obtained as pale yellow color liquid in 55% yield; ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-butyl), 3.1–3.37 (m, 1H, C_4—H), 3.39–3.63 (m, 2H, C_6—H, and C_4—H), 3.6–3.82 (m, 2H, C_6—H, and C_{3a}—H), 4.56 (s, 2H, *N*CH_2—Ph), 4.8 (m, 1H, C_{6a}—H), 7.26–7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$): δ 154.7, 137.7, 128.5, 127.8, 127.7, 127.6, 83.7, 82.9, 79.4, 71.5, 55.5, 54.5, 51.8, 51.4, 50.5, 49.5, 48.6, 28.4; ESI-MS: *m*/z (%) 319 (100, M^++1); IR (neat): ν 2973, 1690 (C=O), 1409 cm^{-1}.

Preparation of tert-butyl hexahydro-2-oxo-3-tosylpyrrolo [3,4-d]oxazole-5-carboxylate, 3c. To a solution of **10** (1.0 g, 0.0044 mol) in dichloromethane (30 mL), DIPEA (1.7 g, 0.013 mol) was added in one portion at room temperature. *p*-Toluene sulfonyl chloride (1.0 g, 0.005 mol) was slowly added to the reaction mixture at 0°C. After 2 h, the reaction mixture was diluted with water. The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the obtained residue was purified by column chromatography eluting with ethyl acetate: hexane (1:1) to give **3c** as yellow viscous liquid in 69% yield (upon long standing in the refrigerator converted to semi-solid); ^{1}H NMR (DMSO-d_6): δ 1.4 (s, 9H, *t*-butyl), 2.4 (s, 3H, CH_3), 3.05–3.1 (m, 1H, C_4—H), 3.22–3.33 (m, 2H, C_6—H and C_4—H), 3.52–3.61 (m, 1H, C_6—H), 3.7–3.73 (m, 1H, C_{3a}—H), 4.8–4.83 (m, 1H, C_{6a}—H), 7.4–7.45 (m, 2H, ArH), 7.78–7.80 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 154.5, 154.1, 143.8, 136.6, 129.8, 127.1, 80.4, 79.5, 78.1, 56.6, 55.7, 55.2, 50.0, 49.1, 48.5, 28.3, 21.5; IR (neat): ν 2973, 1753 (C=O), 1690 (C=O) cm^{-1}; ESI-MS: *m*/z (%) 193.14 (100), 383.26 (45, M^++1).

General procedure for the preparation of hexahydro-3-alkylpyrrolo[3,4-*d*]oxazol-2-one, 3d-f. To a solution of **3a-c** (0.003 mol) in methanol (10 mL), 10% HCl in methanol (2.2 mL, 0.006 mol) was added slowly at 10°C. The reaction mixture was stirred at room temperature for 4–5 h. The solvent was removed under reduced pressure and the residue is diluted with saturated sodium bicarbonate solution. The mixture is extracted with dichloromethane, washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the obtained residue was purified by column chromatography eluting with ethyl acetate: hexane (2:1) to give **3d-f**.

Hexahydro-3-methylpyrrolo[3,4-d]oxazol-2-one, 3d. This compound was obtained as yellow color liquid in 92% yield; ^{1}H NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 3.12–3.25 (m, 4H, C_6—2H and C_4—2H), 4.21–4.26 (m, 1H, C_{3a}—H), 4.81–4.86 (m, 1H, C_{6a}—H), 6.0 (br s, 1H, NH); IR (neat): ν 3223 (NH), 1690 (C=O) cm^{-1}; ESI-MS: *m*/*z* (%) 143.10 (100, M^++1). *Anal*. *Calcd*. for $C_6H_{10}N_2O_2$: C 50.69; H 7.09; N 19.71. Found: C 50.42; H 6.88; N 19.92.

Hexahydro-3-benzylpyrrolo[3,4-d]oxazol-2-one, 3e. This compound was obtained as yellow color liquid in 89% yield; ^{1}H NMR ($CDCl_3$): δ 3.07–3.34 (m, 1H, C_4—H), 3.36–3.61 (m, 2H, C_6—H and C_4—H), 3.63–3.78 (m, 2H, C_6—H and C_{3a}—H), 4.5 (s, 2H, *N*CH_2—Ph), 4.68–4.72 (m, 1H, C_{6a}—H), 7.16–7.28 (m, 5H, ArH); IR (neat): ν 3310 (NH), 1692 (C=O) cm^{-1}; ESI-MS: *m*/*z* (%) 219.09 (100, M^++1). *Anal*. *Calcd*. for $C_{12}H_{14}N_2O_2$: C 66.04; H 6.47; N 12.84. Found: C 66.32; H 6.27; N 12.51.

Hexahydro-3-tosylpyrrolo[3,4-d]oxazol-2-one, 3f. This compound was obtained as yellow color liquid in 87% yield (upon long standing in the refrigerator converted to semi-solid); ^{1}H NMR (DMSO-d_6): δ 2.4 (s, 3H, CH_3), 2.43–2.77 (m, 1H, C_4—H), 2.95–3.0 (dd, 1H, C_6—H), 3.1–3.3 (m, 2H, C_6—H and C_4—H), 3.58–3.60 (m, 1H, C_{3a}—H), 4.81–4.84 (m, 1H, C_{6a}—H), 7.26–7.33 (d, 2H, ArH), 7.75–7.78 (d, 2H, ArH); IR (neat): ν 3305 (NH), 1694 (C=O) cm^{-1}; ESI-MS: *m*/*z* (%) 283.10 (100, M^++1). *Anal*. *Calcd*. for $C_{12}H_{14}N_2O_4S$: C 51.05; H 5.00; N 9.92. Found: C 51.35; H 4.88; N 9.71.

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