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Stereospecific Synthesis of 2-Substituted Bicyclic Thiazolidine Lactams

Nalin L. Subasinghe, Ehab M. Khalil, and Rodney L. Johnson*

Department of Medicinal Chemistry, University of Minnesota,
308 Harvard Street, S.E., Minneapolis, MN 55455

Abstract: Bicyclic thiazolidine lactam **1** was used as a model system for developing synthetic methodology into β-turn mimics that would contain side chain functionality. Treatment of a mixture of **1** and a non-enolizable aldehyde at -100 °C with LDA resulted in a good yield of the aldol adduct when aromatic aldehydes were used. Radical dehydroxylation of the pentafluorophenylcarbonate derivative of the aldol adduct with $(n\text{-Bu})_3SnH$ and AIBN gave a single isomer of the C-2 alkylated bicyclic 5,5-thiazolidine lactam. This methodology was applied to the synthesis of the 2-substituted spiro bicyclic thiazolidine lactam type II' β-turn mimic **14**.

Non-peptide secondary structural mimics and conformational constraints have proven to be extremely useful tools for studying the biologically active conformations of peptides.[1,2] In this regard, there has been considerable work carried out on the design and synthesis of β-turn mimics.[2,3] One general type of β-turn mimic that has been developed and utilized is the bicyclic lactams in which two (ψ_2, ϕ_3) of the four torsion angles which define a β-turn are restricted.[4-8] We have previously reported on the utility of the bicyclic 5,5-thiazolidine lactam system as a type II β-turn mimic (Figure 1).[5]

Although bicyclic lactams such as the bicyclic 5,5-thiazolidine lactam system have been shown to be good mimics of β-turns, the utility of the mimics developed to date has been limited because they have not possessed, in most instances, the side chain functionality of the *i*+1 and *i*+2 amino acid turn residues that they are intending to mimic. Since this usually has been because of synthetic difficulties, synthetic methods to incorporate amino acid side chain functionality at the C-2 and C-7 positions of the bicyclic lactam system have been sought to expand the utility of this particular turn mimic. In this report we describe a method which allows the incorporation of an aryl side chain functionality at the C-2 position.

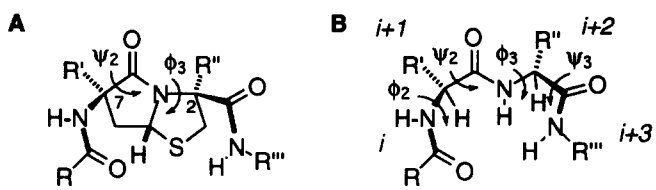
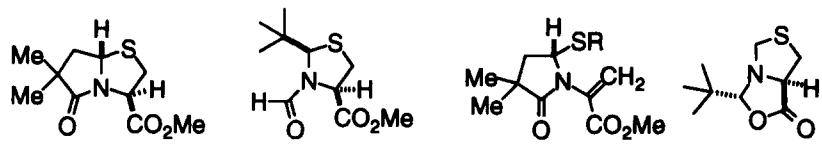


Figure 1. Comparison of the bicyclic 5,5-thiazolidine lactam system (**A**) and a type II β-turn (**B**).

Since it had already been shown that substitution at C-7 could be achieved conveniently by using an α-substituted aspartic acid aldehyde in the synthetic route used to obtain the bicyclic 5,5-thiazolidine lactam system,[9,10] an investigation into obtaining the 2-substituted bicyclic lactam system was undertaken.[11] We envisioned utilizing the inherent chirality of the bridgehead carbon to stereoselectively direct the alkylation at the 2-position. Model compound **1** was synthesized in order to explore this approach.[12] NOE experiments (Figure 2A) were used to assign the stereochemistry at the newly formed bridgehead center.



1 **2** **3** **4**

Although Pattenden et al.[13] had been successful in α-alkylating thiazolidine **2** at -90 °C using LDA as the base, our attempts at alkylating **1** at C-2 by treating this material at -100 °C with either LDA or sodium hexamethyldisilazide followed by an alkyl halide resulted only in the formation of the β-elimination product **3**. This result was consistent with what Seebach et al.[14] observed in the attempted alkylation of thiazolidine **4** with alkyl halides. Since Seebach and Weber[15] had observed that non-enolizable aldehydes add with high diastereoselectivity to the enolate of **4** formed with LDA, we attempted the analogous reaction on **1**. Treatment of a solution of **1** and benzaldehyde with LDA at -100 °C gave adduct **5** in excellent yield as a 1:1 mixture of two diastereoisomers (Scheme 1).[16] Although epimers at C-2 were also possible, the results obtained below indicate that only one is formed. Compound **1** was reacted with a variety of other non-enolizable aldehydes in a similar manner (Scheme 1). When aldehydes *N-tert*-butoxycarbonyl-indole-3-carboxaldehyde and cinnamaldehyde were used, good yields of the corresponding aldol adducts **6** and **7** were obtained.[17] In contrast, the reaction of **1** with either methyl glyoxylate, pivaldehyde, or formaldehyde gave in each case a complex mixture from which only about 10 % of the desired aldol product (**8-10**) could be isolated.

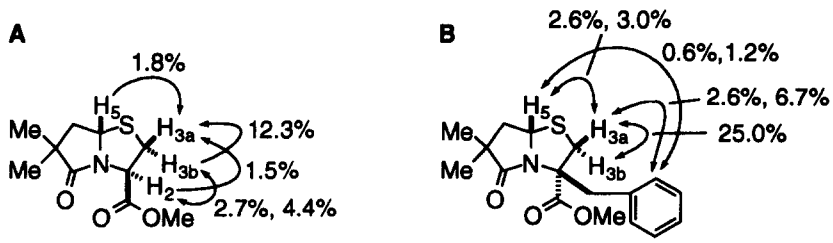
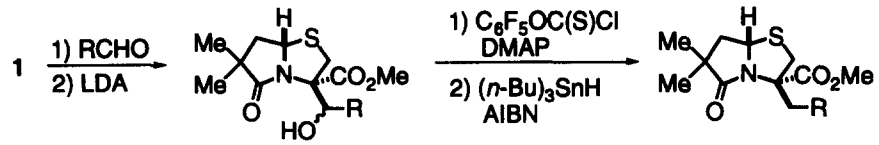


Figure 2. NOEs observed for the bicyclic thiazolidine lactams **1** (**A**) in C_6D_6 and **11** (**B**) in $CDCl_3$.

Compounds **5** and **6** were subjected to the radical dehydroxylation conditions of Barton and Jaszberenyi[18] (Scheme 1) to give the desired C-2 alkylated bicyclic 5,5-thiazolidine lactams **11** and **12**, respectively.[19] Each product was obtained as a single isomer. The absolute configuration of the 2-position of **11** was assigned as *S* on the basis of NOE difference experiments (Figure 2B). The results indicated that formation of the aldol adduct occurred only from the sterically less encumbered *exo* face of the enolate generated from **1**.

Scheme 1

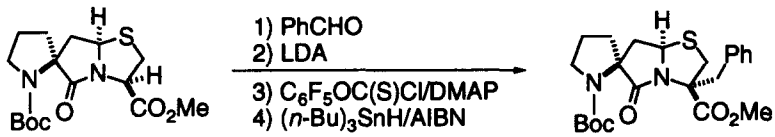


5: R = Ph (93 %)
6: R = *N*-Boc-3-indolyl (73 %)
7: R = PhCH=CH (53 %)
8: R = CO_2Me (~10 %)
9: R = $(CH_3)_3C$ (~10 %)
10: R = H (~10 %)

11: R = Ph
12: R = *N*-Boc-3-indolyl

The above methodology was used to functionalize the analogous position of spiro bicyclic thiazolidine lactam **13**,[20] thereby providing the substituted type II' β-turn mimic **14** (Scheme 2).[21] The structure of **14** was confirmed through single-crystal X-ray analysis.[22] This result further demonstrates the viability of the above methodology to directly functionalize the C-2 position of bicyclic thiazolidine lactam β-turn mimics already functionalized at the C-7 position. Furthermore, the introduction of the C-2 side chain can be achieved stereospecifically, since the chirality of the bridgehead carbon directs the stereochemical outcome.

Scheme 2



13 **14**

Acknowledgment

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11. In one approach, we looked at condensing an aspartic acid aldehyde derivative with D-Cys(α-Me)-OMe under conditions previously shown to give the unsubstituted and 7-substituted bicyclic thiazolidine lactams. Although the intermediate epimeric thiazolidines were formed, this material did not cyclize to the desired 2-substituted bicyclic lactam upon heating.
12. **Methyl (2*R*,5*S*)-1-Aza-7,7-dimethyl-8-oxo-4-thiabicyclo-[3.3.0]octane-2-carboxylate (1)**. Methyl 2,2-dimethyl-4-oxo-butanoate and L-Cys·HCl·H_2O were condensed in pyridine using the same method reported in ref. 5 for construction of the bicyclic thiazolidine lactam system. The compound was obtained as an oil (49%) after flash-

chromatography (hexane/EtOAc 5:1): ^{1}H NMR (300 MHz, C_6D_6) δ 0.94 (s, 3 H), 1.05 (s, 3 H), 1.59 (dd, *J* = 4.9 and 13.4 Hz, 1 H), 1.69 (dd, *J* = 7.3 and 13.4 Hz, 1 H), 2.73 (dd, *J* = 8.5 and 11.0 Hz, 1 H), 2.93 (dd, *J* = 3.7 and 11.0 Hz, 1 H), 3.09 (s, 3 H), 4.89 (dd, *J* = 4.9 and 7.3 Hz, 1 H), 5.03 (dd, *J* = 3.7 and 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.74, 25.82, 35.84, 41.94, 43.66, 52.69, 57.31, 62.85, 170.2, 179.91; FAB MS *m/z* 230 $(MH)^+$. Anal. calcd. for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11 S, 13.98. Found: C, 52.54; H, 6.70; N, 6.04; S, 13.77.

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16. **Methyl (2*S*,5*S*)-1-Aza-2-((*RS*)-hydroxyphenylmethyl)-7,7-dimethyl-8-oxo-4-thiabicyclo[3.3.0] octane-2-carboxylate (5).** Compound **1** (1 mmol) was placed in a dry flask equipped with a stir bar. To this flask, dry THF (5 mL) and aldehyde (1 mmol) previously dried over molecular sieves (4 Å) were added and the flask was placed under an Ar atmosphere. After the solution was cooled to -100 °C in a MeOH/liquid N_2 bath, LDA (1 mmol) was dripped into the flask. The solution was gradually allowed to warm up to 7 °C over a 6 h period. The reaction was quenched with 10% citric acid and then extracted with EtOAc. The EtOAc layer was washed with saturated NaCl, dried over $MgSO_4$ and evaporated under vacuum to give an oil, which was purified by silica gel column chromatography using hexane/EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.17 (s, 3 H), 1.19 (s, 3 H), 1.32 (s, 3 H), 1.89-2.15 (m, 4 H), 3.26 (d, *J* = 12.6 Hz, 2 H), 3.57 (d, *J* = 12.6 Hz, 1 H), 3.79 (s, 3 H), 3.82 (d, *J* = 13.8 Hz, 1 H), 3.85 (s, 3 H), 4.1 (dd, *J* = 6.15 and 8.36 Hz, 1 H), 4.45 (dd, *J* = 6.6 and 8.7 Hz, 1 H), 5.14 (s, 1 H), 5.63 (s, 1 H), 7.2-7.3 (m, 10 H); FAB MS *m/z* 336 $(MH)^+$.

17. Compounds **6** and **7** were obtained in a diastereoisomeric ratio of 2:3 and 1:2, respectively.

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19. **Methyl (2*S*,5*S*)-1-Aza-2-(phenylmethyl)-7,7-dimethyl-8-oxo-4-thiabicyclo-[3.3.0]octane-2-carboxylate (11).** Pentafluorophenyl thionochloroformate (175 mg, 0.67 mmol), dimethylaminopyridine (146.6 mg, 1.2 mmol) and **5** (202 mg, 0.6 mmol) were dissolved in dry CH_3CN (6 mL) and the solution stirred for 24 h under an Ar atmosphere. The CH_3CN was removed under vacuum, and the resulting residue was dissolved in dry CH_2Cl_2 (5 mL). To this solution dry toluene (50 mL) was added and the resulting precipitate was removed by filtration. The solution was concentrated under vacuum to 25 mL. This solution was transferred to a Pyrex culture tube equipped with a screw cap. To this tube AIBN (24 mg) and $(n\text{-Bu})_3$SnH (300 μL) were added. The tube was tightly capped and heated in a 90 °C oil bath for 5.5 h . The tube was cooled to room temperature and the toluene removed under vacuum. The resulting residue was chromatographed on a silica gel column (EtOAc/hexane, 1:6). Further purification by preparative TLC (EtOAc/hexane, 1:6) gave 122 mg (63%) of **11** as an oil: $[\alpha]_D$ -186.5° (*c* 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3 H), 1.24 (s, 3 H), 2.0 (dd, *J* = 9 and 12 Hz, 2 H), 2.08 (dd, *J* = 6 and 12 Hz, 2 H), 3.13 (d, *J* = 13.8 Hz, 1 H), 3.29 (d, *J* = 12.6 Hz, 1 H), 3.57 (d, *J* = 12.6 Hz, 1 H), 3.76 (d, *J* = 13.8 Hz, 1 H), 3.80 (s, 3 H), 4.36 (dd, *J* = 6.0 and 8.4 Hz, 1 H), 7.1-7.35 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.77, 25.05, 37.86, 42.04, 42.74, 46.68, 52.99, 65.29, 67.16, 127.05, 128.16, 131.07, 134.95, 171.17, 176.92; FAB MS *m/z* 320 $(MH)^+$. Anal. calcd. for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39; S, 10.04. Found: C, 64.11; H, 6.85; N, 4.38; S, 9.89.

Methyl (2*S*,5*S*)-1-Aza-2-{3'-[(N-tert-butoxycarbonyl)indolyl]methyl}-7,7-dimethyl-8-oxo-4-thiabicyclo-[3.3.0]octane-2-carboxylate (12). Compound **6** (110 mg, 0.23 mmol) was treated in a manner similar to **5**. The resulting oil was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give 45 mg (42%) of **12** as an oil: $[\alpha]_D$ -83.9° (*c* 1.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 3 H), 1.25 (s, 3 H), 1.65 (s, 9 H), 2.04-2.13 (m, 2 H), 3.13 (d, *J* = 13.8 Hz, 1 H), 3.29 (d, *J* = 12.6 Hz, 1 H), 3.57 (d, *J* = 12.6 Hz, 1 H), 3.76 (d, *J* = 13.8 Hz, 1 H), 3.80 (s, 3 H), 4.36 (dd, *J* = 6.0 and 8.4 Hz, 1 H), 7.1-7.35 (m, 2 H), 7.46 (s, 0.6 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.63 (s, 0.4 H), 8.12 (d, *J* = 8.1 Hz, 0.4 H), 8.18 (d, J = 8.4 Hz, 0.6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.77, 25.05, 37.86, 42.04, 42.74, 46.68, 52.99, 65.29, 67.16, 127.05, 128.16, 131.07, 134.95, 171.17, 176.92; FAB MS *m/z* 459 $(MH)^+$. Anal. calcd. for $C_{24}H_{30}N_2O_5S$: C, 62.86; H, 6.59; N, 6.11. Found: C, 62.70; H, 6.49; N, 5.98.

20. Compound **13** was prepared by condensing (*S*)-Boc-Pro(2-formylmethyl)-OH with L-Cys-OMe in a method analogous to that described in ref. 10. The epimeric thiazolidines which were formed were converted to the corresponding spiro bicyclic products with DCC. Compound **13** was separated from its bridgehead epimer by silica gel chromatography (EtOAc/hexane, 5:2): m.p. 142-143 °C; $[\alpha]_D$ +35.3° (*c* 1.3, $CHCl_3$).

21. **Methyl [3'-(*R*)-[3'β,6'β(*S**),7'aα]]-1-(*tert*-Butoxycarbonyl)tetrahydro-5'-oxospiro[pyrrolidine-2,6' (5'*H*)-pyrrolo[2,1-b]thiazolidine]-3'carboxylate (14).** Compound **13** was converted to the aldol product in a 80% yield using the procedure described in ref. 16. This material was dehydroxylated using the procedures described in ref. 19 to give the product as a solid in a 71% yield: m.p. 186-186 °C; $[\alpha]_D$ +192.2° (*c* 1.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 1.70-2.15 (m, 4 H), 1.97 (dd, *J* = 6.0 and 11.4 Hz, 1 H), 3.03 (dd, *J* = 8.7 and 11.4 Hz, 1 H), 3.11 (d, *J* = 14.0 Hz, 1 H), 3.38 (d, *J* = 12.4 Hz, 1 H), 3.45-3.50 (m, 2 H), 3.55 (d, *J* = 12.4 Hz, 1 H), 3.70 (d, *J* = 14.0 Hz, 1 H), 3.82 (s, 3 H), 4.05 (dd, *J* = 6.0 and 8.7 Hz, 1 H), 7.1-7.3 (m, 5 H). ^{13}C NMR (75 MHz, C_6D_6) δ 23.15, 28.39, 35.56, 37.35, 38.74, 41.93, 48.19, 52.39, 64.08, 66.88, 71.63, 78.90, 127.00, 131.19, 131.46, 136.13. Anal. calcd. for $C_{23}H_{30}N_2O_5S$: C, 61.86; H, 6.77; N, 6.27; S, 7.18. Found: C, 61.06; H, 6.38; N, 6.31; S, 7.19.

22. Atomic coordinates for the crystal structure of **14** have been deposited with the Cambridge Crystallographic Data Centre.

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