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The addition of 2-*tert*-butyldimethylsilyloxyfuran to cyclic *N*-acyliminium ions containing cyclohexyl-based chiral auxiliaries

Marcelo G. M. D'Oca,[a] Ronaldo A. Pilli[a,*] and Ivo Vencato[b]

[a]*Instituto de Química, Unicamp, Campinas SP 13083-970, Brazil*
[b]*Departamento de Química, UFSC, Florianópolis SC 88040-900, Brazil*

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Abstract

The vinylogous Mannich addition of silyloxyfuran **5** to chiral five- and six-membered *N*-acyliminium ions derived from **3**/**4a**,**b** occurred exclusively through the addition to the *N*-acyliminium *Si* face to provide *threo*-**6**/**7a**,**b** as the major isomer (73–84% yield, 2:1–7:1 diastereoisomeric ratio) which were converted to the corresponding bicyclic lactams **10** and **11** with efficient recovery of the chiral auxiliary.

The development of synthetic methodologies for the preparation of optically active pyrrolidine and piperidine derivatives constitutes an area of living interest due to the presence of these heterocycles in many biologically active natural compounds. Particularly, the addition of carbon nucleophiles to *N*-acyliminium ions has been the key step in several approaches to azaheterocycles.[1]

Comins and coworkers revealed that the addition of Grignard reagents[2] and zinc enolates[3] to chiral *N*-acylpyridinium salts containing cyclohexyl-based chiral auxiliaries[4] such as 8-phenylmenthyl and *trans*-2(α-cumyl)cyclohexyl afforded 2,3-dihydro-4-pyridones in good yield and diastereoselectivity.

We were attracted by the possibility of using (1*R*,2*S*)-*trans*-phenylcyclohexyl and (1*R*,2*S*,5*R*)-8-phenylmenthyl as chiral auxiliaries during the addition of carbon nucleophiles to the chiral five- and six-membered *N*-acyliminium ions formed in situ from the corresponding 2-methoxy pyrrolidines **3a**,**b** and 2-methoxy piperidines **4a**,**b** available through anodic oxidation[5] of chiral carbamates **1a**,**b** and **2a**,**b**, respectively (62–76% yield).

Our ongoing interest in the chemistry of the *Stemona*[6] and pumiliotoxin[7] alkaloids led us to investigate the vinylogous Mannich addition of 2-*tert*-butyldimethylsilyloxyfuran (**5**)[8] to chiral

* Corresponding author. E-mail: pilli@iqm.unicamp.br

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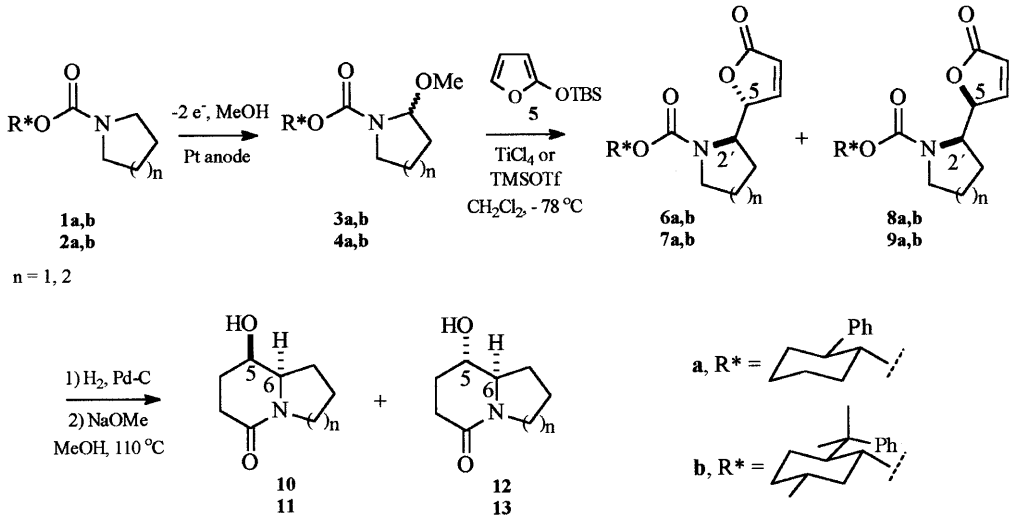
N-acyliminium ions derived from **3a**,**b** and **4a**,**b** (Scheme 1). The reaction of 2-methoxy carbamates **3a** and **4a** with silyloxyfuran **5** was initially carried out in CH_2Cl_2 at −78°C with $TiCl_4$ as the Lewis acid to afford in both cases only two out of four possible diastereoisomers in 60 and 55% yield, respectively. Later, we found that catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[9] afforded improved yields of **6a**/**8a** and **7a**/**9a** (84 and 75%, respectively).



Scheme 1.

The diastereoisomeric ratio for butenolides **6a**/**8a** and **7a**/**9a** could not be unambiguously established at this stage neither by GC–MS analyses (partial thermal epimerization) nor by NMR spectroscopy (broad and multiple signals due to rotational isomers). However, the diastereoisomeric ratios were determined to be 3:1 and 7:1 after hydrogenation of butenolides **6a**/**8a** and **7a**/**9a**, respectively, and GC–MS analyses of the corresponding γ-butyrolactones. The relative stereochemistry of the major diastereoisomer **7a** which crystallized from ethyl acetate–hexane (mp 130.1–130.3°C) was established as 2′*R*,5*R* after X-ray diffraction analysis (Fig. 1),

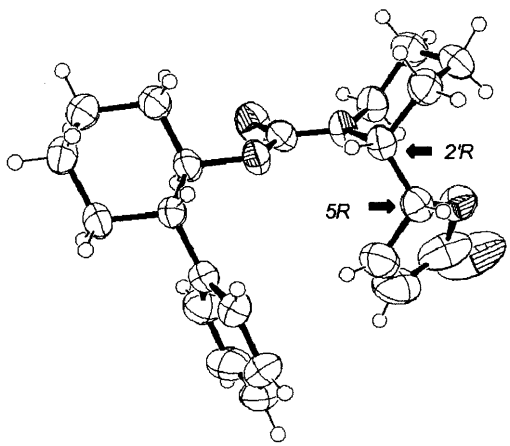


Figure 1. ORTEP drawing of **7a**

in accordance with the relative *threo* stereochemistry reported by Martin,[10] Morimoto[11] and Figadère[12] in the addition of silyloxyfurans to cyclic five-membered *N*-acyliminium ions.

The 2′*R*,5*R* configuration of **6a**, the major butenolide obtained from **3a**, was assigned after X-ray diffraction analysis of the corresponding γ-butyrolactone obtained by catalytic hydrogenation and purified by crystallization from ethyl acetate–hexane (mp 122.3–122.6°C, Fig. 2).

Catalytic hydrogenation of **6a**/**8a** followed by methanolysis afforded hydroxy lactam **10** (70% yield overall) readily separated from the minor isomer **12** by column chromatography on silica gel, accompanied by efficient recovery of (1*R*,2*S*)-*trans*-phenylcyclohexanol (>88% yield). The same experimental protocol afforded hydroxy lactam **11** in 68% yield from **7a**/**9a**. As expected from the 2′*R*,5*R* configuration of **7a**, (5*R*,6*R*)-5-hydroxy-1-azabicyclo[4.4.0]decane-2-one (**11**) displayed *cis* relationship between H-5 and H-6 as shown by NOE experiments: 1.1% increment was observed for H-6 upon irradiation of H-5 while no such increment was observed for **13** thus indicating a *trans* relationship between H-5 and H-6 in the later compound.

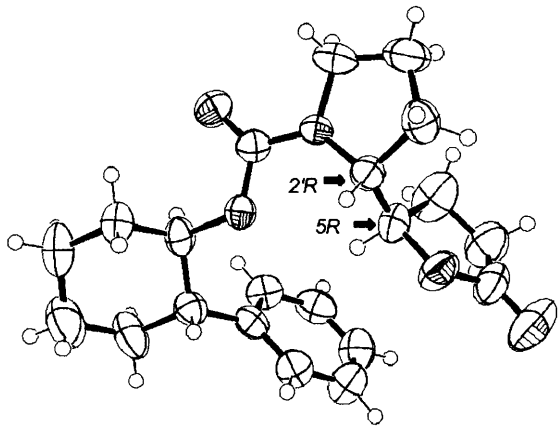


Figure 2. ORTEP drawing of γ-butyrolactone derived from **6a**

The absolute configuration of **13** was suggested to be 5*S*,6*R* after the conversion of both **11** and **13** to the corresponding Mosher esters which revealed H-6 shielded in the ester prepared from **11** and (*S*)-MTPA when compared to the one obtained from (*R*)-MTPA ($\Delta\delta = -0.15$ ppm). The opposite behavior was observed when the Mosher esters derived from **13** and (*S*)- and (*R*)-MTPA ($\Delta\delta = +0.15$ ppm) were compared. The relative shielding observed for H-6 in the (*S*)-MTPA derived from **11** translated into *R* configuration at C-6 when the Mosher model[13] or the Kakisawa model for cyclic secondary alcohols[14] were applied, as expected from the known 5*R*,6*R* configuration of **11**. Accordingly, the relative deshielding of H-6 in the (*S*)-MTPA ester derived from **13** can only be accounted for once *S* configuration is assumed for C-6. Analogous observations for the MTPA esters of (5*R*,6*R*)-5-hydroxy-1-azabicyclo[4.3.0]nonane-2-one (**10**), prepared from the major isomer **6a** and minor isomer **12** (from minor isomer **8a**) led us to assign the 5*S*,6*R* configuration to **12**.

Finally, the diastereoisomeric ratio and the relative configuration of **6b**/**8b** and **7b**/**9b** (obtained from **3b** and **4b** in 80 and 73% yield, respectively) were established after conversion (H_2, Pd–C; then MeONa/MeOH, 110°C) of **6b**/**8b** to a 2:1 mixture of hydroxy lactams **10**/**12** (75% yield) and **7b**/**9b** to a 2:1 mixture of **11**/**13** (70% yield) with recovery of (1*R*,2*S*,5*R*)-8-phenylmenthol in >85% yield.

Overall, these results reveal the exclusive addition of silyloxyfuran **5** to the *Si* face of the *N*-acyliminium ions derived from **3a**,**b** and **4a**,**b** and disclose an attractive route to enantiomerically pure pyrrolidine and piperidine derivatives, particularly bicyclic lactam **11** (45% overall yield from readily prepared **4a**) which is a potentially useful intermediate for the asymmetric synthesis of quinolizidine alkaloids.

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