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A new route to 1,4-oxazepanes and 1,4-diazepanes from Garner aldehyde

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ABSTRACT

A highly efficient and convenient method for the synthesis of substituted chiral 1,4-oxazepanes and 1,4-diazepanes have been described from Garner aldehyde through reductive amination with amino ester hydrochlorides followed by intramolecular cyclization as the key steps.

Due to their diverse biological properties[1], oxazepanes and diazepanes have been the major synthetic targets to synthetic and medicinal chemists.[2] 1,4-Oxazepanes could be found as important structural framework in natural products like neurotoxin batrachotoxin.[3] The analog of Microline A **1** showed potent efficiency as immunosuppressant than the parent compound.[4] Recently Shankaran et al. have reported synthesis and biological evaluation of oxazepanes, diazepanes, and thiazepanes as nitric oxide synthase inhibitor.[5] 1,4-Diazepane scaffold is also frequently encountered in several marketed drugs like tetrazepam, dilazep, chlorpromazine etc.[6] The group of Wattanasin reported a new class of diazepanes as LFA-1 inhibitors.[7] Diazepane and its derivatives are also known as CGRP receptor antagonists.[8] Complex nucleoside antibiotics Liposidomycin B **2** and C **3** inhibit bacterial peptidoglycan synthesis (Fig. 1).[9]

Despite wide occurrence and importance of oxazepane and diazepane core, very few synthetic routes have been reported till date. Clark and Osborn reported a synthetic strategy with moderate overall yield for substituted and functionalized 7-methoxy [1,4]-oxazepanes[10] through careful control of sodium periodate ring cleavage of methyl α-D-glucopyranoside followed by condensation with amine in the presence of $NaCNBH_3$. Recently, Bedurftig and Wunsch published a four- step sequence involving high temperature, long reaction time with harsh conditions for chiral non-racemic 2-hydroxymethyl-substituted 1,4-diazepanes[11] from methyl ester of (*S*)-serine. Wlodarczyk et al. also reported 1,4-diazepanes along with byproducts through microwave-assisted cyclization and $LiAlH_4$ reduction of cyclic lactams.[12] Crestey et al. have recently described a protocol to chiral 1,4-diazepanes utilizing activated aziridines ring opening with α-amino alcohols followed by Fukuyama–Mitsunobu cyclization.[6]

In our ongoing research program, we are engaged in the synthesis and bioevaluation of amino acid-based polycycles[13a–h] in chirally pure form using inter and intramolecular Mitsunobu reactions. Amino acid-derived Garner aldehyde[14] was used for synthesis of all stereoisomers of natural products such as Balanol, Ophiocordin,[13d] and Epiquinamide.[13e] To further diversify our methodology, we were interested to find a new and easy synthetic access to amino acid-based chiral oxazepanes and diazepanes. Incorporation of different amino acids in the ring generates structural as well as stereochemical diversity due to their wide availability and diversity in their structures. The amino acid based-diazepanes and oxazepanes are also important as they can be used as building blocks for the synthesis of peptide nucleic acids (PNAs) to control the biological function in the desired manner.[15]

To the best of our knowledge, there is no report for chiral 3-substituted 1,4-oxazepane and 2-substituted 1,4-diazepane derivatives. Herein we present a simple and scalable approach for the synthesis of 3,6-disubstituted 1,4-oxazepanes and 2,6-disubstituted 1,4-diazepanes from L-Garner aldehyde[14] in enantiomerically pure form. The methodology is highly diverse from the

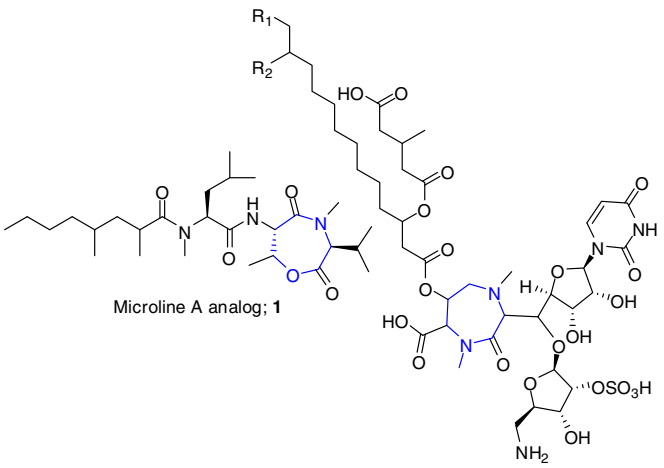

Figure 1. Some bioactive 1,4-oxazepane and 1,4-diazepanes.

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Table 1
Synthesized 3,6-disubstituted chiral 1,4-oxazepanes

Entry	Product	R	Overall yield (%)	$[\alpha]_D^{25}$
1	**9a**	$-CH_3$	60	50.1
2	**9b**	$-CH_2Ph$	55	46.3
3	**9c**	$-CH_2(C_6H_4)OBn$	62	54.2
4	**9d**	$-CH_2CH(CH_3)_2$	59	48.4

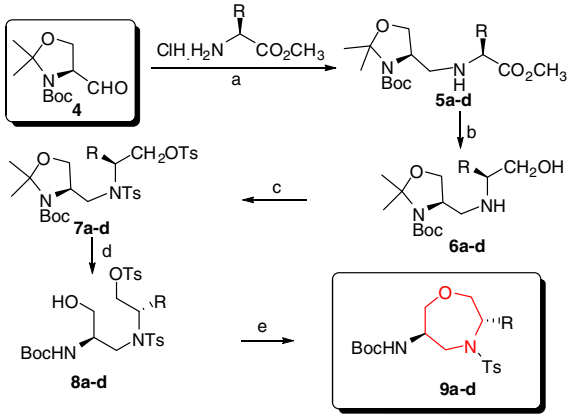
synthetic point of view and can be applied for the synthesis of several chiral 1,4-oxazepane and diazepane series.

The synthesis of oxazepanes **9a–d** (Table 1) started from the reductive amination of L-Garner aldehyde with amino acid methyl ester hydrochlorides using $NaCNBH_3$ to give the products **5a–d** in very good yields (95–97%). The coupled products were exposed to lithium aluminum hydride reduction at 0 °C to furnish Boc-protected amino alcohols **6a–d** in excellent yields (85–88%) (see Scheme 1).

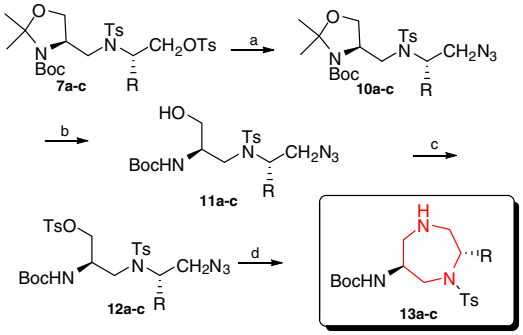
The amino alcohols were further converted into their tosyl derivatives **7a–d** (88–92%) using $TsCl/Et_3N$ in dry DCM and then acetonides were cleaved by catalytic amount of *p*-TSA in methanol at 0 °C to provide compounds **8a–d** (84–89%). In the final step, with the compounds **8a–d** in hand, we examined the kinetically unfavorable seven-membered ring cyclization via simple intramolecular nucleophilic substitution (S_N2) under mild reaction condition (K_2CO_3/CH_3OH/rt). Surprisingly, we found that the cyclization proceeded very efficiently yielding chiral oxazepanes **9a–d** (ee's >99%, 90–93%)[16] in very good overall yields (55–62%).

After successful exploration of our methodology, we targeted to synthesize the nitrogen counterpart of the above-mentioned oxazepanes by utilizing the intermediates **7a–c**. The ditosyl derivatives **7a–c** were then reacted with sodium azide in DMF at 70 °C for 4 h to obtain the azido products **10a–c** in good yields (84–88%). The acetonide group was cleaved using catalytic amount of *p*-TSA in methanol at 0 °C to produce azido alcohols **11a–c** (82–84%) which were then converted into tosyl derivatives **12a–c** in good yields (76–81%). With the tosyl derivatives in hand, reduction of the azides using 10% Pd–C in methanol followed by K_2CO_3-mediated cyclization was found to be effective to afford diazepanes **13a–c** (ee's >99%, 66–72% over two steps)[17] in good overall yields (22–24%) (see Scheme 2 and Table 2).

In conclusion, we have described a new method for the synthesis of chiral amino acid-based oxazepane and diazepane scaffolds from easily available Garner aldehyde. The methodology is quite diverse with incorporation of natural and unnatural amino acids



Scheme 1. Synthesis of 3-alkyl-6-amino-1,4-oxazepanes. Reagents and conditions: (a) NaOAc, $NaCNBH_3$, dry MeOH, rt, overnight, (95–97%); (b) LAH/THF, 0 °C, 2 h, (85–88%); (c) *p*-TsCl, Et_3N, DCM, 0 °C, 2 h, (88–92%); (d) cat. *p*-TsOH, MeOH, 0 °C, 5 h, (84–89%); (e) K_2CO_3, MeOH, rt, (90–93%).



Scheme 2. Synthesis of 2-alkyl-6-amino-1,4-diazepanes. Reagents and conditions: (a) NaN_3, DMF, 70 °C, (84–88%); (b) cat. *p*-TsOH, MeOH, 0 °C, (82–84%); (c) *p*-TsCl, Et_3N, DCM, 0 °C, 2 h, (76–81%); (d) (i) H_2, Pd/C, MeOH, (ii) K_2CO_3, rt, (66–72% over two steps).

Table 2
Synthesized 2,6-disubstituted chiral 1,4- diazepanes

Entry	Product	R	Overall yield (%)	$[\alpha]_D^{25}$
1	**13a**	$-CH_3$	24	148.3
2	**13b**	$-CH_2Ph$	22	106.3
3	**13c**	$-CH_2(C_6H_4)OBn$	22	80.6

for the generation of new bioactives which can be utilized as peptidomimetics. Biological testing of these molecules is currently underway and will be reported elsewhere.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.035.

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16. *tert-Butyl (3S,6R)-3-benzyl-4-tosyl-1,4-oxazepan-6-ylcarbamate* (**9b**): To a methanolic solution of the compound **8b** (1 equiv), K_2CO_3 (5 equiv) was added at room temperature and stirred at the same temperature for 8 h. Methanol was removed under reduced pressure and water was added. The solution was then extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under vacuum. The residue was purified over silica gel column (20% ethyl acetate in *n*-hexane) to furnish yellow colored oil **9b** (92%). $[\alpha]_D^{25}$ 106.3 (*c* 0.040, CH_3OH). R_f 0.6 (50% ethylacetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, 2H, *J* = 8.2 Hz, ArH), 7.26–7.19 (m, 5H, ArH), 7.01–6.99 (m, 2H, ArH), 4.29–4.13 (m, 3H), 3.88–3.83 (m, 1H), 3.60–3.55 (m, 3H), 3.42–3.35 (m, 1H), 2.88–2.80 (m, 1H), 2.48–2.44 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 143.6, 137.2, 136.9, 129.8, 129.2, 128.7, 126.9, 126.7, 79.5, 75.5, 60.4, 59.5, 51.4, 46.2, 34.9, 28.4, 21.5. IR (neat, cm^{-1}): 3020, 2360, 1681, 1423, 1216, 1044, 760, 671. Mass (ESI-MS): *m/z*; 483.1 (100, $[M+Na]^+$), 461.1(12, $[M+H]^+$), 361.2(28, $[M-{}^tBoc]^+$). Anal. Calcd for $C_{24}H_{32}N_2O_5S$: C, 62.58; H, 7.00; N, 6.08. Found: C, 62.67; H, 7.08; N, 6.00.
17. *tert-Butyl (2S,6S)-2-benzyl-1-tosyl-1,4-diazepan-6-ylcarbamate* (**13b**): To a methanolic solution of **12b**, Pd/C (10%) was added and after hydrogenation, the mixture was filtered and K_2CO_3 was added to the filtrate. The solution was stirred at room temperature for 5 h and the methanol was removed under reduced pressure. Water was then added and the solution extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified over silica gel column (3% methanol in chloroform) to furnish colorless oil **13b** (69%). $[\alpha]_D^{25}$ 46.3 (c 0.156, CH_3OH). R_f 0.4 (70% ethylacetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.53 (m, 2H, ArH), 7.33–7.00 (m, 7H, ArH), 4.23–2.06 (m, 14H), 2.00 (s, 1H), 1.25 (s, 9H). IR (neat, cm^{-1}): 3021, 2361, 1647, 1519, 1216, 761, 670. Mass (ESI-MS): *m/z*; 482.7 (52, $[M+Na]^+$), 459.6 (42, $[M]^+$), 403.5 (100, $[M-{}^tBu]$, 359.8 (36, $[M-{}^tBoc]^+$). Anal. Calcd for $C_{24}H_{33}N_3O_4S$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.78; H, 7.18; N, 9.07.