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Enhanced *trans* diastereoselection in the allylation of cyclic chiral *N*-acyliminium ions. Synthesis of hydroxylated indolizidines

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Abstract—A short synthesis of hydroxylated indolizidines is reported. The key steps were the allylation of chiral cyclic *N*-acyliminium ions derived from malic and tartaric acids, followed by ring-closing metathesis.

Polyhydroxylated indolizidine alkaloids are sugar mimics which inhibit glycosidases with promising potential as drugs against viruses, cancers and diabetes.[1] A large number of representative structures were isolated from natural sources and the synthesis of the corresponding stereoisomers and analogues is actively pursued particularly for structure–activity studies.[1,2] A variety of methods have been reported for the synthesis of indolizidine alkaloids and lentiginosine, swainsonine, and castanospermine (Fig. 1) rank among the more popular synthetic targets.

An useful synthetic approach to the structural motif found in this family of alkaloids is the allylation of the *N*-acyliminium ion derived from malic or tartaric acids. In fact, the stereochemical outcome of the addition of allyltrimethylsilane to *N*-acyliminium ions derived from imides **2** and **3** has being examined previously. Speckamp[3a] and Scolastico[3b] reported on the moderate *trans* preference (up to 3:1 ratio) in the addition of allyltrimethylsilane to the *O*-acetyl *N*-benzyl acyliminium ion derived from malic acid and reversal of the sense of diastereoselection (up to 4:1 *cis*:*trans* ratio) was observed when *O*-TBS and *O*-benzyl derivatives were employed.[3b,c]

In the course of an investigation aimed to prepare C-1/C8a *trans*-configured hydroxylated indolizidines, we evaluated the influence of the Lewis acid on the addition of allyltrimethylsilane and allyltributyltin to *N*-acyliminium ions[4] derived from malic and tartaric acids.

To this purpose, *N*-allyl imide **2** was prepared from inexpensive L-malic acid in 92% yield, according to literature procedure (Scheme 1).[3a] In order to investigate the effect of the nature of the *O*-protective group in the allylation reaction, imide **2** was converted to **3** by treatment with acetyl chloride in ethanol, followed by TBS protection. Regioselective reduction of **2** and **3**, and acetylation provided intermediates **4** and **5** in good yield.

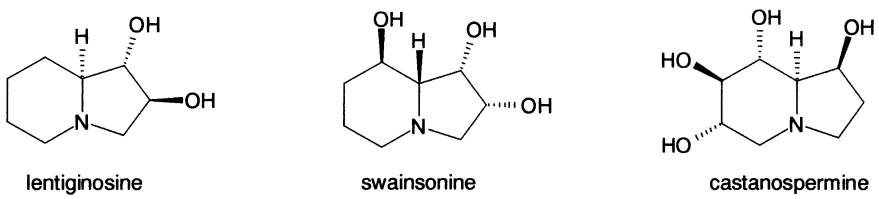

Figure 1.

Keywords: hydroxylated indolizidines; allylation; *N*-acyliminium ions; olefin metathesis.

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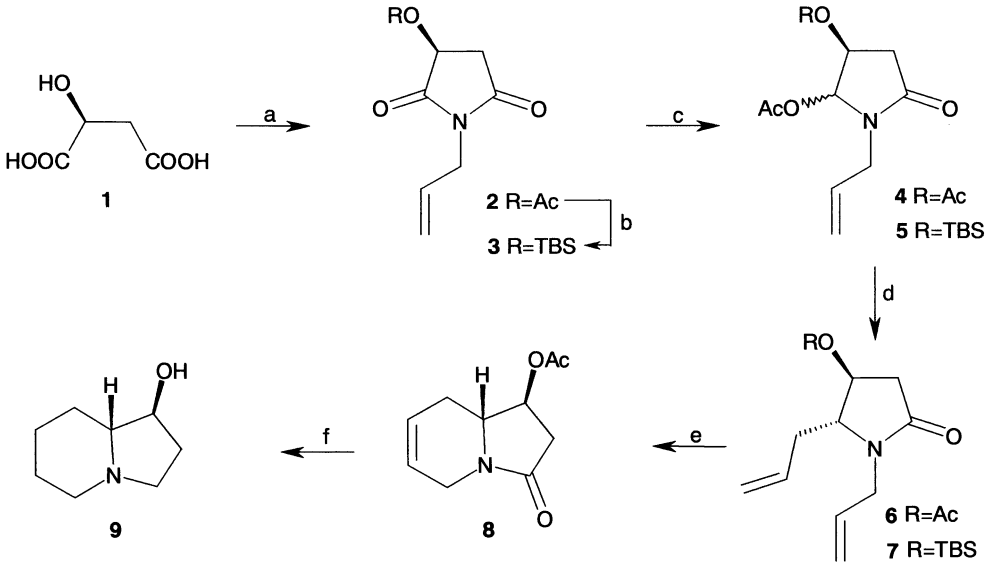


Scheme 1. *Reagents and conditions:* (a) (i) AcCl, reflux; (ii) allylamine, CH_2Cl_2, rt; (iii) AcCl, reflux (**2**, 92%); (b) (i) AcCl, EtOH; (ii) TBSCl, imidazole, DMF (**3**, 80%); (c) (i) $NaBH_4$, EtOH, –23°C; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (**4**, 73%; **5**, 65%); (d) see Table 1; (e) 4 mol% Grubbs' catalyst, CH_2Cl_2 (**8**, 82%; 95% d.e.); (f) (i) H_2, Pd/C, AcOEt; (ii) $LiAlH_4$, THF, reflux (**9**, 78%).

N-allyl lactams **4** and **5** were treated with Lewis acids (4.0 equiv.) to ensure in situ formation of the corresponding *N*-acyliminium ion, followed by the addition of the allyltrimethylsilane or tri-*n*-butylallyltin (Table 1). With most of the Lewis acid investigated, the addition to **4** proceeded in good yield but with *trans* preference within the same range as observed earlier for the *N*-benzyl analogue,[3a,b] including the use of 1.0 equiv. of $TiCl_4$.[5] However, with 4.0 equiv. of $TiCl_4$ preparatively useful 7:1 *trans*:*cis* ratio (83% yield) was observed (entry 6). Coordination of the oxophilic Lewis acid at the neighboring OAc group enforced by the excess of $TiCl_4$ may be the reason for the enhancement of *trans* selectivity.

The addition of allyltributyltin afforded low *trans* selectivity possibly as a result of its superior nucleophilicity.[6] Surprisingly, allyltribuyltin did not react when $SnCl_4$ or $InCl_3$[7] were used as Lewis acid (entry 9 and 10) and the use of $TiCl_4$ led to reversal of selectivity (entry 12). At this point, transmetalation to an allyltitanium species able to coordinate to the *O*-acetyl group cannot be ruled out to explain the *cis* preference observed in this case.[8]

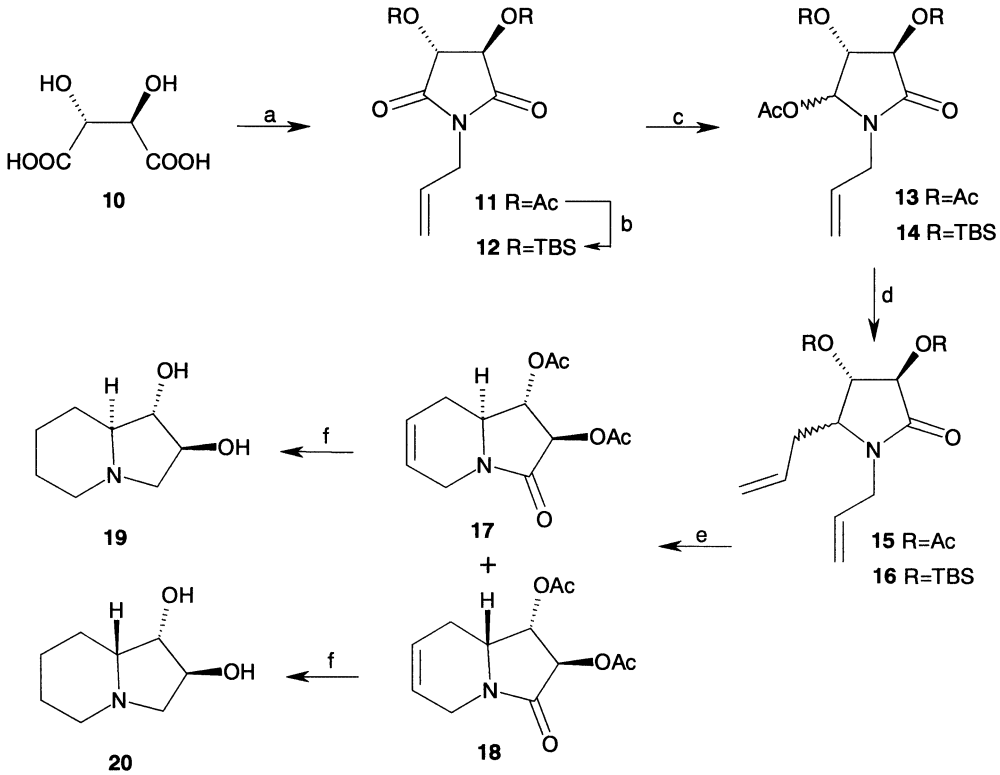
In analogy with previous results,[3c] low *cis* preference (1.8–2.2:1 ratio) was observed for 3-*O*-TBS *N*-allyl lactam **5** (entries 13–17), a result which may be rationalized through the stabilization of the emerging σ* orbital by interaction with the adjacent and antiperiplanar σ_{CH} bond.[9]

The addition of allyltrimethylsilane to *N*-allyl lactam **13** derived from (2*R*,3*R*)-tartaric acid (Scheme 2) either in the presence of 4.0 equiv. of $TiCl_4$ or $BF_3{\cdot}OEt_2$ occurred without stereochemical preference (entries 18 and 19). In order to enforce *cis* addition to *N*-allyl 3-*O*-TBS lactam **14**, the use of $BF_3{\cdot}OEt_2$ and allytributyltin was necessary (entry 21).[10]

Table 1. Effect of Lewis acid and nucleophile in the allylation of chiral cyclic *N*-acyliminiumions derived from malic and tartaric acids (See Scheme 1)[a]

Entry	Substrate	Nucleophile	Lewis acid	*cis*:*trans* ratio[b]
1	**4**	Allylsilane	TMSOTf	1:3.5
2	**4**	Allylsilane	$BF_3{\cdot}OEt_2$	1:2.5
3	**4**	Allylsilane	$SnCl_4$	1:3.2
4	**4**	Allylsilane	$InCl_3$	1:4
5	**4**	Allylsilane	TiF_4[c]	1:2
6	**4**	Allylsilane	$TiCl_4$	1:7
7	**4**	Allylsilane	K-10[d]	1:2.5
8	**4**	Allylstannane	$BF_3{\cdot}OEt_2$	1:1.8
9	**4**	Allylstannane	$SnCl_4$	–[e]
10	**4**	Allylstannane	$InCl_3$	–[e]
11	**4**	Allylstannane	TiF_4[c]	1:1
12	**4**	Allylstannane	$TiCl_4$	2:1
13	**5**	Allylsilane	$BF_3{\cdot}OEt_2$	1.8:1
14	**5**	Allylsilane	$TiCl_4$	2.2:1
15	**5**	Allylstannane	$BF_3{\cdot}OEt_2$	2.2:1
16	**5**	Allylstannane	$MgBr_2$[f]	2.2:1
17	**5**	Allylstannane	$TiCl_4$	1.8:1
18	**13**	Allylsilane	$BF_3{\cdot}OEt_2$	1:1
19	**13**	Allylsilane	$TiCl_4$	1:1
20	**14**	Allylsilane	$BF_3{\cdot}OEt_2$	2.5:1
21	**14**	Allylstannane	$BF_3{\cdot}OEt_2$	4:1

[a] Unless otherwise stated, all reactions were performed in dry CH_2Cl_2 at 0°C, adding 4 equiv. of Lewis acid to a solution of the substrate and 3 equiv. of the nucleophile.
[b] Determined by ^1H NMR and/or GC analysis.
[c] Reaction peformed in CH_3CN/CH_2Cl_2.
[d] 80 mg Montmorillonite K-10 per mmol of substrate, rt.
[e] 5-Hydroxy lactam recovered.
[f] Reaction performed in toluene, rt.



Scheme 2. *Reagents and conditions:* (a) (i) AcCl, reflux; (ii) allylamine, CH_2Cl_2, rt; (iii) AcCl, reflux (**11**, 99%); (b) (i) AcCl, EtOH; (ii) TBSCl, imidazole, DMF (**12**, 83%); (c) (i) $NaBH_4$, EtOH, −23°C; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (**13**, 76%; **14**, 69%); (d) see Table 1 (**15**, 89%; *cis*:*trans* 1:1; **16**, 95%; *cis*:*trans* 2.5:1); (e) 4 mol% Grubbs' catalyst, CH_2Cl_2 (**17**, 44%; **18**, 44%); (f) (i) H_2, PtO_2, AcOEt; (ii) $LiAlH_4$, THF, reflux (**19**, 82%; **20**, 60%).

The results discussed above paved the way to convert **6** to bicyclic lactam **8** (82% yield) through ring-closing metathesis[11] which also provided a convenient way to separate the minor epimer formed by column chromatography (Scheme 1). Finally, hydrogenation and reduction of **8** afforded (1*S*,8a*R*) 1-hydroxyindolizidine(**9**), the enantiomer of the biosynthetic precursor of swainsonine.[12]

Analogously, ring-closing metathesis of a 1:1 mixture of **15** led to a separable mixture of bicylic lactams **17** and **18**, in 88% yield (Scheme 2). After separation by column chromatography, double bond hydrogenation of **17** and **18**, followed by $LiAlH_4$ reduction, afforded lentiginosine[13] (**19**) and 8a-*epi*-lentiginosine[14] (**20**), respectively.

In conclusion, the strategy reported above provides a short synthesis of hydroxylated indolizidine alkaloids. (1*S*,8a*R*) 1-hydroxyindolizidine (**9**) was efficiently prepared in six steps and 38% overall yield from imide **2**. Lentiginosine (**19**) and 8a-*epi*-lentiginosine (**20**) were synthesized in six steps from imide **11** in 24 and 18% overall yield, respectively.[15]

Further transformations of the bicyclic lactams described herein are in progress.

Acknowledgements

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15. All new compounds gave spectral and analytical data in accordance with the proposed structures. Compound **8**: $[\alpha]_D^{26}$ +14.3 (*c* 2.37, $CHCl_3$); IR (neat) 3037, 2929, 2848, 1737, 1699, 1656, 1440, 1375, 1236, 1055; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95–2.09 (m, 1H), 2.05 (s, 3H), 2.37–2.47 (m, 2H), 2.77 (dd, *J* 8.1 and 18.4 Hz, 1H), 3.50–3.57 (m, 2H), 4.32 (dd, *J* 2.7 and 18.4 Hz, 1H), 4.94 (dt, *J* 2.5 and 7.7 Hz, 1H), 5.64–5.68 (m, 1H), 5.73–5.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.72, 28.62, 36.30, 39.85, 59.28, 71.67, 123.77, 123.81, 170.63, 170.66; HRMS (EI) calcd for $C_{10}H_{13}NO_3$ ($M^{+\cdot}$) 195.0895, found 195.0895. Compound **17**: $[\alpha]_D^{24}$ +94.5 (*c* 1.35, $CHCl_3$); IR (neat) 3016, 2936, 2852, 1749, 1725, 1653, 1432, 1371, 1239, 1058; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.16 (s, 3H), 2.19–2.26 (m, 1H), 2.57 (dl, *J* 16.8 Hz, 1H), 3.51 (dt, *J* 4.6 and 10.5 Hz, 1H), 3.64 (d, *J* 18.8 Hz, 1H), 4.33 (dd, *J* 2.9 and 18.8 Hz, 1H), 5.08 (dd, *J* 5.1 and 5.3 Hz, 1H), 5.46 (dd, *J* 1.4 and 5.3 Hz, 1H), 5.72–5.75 (m, 1H), 5.82–5.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.67, 20.75, 30.02, 40.16, 55.22, 74.39, 77.69, 122.29, 123.53, 166.44, 170.00, 170.36; HRMS (EI) calcd for $C_{12}H_{15}NO_5$ ($M^{+\cdot}$) 253.0950, found 253.0950. Compound **18**: $[\alpha]_D^{24}$ +167.1 (*c* 1.12, $CHCl_3$); IR (neat) 3040, 2935, 2858, 1744, 1715, 1595, 1433, 1375, 1256, 1069; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01–2.19 (m, 2H), 2.14 (s, 3H), 2.17 (s, 3H), 3.61 (d, *J* 18.3 Hz, 1H), 4.02 (ddd, *J* 4.4, 6.9 and 11.2 Hz, 1H), 4.38 (dd, *J* 2.9 and 18.3 Hz, 1H), 5.43–5.50 (m, 2H), 5.70–5.74 (m, 1H), 5.80–5.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.37, 20.51, 24.95, 40.46, 52.35, 72.71, 73.71, 123.59, 123.84, 165.98, 170.09, 170.44; HRMS (EI) calcd for $C_{12}H_{15}NO_5$ ($M^{+\cdot}$) 253.0950, found 253.0956. Spectral and analytical data of **9**, **19**, and **20** are in agreement with those described in Refs. 12, 13 and 14, respectively.