Towards Simplifying the Chemistry of *N*-Acyliminium Ions: A One-Pot Protocol for the Preparation of 5-Acetoxy Pyrrolidin-2-ones and 2-Acetoxy *N*-Alkoxycarbonyl Pyrrolidines from Imides

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Abstract: A new one-step protocol for the synthesis of acetoxy lactams starting from imides has been developed. This method involves regiospecific reduction of the imide with $LiEt_3BH$, then capture of the transient lithium alkoxide by acetic anhydride.

Key words: *N*-acyliminium ion precursors, imide reduction, $LiEt_3BH$, one-pot process

Reactions between *N*-acyliminium ions and enoxy silanes (the so-called Mannich reaction) have recently emerged as one of the more useful processes in the field of *N*-acyliminium chemistry.[1] Of particular interest are reactions involving chiral *N*-acyliminium ions, which undergo C–C bond formation providing highly substituted adducts bearing at least two controlled stereogenic centers.

As part of a new research programme towards the total synthesis of polyhydroxylated alkaloids based on the Mannich reaction, we needed a straightforward access to enantiopure precursors of endocyclic *N*-acyliminium ions. Although alkoxy lactams can successfully serve this purpose,[2] a literature survey revealed that acetoxy lactams are in general more convenient synthons in such situations.[3] Previous reports have shown that formation of acetoxy lactams from either malic acid,[3a–d] tartaric acid,[3b,3c,3e] or pyroglutamic acid[3j,3k] invariably involves two distinct steps: reduction of the imide with a hydride reagent[3a–f,3j,3k] or cyclization of an amino aldehyde[3g,3i] followed by acetylation of the resulting hydroxy lactam. Even if the more usual reduction–acetylation sequence is high-yielding, it suffers from some drawbacks. For instance, the reduction step has to be conducted very carefully in order to avoid ring-opening due to over reduction of the hydroxy lactam.[4] Moreover, the latter generally needs purification in order to ensure an efficient acylation process. We realized that the preparation of such acetoxy lactams could be improved upon development of a one-pot protocol. Our idea capitalized on the possibility of reduction of the imide by a strong hydride in aprotic medium, and subsequent trapping of the transient metal alkoxide ion in situ with acetic anhydride (Scheme 1).

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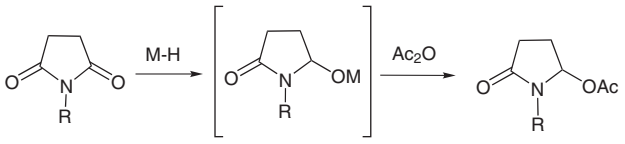
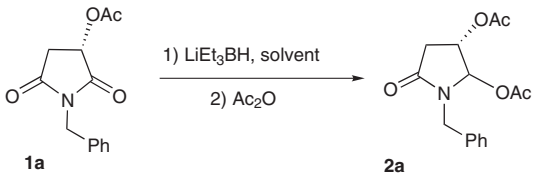
Such tandem reactions are known in the ester[5] and lactone series[6] for the preparation of mixed acetals, and also in the conversion of acyclic imides to amino acetals.[7] However, reports dealing with the preparation of acetoxy lactams using a similar strategy were not known.[8]

Herein we report some preliminary results demonstrating the feasibility of the hypothesis described above.



Scheme 1

Our first experiments focused on the well-known (*3S*)-acetoxy imide **1a** derived from L-malic acid.[3a–d] In a recent report dealing with a similar one-pot preparation of medium-sized ring *N*-acyliminium ion precursors using DIBAL-H as the reductant, it was shown that acetic anhydride was unreactive towards the alkoxide ion intermediate.[8] Also, other unsuccessful attempts made by our group in relation to ester reduction (DIBAL-H) followed by in situ tosylation prompted us to use $LiEt_3BH$ as the reductant.[9] We expected that the transient lithium alkoxide would be more nucleophilic toward acetic anhydride (Scheme 2).



Scheme 2

A series of feasibility experiments were conducted on a 100 mg scale and we found the overall process quite effective using a small excess of $LiEt_3BH$ (1.15 equiv), followed by immediate addition of acetic anhydride (1.35 equiv). Dichloromethane appeared to be superior to THF as solvent and the best yields (90%) were achieved when both reduction and acylation were performed at –78 °C. We also found that the majority of residues could be removed by addition of charcoal to the reaction mixture and

subsequent filtration through a Celite pad, thus avoiding hydrolysis of the water-sensitive acetoxy lactams. Under these conditions, only trace amounts of acetic anhydride were observed in the crude products by ^{1}H NMR spectroscopy, making **2a** ready for further synthetic manipulations without the need for purification. Importantly, the reaction could be successfully scaled up to 15 g without loss of efficiency, further demonstrating the synthetic relevance of our protocol.

The ^{1}H NMR spectrum of the crude product proved that the reaction occurred with complete stereoselectivity. The values of the chemical shifts and coupling constants were in accordance with a *cis* relationship between the two acetate groups.[3a]

Having demonstrated that our process rivaled Speckamp's two-step method[3a–e] in terms of both yield and stereoselectivity, we focused on extending its scope. Other chiral and achiral cyclic imides **1b–q** (Figure 1) were synthesized according to known procedures either from L-malic acid (**1b–e**),[10,11] L-tartaric acid (**1f–h**),[12–14] phthalamide anhydride (**1i–k**), or succinic anhydride (**1l–p**). Various *N*-alkoxycarbonyl pyrrolidines, readily available from (*R*) and (*S*)-pyroglutamic acid (**3a–e**)[15–18] were also evaluated.

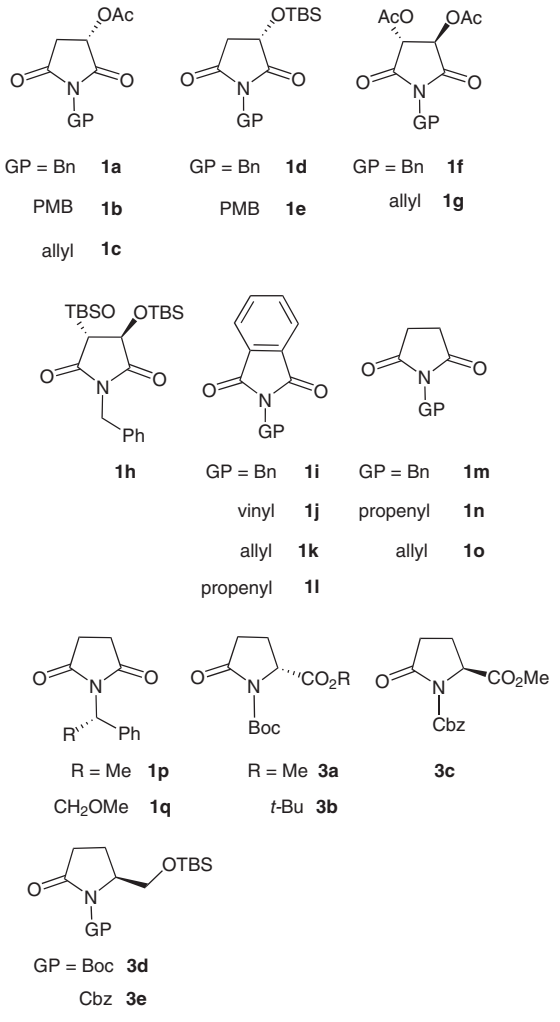


Figure 1

Reaction of **1d** (1 g scale) under the optimized conditions gave the expected amide **2d** as a single stereomer in good yield (Table 1, entry 3), demonstrating that a trialkylsilyl protecting group is tolerated. It is noteworthy that the reaction could not be extrapolated as well as in the case of the acetate **1a**, since a decreased yield was observed when the reaction was scaled up.[19] Steric effects seem then to be a limiting factor in this reaction. Both PMB and allyl protecting groups are well tolerated, as demonstrated by the good yields obtained for the acetoxy lactams **2b**, **2c**, and **2e** (Table 1, entries 1, 2, and 4).

Table 1 Reduction–Acetylation of Chiral Imides under Optimized Reaction Conditions[a]

Entry	Imides	Acetoxy lactams (isolated yield)	*trans*/*cis*
1[b]	**1b**	**2b** (88%)	0:100
2[c]	**1c**	**2c** (79%)	0:100
3[b]	**1d**	**2d** (75%)	0:100
4[b]	**1e**	**2e** (76%)	8:92
5[b]	**1f**	**2f** (95%)	100:0
6[b]	**1g**	**2g** (80%)	100:0
7	**1h**	**2h** (30%)	100:0
8	**1i**	**2i** (50%)	–
9	**1j**	**2j** (81%)	–
10	**1k**	**2k** (83%)	–
11	**1l**	**2l** (60%)	–
12	**1m**	see text	–
13	**1n**	**2n** (60%)	–
14	**1o**	see text	–
15	**1p**	**2p** (0%)	–
16	**1q**	**2q** (0%)	–
17	**3a**	**4a** (100%)[c,d,e]	–
18	**3b**	**4b** (96%)[c,d,e]	–
19	**3c**	**4c** (77%)[c]	–
20	**3d**	see text	–
21	**3e**	see text	–

[a] The reaction was carried out on a 1 mmol scale unless otherwise indicated.
[b] The reaction was carried out on a 1 g scale.
[c] The reaction was carried out on a 5 g scale.
[d] A mixture of stereomers and/or N-invertomers was detected in the ^{1}H NMR spectrum; the stereochemistry was not determined.
[e] Crude yield is given.

The easy access to acetates **2f–h** (Table 1, entries 5–7) proves that our protocol can be applied to tartarimides bearing different protecting groups. The reaction occurred with high to complete diastereoselectivity. Based on the $J_{4,5}$ coupling constant values (1.5–2.3 Hz), and in contrast to the malic acid series, the hydride delivery seems to have proceeded with *trans* stereoselectivity with respect to the neighboring hydrogen. The moderate yield obtained by starting from the *bis*-OTBS compound **1h** confirms that sterics can limit the scope of the process (Table 1, entry 7).[20] Not unexpectedly taking steric considerations into account, imides **1p–q** bearing chiral auxiliaries at nitrogen proceeded unfavorably in the reduction–acetylation process, affording hydroxy lactams exclusively, instead of the desired acetoxy lactams after work-up (Table 1, entries 15 and 16).[21] The presence of an additional oxygen atom in **1q** significantly retarded the reduction step, for which 2.5 equivalents of reductant was necessary to ensure complete reaction.

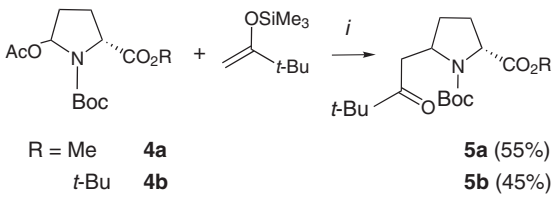
Succimide and glutarimide derivatives bearing no substituent on their carbon framework are known to be prone to competitive ring-opening during reduction.[4,22]

Accordingly, the reduction–acetylation of *N*-allyl and *N*-benzyl succinimides **1m** and **1o** furnished complex reaction mixtures containing recovered starting material, hydroxy lactams, and the linear amido acetates (Table 1, entries 12 and 14). On the other hand, the *N*-propenyl succinimide **1n**, in which the lone pair of electrons on the nitrogen is conjugated with the pendant double bond, gave the desired acyloxy lactam **2n** in good yield (Table 1, entry 13). As expected, the analogous and less sensitive phthalimides were readily reduced and acetylated to afford acetates **2i–l** in fair to good yields (Table 1, entries 8–11).

N-Acyl pyrrolidine esters **3a–c** derived from pyroglutamic acid gave clean reduction–acetylation processes as judged by TLC and the ^{1}H NMR spectra of the crude products **4a–c** (Table 1, entries 17–19). The stereochemical assignment of the products formed by ^{1}H NMR spectroscopy proved to be difficult due to the presence of rotamers. The *N*-Boc adducts **4a** and **4b** turned out to be very sensitive – after purification on silica gel, only the corresponding hydroxy lactams were obtained. This stands in sharp contrast with results previously reported by Barrett, in which related products were synthesized and successfully purified on silica gel,[23] but corroborates recent observations made by Kobayashi and co-workers in the piperidine series.[24]

Fortunately, our work-up procedure with charcoal and Celite resulted in the removal of almost all residues originating from the reagents as evidenced by ^{1}H NMR spectroscopy (Table 1, entries 17 and 18). Virtually pure acetoxy lactams **4a** and **4b** were then obtained without the need for further purification and were easily alkylated as such through their *N*-acyliminium ions (Scheme 3, yields unoptimized).

The *N*-Cbz acetate **4c** appeared to be more robust and could be purified on silica gel without difficulty (Table 1, entry 19). On the other hand, reduction and acetylation of both the *N*-Boc and *N*-Cbz protected alcohols **3d** and **3e** gave troublesome results, with formation of at least three products (TLC, Table 1, entries 20 and 21). Examination of the ^{1}H NMR spectra of the crude mixtures revealed small integration values for the proton adjacent to the newly formed acetate group (δ = 6 ppm) and the related methyl group (δ = 2 ppm), suggesting the formation of competitive ring-opening products.[4]



Scheme 3 *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$ (1.2 equiv), CH_2Cl_2, –65 °C to –50 °C, work-up.

Similar results were obtained with *N*-Cbz pyrrolidine and piperidine (results not shown). In these cases, even the usual two-step strategy failed to produce the desired acetoxy lactams probably due to their instability. In light of these results, we recommend the use of 2-methoxy or 2-ethoxy derivatives as *N*-acyliminium ion precursors for pyrrolidines and piperidines bearing no substituent on their C3 and C4 (pyrolidine) or C3–C5 (piperidine) fragment and lacking an alkoxycarbonyl substituent at C5 and C6.

In summary, we have developed a new protocol for accessing 2-acetoxy pyrrolidin-5-ones from parent cyclic imides. These are useful precursors of *N*-acyliminium ions. Our one-pot procedure provides a shortened alternative to known methodologies and is especially relevant for chiral compounds derived from malic and tartaric acids. This process proved to be competitive with the usual two-step procedure in terms of efficiency, rapidity, generality, and stereochemistry and could also be applied to esters of pyrroglutamic acid.

All melting points were measured on a Boetius micro hotstage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ at 25 °C. IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 Spectrometer. TLC were performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc–hexanes as eluent. Reaction components were then visualized under UV light and dipped in Dragendorff solution. Silica gel (230–400 mesh) was used for flash chromatography. All reactions were performed under an inert atmosphere. MS and elemental analyses were not carried out due to the thermal sensitivity of the acetates. Analytical data of **2a**,[3a] **2b**,[3a] and **2h**[13] were identical to those reported in the literature.

One-Pot Reduction–Acetylation Process; Typical Procedure

To a solution of imide **1a** (15 g, 60.7 mmol) in anhyd CH_2Cl_2 (250 mL) was added dropwise at –78 °C a commercially available solution of $LiEt_3BH$ (1 M in THF; 69.8 mL, 69.8 mmol). The solution was stirred for 15 min and Ac_2O (7.75 mL, 81.9 mmol) was added dropwise at –78 °C. The solution was allowed to slowly warm to r.t. and stirred for an additional 20 h. Charcoal was added to the solu-

tion, which was then stirred for 15 min and filtered through a Celite pad. The solvents were carefully removed under vacuum to give white crystals which were purified by flash chromatography (cyclohexane–EtOAc, 1:1) to give acetoxy lactam **2a**[1] in 90% yield; mp 83–84 °C; $[\alpha]_D^{25}$ +2.8 (*c* 0.5, acetone).

(2*S*,3*S*)-1-Allyl-5-oxopyrrolidine-2,3-diyl Diacetate (2c)
Colorless oil; $[\alpha]_D^{25}$ –32.9 (*c* 0.9, EtOH).

IR ($CHCl_3$): 1733, 1673, 1644 cm^{-1}.

^1H NMR: δ = 2.09 (s, 3 H), 2.11 (s, 3 H), 2.59 (dd, *J* = 9.4, 16.4 Hz, 1 H), 2.73 (dd, *J* = 7.8, 16.4 Hz, 1 H), 3.66 (dd, *J* = 7.0, 15.6 Hz, 1 H), 4.12 (dd, *J* = 5.4, 15.6 Hz, 1 H), 5.07–5.20 (m, 2 H), 5.30 (ddd, *J* = 4.7, 7.8, 9.4 Hz, 1 H), 5.60–5.82 (m, 1 H), 6.27 (d, *J* = 4.7 Hz, 1 H).

^{13}C NMR: δ = 20.8, 21.0, 34.2, 43.8, 66.3, 81.8, 118.9, 131.9, 170.2, 170.4, 171.6.

(2*S*,3*S*)-1-Benzyl-3-{[*tert*-butyl(dimethyl)silyl]oxy}-5-oxopyrrolidin-2-yl Acetate (2d)
Colorless oil; $[\alpha]_D^{25}$ +12 (*c* 0.098, EtOH).

IR ($CHCl_3$): 1745, 1712, 1246, 730 cm^{-1}.

^1H NMR: δ = 0.02 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 1.95 (s, 3 H), 2.49 (dd, *J* = 8.6, 15.7 Hz, 1 H), 2.59 (dd, *J* = 7.8, 15.7 Hz, 1 H), 4.21 (d, *J* = 14.9 Hz, 1 H), 4.37 (ddd, *J* = 4.7, 7.8, 8.6 Hz, 1 H), 4.70 (d, *J* = 14.9 Hz, 1 H), 6.11 (d, *J* = 4.7 Hz, 1 H), 7.20–7.40 (m, 5 H).

^{13}C NMR: δ = –5.0, –4.9, 18.0, 20.9, 25.7, 37.6, 44.8, 66.4, 83.3, 127.9, 128.6, 128.9, 136.3, 170.5, 173.0.

(2*S*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(4-methylbenzyl)-5-oxopyrrolidin-2-yl Acetate (2e)
White solid; mp 51 °C; *cis*/*trans*, 92:8.

IR ($CHCl_3$): 1740, 1709, 1248 cm^{-1}.

^1H NMR: δ = 0.00 (s, 3 H, *cis*, 92%), 0.02 (s, 3 H, *cis*), 0.12 (s, 3 H, *trans*, 8%), 0.15 (s, 3 H, *trans*), 0.81 (s, 9 H, *cis*), 0.88 (s, 9 H, *trans*), 1.95 (s, 3 H, *cis*), 2.02 (s, 3 H, *trans*), 2.47 (dd, *J* = 8.6, 15.7 Hz, 1 H, *cis*/*trans*), 2.57 (dd, *J* = 7.8, 15.7 Hz, 1 H, *cis*/*trans*), 3.77 (s, 3 H, *cis*/*trans*), 4.06 (d, *J* = 14.9 Hz, 1 H, *cis*/*trans*), 4.30 (ddd, *J* = 4.7, 7.8, 8.6 Hz, 1 H, *cis*/*trans*), 4.64 (d, *J* = 14.9 Hz, 1 H, *cis*), 4.65 (d, *J* = 14.9 Hz, 1 H, *trans*), 5.95 (dd, *J* = 2.2, 6.3 Hz, 1 H, *trans*), 6.05 (d, *J* = 4.7 Hz, 1 H, *cis*), 6.82 (d, *J* = 8.6 Hz, 2 H, *cis*/*trans*), 7.15 (d, *J* = 8.6 Hz, 2 H, *cis*/*trans*).

^{13}C NMR: δ = –4.8, –4.7, 18.2, 21.2, 25.8, 37.8, 44.2, 55.6, 66.6, 83.4, 114.4, 128.5, 130.2, 159.5, 170.7, 173.0.

(2*S*,3*R*,4*R*)-1-Benzyl-5-oxopyrrolidine-2,3,4-triyl Triacetate (2f)
Colorless oil; $[\alpha]_D^{25}$ +22.9 (*c* 0.11, EtOH).

IR ($CHCl_3$): 2252, 1753, 1731, 1371 cm^{-1}.

^1H NMR: δ = 1.90 (s, 3 H), 2.09 (s, 3 H), 2.20 (s, 3 H), 4.36 (d, *J* = 14.9 Hz, 1 H), 4.67 (d, *J* = 14.9 Hz, 1 H), 5.22 (dd, *J* = 1.6, 3.9 Hz, 1 H), 5.37 (d, *J* = 3.9 Hz, 1 H), 6.06 (d, *J* = 1.5 Hz, 1 H), 7.20–7.40 (m, 5 H).

^{13}C NMR: δ = 20.6, 20.7, 45.0, 73.3, 76.0, 83.6, 128.1, 128.3, 128.9, 135.3, 167.9, 169.7, 169.8, 169.9.

(2*S*,3*R*,4*R*)-1-Allyl-5-oxopyrrolidine-2,3,4-triyl Triacetate (2g)
White solid; mp 48–49 °C; *trans* (2*S*,3*R*)/*cis* (2*R*,3*R*), 86:14.

IR ($CHCl_3$): 1732, 1675, 1646 cm^{-1}.

^1H NMR: δ = 2.09 (s, 3 H), 2.11 (s, 3 H), 2.15 (s, 3 H), 3.45 (dd, *J* = 7.0, 15.7 Hz, 1 H), 4.11 (dd, *J* = 5.5, 15.7 Hz, 1 H, *cis*, 14%), 5.14–5.36 (m, 4 H), 5.62–5.82 (m, 1 H), 6.11 (d, *J* = 1.5 Hz, 1 H), 6.31 (d, *J* = 4.7 Hz, 1 H, *cis*).

^{13}C NMR: δ = 20.5, 20.7, 26.8, 43.4, 73.9, 75.9, 83.5, 118.5, 131.1, 167.4, 169.5, 169.7.

2-Benzyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl Acetate (2i)
White solid; mp 73–75 °C.

IR ($CHCl_3$): 1776, 1740, 1709 cm^{-1}.

^1H NMR: δ = 1.88 (s, 3 H), 4.56 (d, *J* = 14.8 Hz, 1 H), 4.84 (d, *J* = 14.8 Hz, 1 H), 6.86 (s, 1 H), 7.13–7.29 (m, 5 H), 7.40–7.54 (m, 3 H), 7.77–7.97 (m, 1 H).

^{13}C NMR: δ = 21.0, 44.5, 81.1, 124.0, 127.9, 128.5, 128.9, 130.5, 132.0, 132.8, 136.9, 141.2, 168.1, 171.2.

2-Vinyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl Acetate (2j)
White solid; mp 70–72 °C.

IR ($CHCl_3$): 1723, 1643 cm^{-1}.

^1H NMR: δ = 2.11 (s, 3 H), 4.55 (d, *J* = 16.4 Hz, 1 H), 4.59 (d, *J* = 9.4 Hz, 1 H), 7.04 (dd, *J* = 9.4, 16.4 Hz, 1 H), 7.45–7.60 (m, 3 H), 7.80 (d, *J* = 6.2 Hz, 1 H).

^{13}C NMR: δ = 21.1, 79.5, 95.8, 124.3, 124.4, 127.0, 130.9, 131.2, 133.7, 141.1, 165.8, 171.1.

2-Allyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl Acetate (2k)
White solid; mp 62–63 °C.

IR ($CHCl_3$): 1740, 1712, 1645 cm^{-1}.

^1H NMR: δ = 2.11 (s, 3 H), 3.91 (ddt, *J* = 1.5, 6.2, 15.6 Hz, 1 H), 4.35 (ddt, *J* = 1.5, 6.2, 15.6 Hz, 1 H), 5.15–5.24 (m, 2 H), 5.72–5.91 (m, 1 H), 7.00 (s, 1 H), 7.40–7.76 (m, 3 H), 7.78–7.82 (m, 1 H).

^{13}C NMR: δ = 21.2, 43.2, 81.2, 118.1, 123.9, 124.1, 130.5, 132.1, 132.7, 132.8, 141.2, 167.8, 171.2.

2-Propenyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl Acetate (2l)
White solid; mp 57–59 °C.

IR ($CHCl_3$): 1739, 1644 cm^{-1}.

^1H NMR: δ = 1.78 (dd, *J* = 1.5, 7.0 Hz, 3 H), 2.16 (s, 3 H), 5.20 (qd, *J* = 7.0, 14.8 Hz, 1 H), 6.87 (qd, *J* = 1.5, 14.8 Hz, 1 H), 7.50–7.64 (m, 3 H), 7.78–7.82 (m, 1 H), 7.81–7.86 (m, 1 H).

^{13}C NMR: δ = 15.9, 21.2, 80.1, 108.6, 122.0, 124.2, 124.3, 130.8, 131.5, 133.3, 141.1, 165.5, 171.2.

1-Propenyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl Acetate (2n)
Colorless oil.

IR ($CHCl_3$): 1707, 1674 cm^{-1}.

^1H NMR: δ = 1.68 (dd, *J* = 1.5, 6.2 Hz, 3 H), 2.08 (s, 3 H), 2.23–2.80 (m, 4 H), 5.12 (qd, *J* = 7.0, 14.0 Hz, 1 H), 6.45 (d, *J* = 5.5 Hz, 1 H), 6.62 (dd, *J* = 1.5, 14.0 Hz, 1 H).

^{13}C NMR: δ = 15.7, 21.3, 26.6, 28.9, 83.12, 109.45, 122.2, 170.7, 173.4.

(5*R*)-2-Acetoxy-1,5-pyrrolidinedicarboxylic Acid 5-Methyl 1-*tert*-Butyl Diester (4a)
Colorless oil.

IR ($CHCl_3$): 2253, 1734, 1707, 1380 cm^{-1}.

^1H NMR: δ = 1.43 (s, 9 H), 1.95–2.15 (m, 3 H), 2.08 (s, 3 H), 2.30–2.40 (m, 1 H), 3.77 (s, 3 H), 4.20–4.35 (m, 1 H), 6.48 (br s, 1 H).

^{13}C NMR: δ = 22.3, 27.2, 27.9, 28.3, 32.2, 32.7, 52.3, 59.6, 60.2, 81.5, 83.4, 84.0, 152.7, 153.0, 166.6, 170.5, 170.7, 172.6, 172.9.

(5*R*)-2-Acetoxy-1,5-pyrrolidinedicarboxylic Acid 1,5-di-*tert*-Butyl Diester (4b)
White solid; mp 74–76 °C.

IR ($CHCl_3$): 2973, 1728, 1707, 1394, 1369 cm^{-1}.

^1H NMR: δ = 1.45 (s, 9 H), 1.49 (s, 9 H), 1.52–1.67 (m, 1 H), 1.75–1.95 (m, 1 H), 1.90–2.10 (m, 1 H), 2.07 (s, 3 H), 2.23–2.37 (m, 1 H), 4.05–4.3 (m, 1 H), 6.40–6.50 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4, 21.5, 21.7, 27.2, 28.1, 28.2, 28.4, 32.1, 32.7, 60.1, 60.2, 60.5, 60.7, 60.8, 81.3, 83.5, 84.3, 88.6, 88.9, 89.5, 93.3, 170.5, 170.7, 171.2, 171.5, 171.9.

(5*R*)-2-Acetoxy-1,5-pyrrolidinedicarboxylic Acid 1-Benzyl 5-Methyl Diester (4c)

Colorless oil.

IR ($CHCl_3$): 3153, 2253, 1740, 1713 cm^{-1}.

^1H NMR: δ = 1.95–2.15 (m, 3 H), 2,04 (s, 3 H), 2.28–2.34 (m, 1 H), 3.58 (s, 0.5 H, *N*-invertomer), 3.75 (s, 0.5 H, *N*-invertomer), 4.26–4.35 (m, 1 H), 5.00–5.18 (m, 2 H), 6.51 (br s, 1 H).

^{13}C NMR: δ = 21.0, 24.4, 26.7, 27.6, 31.5, 31.7, 32.3, 52.1, 59.5, 67.3, 83.0, 84.0, 127.5, 127.5, 127.7, 127.7, 127.9, 128.2, 135.7, 170.1, 170.1, 171.3, 171.8, 172, 174.3.

References

(1) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(2) (a) Lennartz, M.; Sadakane, M.; Stekhan, E. *Tetrahedron* **1999**, *55*, 14407. (b) deKoning, H.; Hiemstra, H.; Speckamp, W. N.; Moolenaar, M. J. *Eur. J. Org. Chem.* **1998**, 1729. (c) Pilli, R. A.; Diaz, C. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717. (d) Dhimane, H.; Vanucci-Bacque, C.; Hamon, L.; Lhommet, G. *Eur. J. Org. Chem.* **1998**, 1555. (e) Shono, T.; Matsumara, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. For some recent reviews, see: (f) DeShong, P.; Pilcher, A. S. *J. Org. Chem.* **1996**, *61*, 6901. (g) Konno, H.; Toshiro, E.; Hinoda, N. *Synthesis* **2003**, 2161. (h) Satoh, T.; Shimura, T.; Sakai, K. *Heterocycles* **2003**, *59*, 137. (i) Amishiro, N.; Denmark, S. E. *J. Org. Chem.* **2003**, *68*, 6997.

(3) (a) Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603. (b) Russowski, D.; Pilli, R. A.; Petersen, R. Z.; Godoi, M. N. *Tetrahedron Lett.* **2000**, *41*, 9939. (c) Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605. (d) Russowski, D.; Pilli, R. A. *J. Org. Chem.* **1996**, *61*, 3187. (e) Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenar, M. J.; Speckamp, W. N.; Kaptein, B.; Schoenmaker, H. E. *Tetrahedron Lett.* **1994**, *35*, 1087. (f) Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron* **2002**, *58*, 9359. (g) MacDonald, S. F. J.; Spooner, J. E.; Dowle, M. D. *Synlett* **1998**, 1375. (h) Smith, A. B. III; Salvatore, B. A.; Hull, K. G.; Duan, T. J. W. *Tetrahedron Lett.* **1991**, *32*, 4859. (i) Katsuki, H.; Iwasaki, M.; Ochi, M. *Heterocycles* **1994**, *38*, 17. (j) Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G. *Tetrahedron Lett.* **1994**, *35*, 4019. (k) Altman, K. H. *Tetrahedron Lett.* **1993**, *34*, 7721.

(4) Altman, K. H.; Freier, S. M.; Pieles, U.; Winkler, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1654; see also references 3i and 3j.

(5) (a) Dahanukar, V. H.; Rychnowski, S. D. *J. Org. Chem.* **1996**, *61*, 8317. (b) Kopecky, D. J.; Rychnowski, S. D. *J. Org. Chem.* **2000**, *65*, 191.

(6) Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747; see also reference 5a.

(7) Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Commun.* **2002**, 1064.

(8) As our study was in progress a publication dealing with the one-pot synthesis of 7–9-membered ring *N*,O-acetal TMS ethers from the parent imides was reported: Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Tetrahedron Lett.* **2002**, *43*, 3165.

(9) For the conversion of imides into hydroxy lactams by $LiEt_3BH$, see: (a) Zanardi, P.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1167. (b) Vittoria-Chiesa, M.; Manzoni, L.; Scholastico, C. *Synlett* **1996**, 441. (c) Kim, Y. K.; Kitahara, T. *Tetrahedron Lett.* **1997**, *38*, 3423. (d) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011; see also references 2d and 3i.

(10) (a) Wistrand, L. G.; Thaning, M. *J. Org. Chem.* **1990**, *55*, 1406. (b) Keum, G.; Kim, G. *Bull. Korean Chem. Soc.* **1994**, *15*, 278.

(11) Chamberlin, A. R.; Chung, J.-Y.-L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(12) Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022.

(13) Ryu, Y.; Kim, G. *J. Org. Chem.* **1995**, *60*, 103.

(14) (a) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054. (b) Ohwada, J.; Inouye, Y.; Kimura, M.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 287.

(15) Compound **5a** was prepared according to the procedure described in the following article: Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789.

(16) For the preparation of **5c**, see: Lee, Y. S.; Cho, D. J.; Kim, S. N.; Choi, J. H.; Park, H. *J. Org. Chem.* **1999**, *64*, 9727.

(17) For preparation of **5b**, see: Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353.

(18) Compounds **5d** and **5e** were prepared from (*S*)- and (*R*)-pyroglutamic acid using typical procedures for functional-group transformations similar to those employed for **5a–c**.

(19) The yield of **2b** fell to 63% when 5 g of **1b** was used (the corresponding hydroxy lactam was also isolated in 16% yield) and to 40% when the reaction was carried out on a 7.5 g scale.

(20) The acetate **2h** was obtained in high yield by using a conventional acetylation procedure: (a) Kim, G.; Ryu, Y. *J. Org. Chem.* **1995**, *60*, 103. (b) Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron* **2002**, *58*, 9359.

(21) Hydroxy lactams derived from imides **1p–q** can be acetylated under usual acetylation conditions: Ukaji, Y.; Tsukamoto, K.; Nasada, Y.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1993**, 221.

(22) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(23) Barrett, A. G. M.; Philipauskas, D. *J. Org. Chem.* **1991**, *56*, 2787.

(24) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.