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LETTERS

[3+2] Cycloaddition of trimethylenemethane (TMM) to α,β-unsaturated γ-lactam. Preparation of 5,5-fused proline surrogates

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Abstract—Unsaturated lactam derived from (*S*)-pyroglutaminol undergoes a totally stereoselective cycloaddition reaction with (2-(acetoxymethyl)-3-allyl)trimethylsilane in the presence of Pd(P(O*i*Pr)$_3$)$_4$ in refluxing toluene. This step was efficiently used to introduced the 5,5-fused framework desired for the preparation of novel proline surrogates. © 2003 Published by Elsevier Science Ltd.

Trost's palladium-assisted trimethylenemethane (TMM) [3+2] cycloaddition reaction[1,2] is a very versatile ring-construction methodology. The generality of this process has been extensively illustrated by its use in the preparation of various cyclopentanes from electron-deficient olefins like α,β-unsaturated ketones, esters, nitriles, sulfones and lactones. Nickel(0) [3+2] cycloadditions of methylene-cyclopropanes have been published with *N*-subsituted maleimides[3] but no (TMM) [3+2] cycloaddition on α,β-unsaturated amide has been reported.

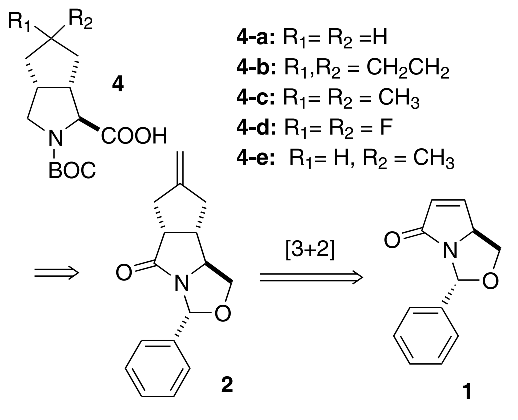
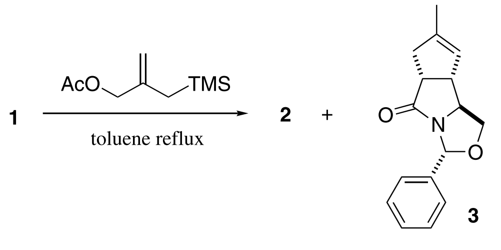


Figure 1.

In one of our medicinal chemistry program, we needed to prepare new 5,5-fused proline analogs **4a**–**e**. α,β-Unsaturated lactam[4] **1** derived from commercially available (*S*)-pyroglutaminol has been successfully used as substrate for 1,3-dipolar cycloadditions of nitrones[5] and cyclopropanation reactions.[6] Because of such reactivity, we anticipated that the Trost [3+2] cycloaddition reaction on lactam **1** (Fig. 1) might be an attractive method for the preparation of the 5,5-fused framework of novel proline analogs **4** and herein we report on the efficiency of such methodology.

Lactam **1** was prepared according to known procedure.[4] To our satisfaction, the initial attempt to cyclize **1** through the action of 1.4 equiv. of (2-(acetoxymethyl)-3-allyl)trimethylsilane, 8 mol% of tetrakis-(triphenylphosphine)palladium(0) in refluxing toluene turned out to be successful, albeit proceeding in low



Pd(Ph$_3$)$_4$	**2:** 9%	**3:** 8%
Pd(P(O^{i}Pr)$_3$)$_4$	**2:** 80%	**3:** Not detected

Scheme 1.

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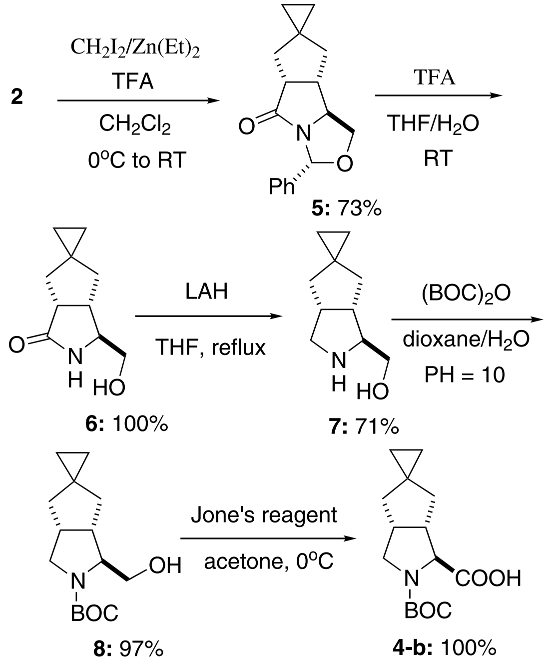

Scheme 2.

yield. The reaction did provide the desired 5,5,5-fused ring system **2**[7] but was accompanied by cycloadduct **3**[8] where the double bond had migrated in the endocyclic position (Scheme 1). Encouraged by this first attempt, we then investigated different conditions aimed at improving the yield of this sequence. The best result was obtained with the use of $Pd(P(OiPr)_3)_4$ (generated in situ with palladium(II) acetate (20 mol%) and triisopropyl phosphite (160 mol%)). The reaction of **1** proceeded cleanly in refluxing toluene to afford exclusively the desired cycloadduct **2**[9] in 80% isolated yield with no detectable amount of byproduct **3**.

With intermediate **2** in hand, we turned our efforts towards preparation of 5,5-fused proline analogs **4**. Synthesis of proline analog **4-b** is illustrated in Scheme 2. Simmons–Smith[10] cyclopropanation of **2**, accomplished via the modified procedure of Shi,[11] led to tetracyclic intermediate **5** in 71% yield. Alcohol **6**, quantitatively obtained from **5** by acidic deprotection of the *N*,*O*-benzylidene acetal was reduced with excess LAH in refluxing THF to give amino alcohol **7**[12] in 71% yield. Protection of **7** under Schotten–Bauman conditions led to the *N*-Boc prolinol **8** in 97% yield. The latter was further oxidized with Jones' reagent to give quantitatively the novel 5,5-fused proline **4-b**[13] in an overall yield of 40% from lactam **1**. Other prolines (Fig. 1) have been synthesized with similar yield and full details regarding their preparation will be published elsewhere.

In conclusion, we have shown that lactam **1** was an excellent substrate for a palladium-assisted trimethylene-methane (TMM) [3+2] cycloaddition reaction. This efficient process was used to quickly assemble the desired framework for the preparation of novel 5,5-fused proline surrogates.

Acknowledgements

We thank Drs. T. M. Chan and A. Evans for HSQC, HSQC-TOCSY experiments and NOE studies, Dr. B. Pramanik, Mr. P. Bartner for high resolution mass spectral data and Drs. J. Wong, J. Kong, and Mr. T. Meng for the preparation of lactam **1**.

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1. Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315–2325.
2. For some reviews, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1; (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49; For an example where TMM entity is incorporated into a five-membered ring, see: (c) Romero, J. M. L.; Sapmaz, S.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2001**, 767–773.
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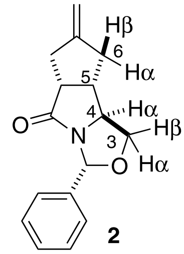
7. Compound **2**:



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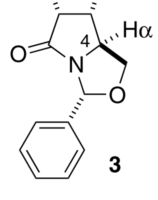
The skeleton of the molecule is readily traced by HSQC and HSQC-TOCSY experiments. The *trans* nature of the cyclization is shown by the presence of a 5-3Hβ NOE and by the larger 6Hα-4Hα than 5-4 interaction. If the addition had been *cis* the 6-4Hα interaction would probably be absent as would the 5-3Hβ NOEs. Also, 5H has a large 6β-5 whereas 4H has large 6Hα-4Hα consistent with 4H and 5H being on opposite sides of the molecule. ^{1}H NMR (DMSO, 300 MHz): δ 7.39–7.30 (m, 5H); 6.04 (s, 1H); 4.84 (bs, 2H); 4.20 (dd, $J=8.5$, 6.0 Hz, 1H); 3.69–3.63 (m, 1H); 3.70–3.48 (m, 1H); 3.17–3.09 (m, 1H); 2.84–2.76 (m, 1H); 2.68–2.54 (m, 2H); 2.30 (dd, $J=22.8$, 16.5 Hz, 2H). ^{13}C NMR (DMSO, 125 MHz): δ 180.8, 149.6, 139.5, 128.4, 128.3 (2C), 125.9 (2C), 107.3, 87.0, 70.2, 65.2, 48.5, 39.4, 38.0, 35.9. HMRS calculated for $C_{16}H_{18}NO_2$ (M+H)=256.1338, found 256.1340. Rotation: $[\alpha]_D=+132°$ (*c* 1, $CHCl_3$).

8. Compound **3**:



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Assignments were made by HSQC and HSQC-TOCSY experiments. The *anti* stereochemistry of addition and the position of the *endo*-double bond is indicated by the presence of a 6-4Hα NOE. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.27 (m, 5H); 6.06 (bs, 1H); 5.34 (bs, 1H); 4.18 (dd, $J = 7.8$, 6.3 Hz, 1H); 3.73 (dd, $J = 9.0$, 6.0 Hz, 1H); 3.32–3.21 (m, 3H); 2.65–2.57 (m, 1H); 2.35–2.29 (m, 1H); 1.65 (s, 3H). ^{13}C NMR (DMSO, 75 MHz): δ 176.6, 143.5, 141.9, 139.1, 137.6, 128.6, 128.4, 127.5, 126.5, 126.4, 112.3, 87.0, 68.5, 63.1, 33.0, 22.2. HMRS calculated for $C_{16}H_{18}NO_2$ (M+H) = 256.1338, found 256.1340.

9. *Procedure*: To a room temperature solution of lactam **1** (17.2 g, 85 mmol) and (2-(acetoxymethyl)-3-allyl)-trimethylsilane (2.5 equiv., 212 mmol, 39.47 g) in 50 mL of toluene was added under argon $Pd(OAc)_2$ (20 mol%, 17 mmol, 3.8 gram) and $P(OiPr)_3$ (1.6 equiv., 138 mmol, 28.70 g). The mixture was refluxed for 13 h, cooled down then directly loaded on a Biotage 75M (400 g Silica) cartridge. Flash chromatography (30 to 100% EtOAc–hexane) afforded **2** (17.34 g, 80% yield) as a colorless oil.
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12. Work-up was carried out following Micovic's procedure. See: Micovic, V. M.; Mihailovic, M. L. J. *J. Org. Chem.* **1953**, *18*, 1190.
13. Compound **4-b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (dd, $J =$ 17.1, 2.4 Hz, 1H); 3.55–3.32 (m, 2H); 2.74–2.69 (m, 2H); 1.90–1.73 (m, 2H); 1.55–1.37 (m, 2H); 1.32 (s, 9H); 0.50–0.32 (m, 4H). HMRS calculated for $C_{15}H_{24}NO_4$ (M+H) = 282.1705, found 282.1710. Rotation: $[\alpha]_D = -16.4°$ (*c* 0.9, MeOH).