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Constrained analogs of methionine: asymmetric synthesis of χ-angle restricted methionine derivatives through [3.1.0]-γ-lactone cyclopropane ring opening

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Abstract—Regiospecific and stereoselective ring opening of a [3.1.0]-γ-lactone intermediate by sulfur-containing nucleophiles has been developed. The reaction product was confirmed by NMR techniques and chemical equilibrium processes. Using this approach, all four possible diastereomers of χ-angle restricted methionine surrogates have been synthesized by electrophilic azidation and reduction to the amino group. These constrained analogs can be used in the preparation of peptidomimetics of sequences containing methionine in the C-terminal position. © 2000 Published by Elsevier Science Ltd.

In recent years, there has been great interest in the synthesis of peptidomimetics as potential therapeutic agents.[1] In particular, rational drug design often requires conformationally constrained small peptides and peptidomimetics to establish the optimum conformation of a flexible peptide that is necessary for high binding affinity and selectivity against a target protein. We have been interested in the design of peptidomimetics to target signal transduction pathways for several years.[2] As part of our continuing search for farnesyltransferase inhibitors based on peptidomimetics of the CysValIleMet sequence from K_B-Ras, we sought constrained methionine surrogates to evaluate its electronic and conformational importance at the C-terminus of many farnesylated proteins.

Methionine has many important biological functions, including as a methylating agent through *S*-adenosylmethionine formation. Although methionine has special binding properties as a result of n–π nonbonding interactions and its conformational preferences,[3] there have been few efforts to modify it for molecular recognition and drug discovery purposes.[4] Herein, we report the synthesis of a methionine surrogate that is conformationally constrained by fixing the χ-angle (Fig. 1) in a lactone ring with the carboxyl group. The amino acid mimetic is prepared by cyclopropane ring opening of the [3.1.0]-γ-lactone system using sulfur-containing nucleophiles (Scheme 1).

Pirrung and Burgess have reported the synthesis of cyclopropyl-containing amino acid analogs that have found several applications, including in the inhibition of ethylene production in plants and as peptidomimetics for metalloenzyme binding. In these approaches, [3.1.0]-γ-lactone (**1**) was used as a key intermediate and was prepared by sequential nucleophilic substitutions in 48% yield and 91% ee. The lactone ring was opened by

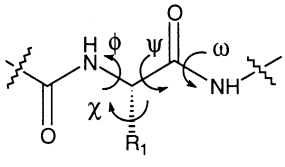
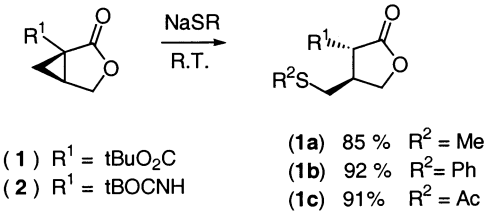


Figure 1. Dihedral angles of a substituted peptide.



Scheme 1. Regiospecific and stereospecific ring opening.

Keywords: [3.1.0]-γ-lactone; constrained methionine analogs; peptidomimetics.

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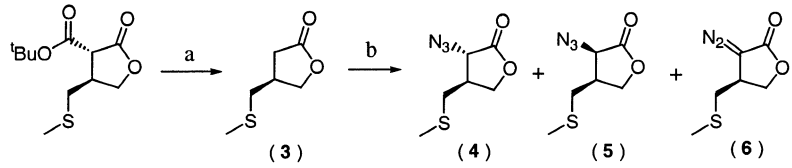

Scheme 2. (a) TFA/CH_2Cl_2; *p*-TsOH/*t*BuOH, 88%; (b) Base/THF/−78°C; Tris-N_3 then HOAc.

ammonium hydroxide and the products were converted to 2,3-methanocyclopropyl methionine derivatives.[5] Lactone **1** provided an excellent starting point for our synthesis of χ-angle fixed methionine analogs.

When sulfur-containing nucleophiles were applied to this bicyclic lactone **1** in DMF at ambient temperature, the cyclopropyl ring opened in regiospecific and stereoselective manner (>85% yield, >95% de). The structures were confirmed by COSY, DEPT, and HETCO NMR spectroscopy,[6] and showed no γ-lactone ring-opened product. From the coupling constant (C(3), $J = 8.1$ Hz) and NOE experiments that showed no significant amount of polarization transfer, we confirmed that the cyclopropyl ring had opened to give the more stable *trans* product that may come from the thermodynamic protonation. This was further supported by the lack of chemical equilibration between *trans* and *cis* forms when **1a** was treated with KO*t*Bu. Presumably, the driving force for this pathway is formation of a stable cyclic malonate anion with relief of ring strain.[7] Although it is possible that nucleophilic attack may occur at the acyloxymethylene,[8] a reverse intramolecular reaction would reform starting material, due to the very high effective molarity.[9] In the ground state of compound **1**, the bisected cyclopropane ring seems from molecular modeling to have effective overlap with the carbonyl group of the *tert*-butyl ester, which may further satisfy the stereoelectronic requirements for ring opening.[10]

We also prepared compound **2** from **1** by Curtius rearrangement[5a] to test the generality of the nucleophilic ring-opening reaction. However, **2** was not affected by sulfur-containing nucleophiles and gave only starting material despite the electrophilic character of the α-position.

Attempts to convert intermediate **1a** to a methionine isostere by deprotection of the *tert*-butyl group followed by Curtius rearrangement only produced decarboxylated compound **3**.[11] To overcome this problem, we adopted a process involving electrophilic addition of the azide.[12] By variation of the reaction conditions, we found that the optimum procedure used LiHMDS for the enolate formation and HOAc as the quenching reagent (Scheme 2).

Table 1. Product distribution depending on the base via Scheme 2[a]

Base	N_3(*trans*) (%) (**4**)	N_3(*cis*) (%) (**5**)	N_2 (%) (**6**)
KHMDS	26	4.2	28
NaHMDS	20	3.9	9.0
LiHMDS	45	6.7	–[b]

[a] Percentage ratio comes after purification by HPLC.
[b] No detectable amount by HPLC and NMR.

Although product distribution was highly dependent on the metal base and quenching reagent used, the *trans*/*cis* ratio of the azide derivative was around 6.5 in each case (Table 1).

To avoid sulfur poisoning of the Pd–C catalyst, the alkyl azide was reduced using stannous chloride or Staudinger's method with triphenylphosphine–water to provide methionine surrogate **7** (Scheme 3).[13] In a parallel study, we also prepared the other enantiomer of **7** starting from the enantiomer of **1**. We also synthesized the *cis*-diastereomer **9**[14] by bromide introduction followed by azide displacement with TMGA or sodium azide.[15] However, in this case, the *cis*/*trans* ratio is about 1.3. Presumably, the *trans*-product comes from intramolecular methylthioether attack on the bromide followed by azide reaction with this cyclic sulfonium intermediate.[16]

In conclusion, we have synthesized all four diastereomers of a new rigid methionine surrogate by a nucleophilic ring-opening reaction of the [3.1.0]-γ-lactone system. We are now exploring ways to expand this ring opening chemistry with the [3.1.0]-γ-lactone system and to synthesize a wider range of peptidomimetics.

Acknowledgements

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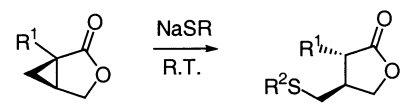

(**1**) R^1 = $tBuO_2C$
(**2**) R^1 = tBOCNH

(**1a**) 85 % R^2 = Me
(**1b**) 92 % R^2= Ph
(**1c**) 91% R^2 = Ac

Scheme 3. (a) LiHMDS, −78°C; Tris-N_3 then HOAc 45%; (b) $SnCl_2$ or PPh_3, H_2O; BOC_2O, 80%; (c) LiHMDS, −78°C; NBS, THF, 48%; (d) TMGA, CH_2Cl_2; PPh_3, H_2O, THF; BOC_2O, 60% (1.3:1).

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6. **1a**; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.53 (dd, 1H, $J1 =$ 8.7, $J2 = 7.2$ Hz), 4.01 (dd, 1H, $J1 = 8.7$, $J2 = 7.2$ Hz), 3.32 (d, 1H, $J = 8.1$ Hz), 3.20 (m, 1H), 2.64 (d, 1H, $J = 6.9$ Hz), 2.13 (s, 3H), and 1.50 (s, 9H).
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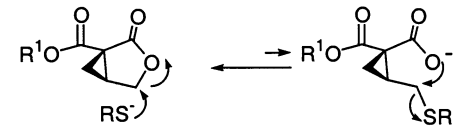

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13. (**7**) Mp 122°C; $[\alpha]_D^{20}$ −19.5 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.01 (br, 1H), 4.56 (dd, 1H, $J1 =$ 9.3 Hz, $J2 = 8.1$ Hz), 4.21 (t, 1H, $J = 8.7$ Hz), 3.99 (t, 1H, $J = 9.3$ Hz), 3.01 (dd, 1H, $J1 = 12.3$ Hz, $J2 = 3.6$ Hz), 2.75 (m, 1H), 2.65 (dd, 1H, $J1 = 12.3$ Hz, $J2 = 9.6$ Hz), 2.15 (s, 3H), and 1.47 (s, 9H).
14. (**9**) Mp 149°C; $[\alpha]_D^{20}$ +120.4 (*c* 0.4, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.06 (br, 1H), 4.55 (dd, 1H, $J1 =$ 3.9 Hz, $J2 = 3.3$ Hz), 4.50 (d, 1H, $J = 5.7$ Hz), 4.36 (dd, 1H, $J1 = 3.9$ Hz, $J2 = 3.3$ Hz), 3.05 (m, 1H), 2.64 (dd, 1H, $J1 = 8.0$ Hz, $J2 = 1.5$ Hz), 2.29 (dd, 1H, $J1 = 8.0$ Hz, $J2 = 6.3$ Hz), 2.12 (s, 3H), and 1.47 (s, 9H).
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