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Solid-phase access to polyhydroxypyrrolizidines by 1,3-dipolar cycloaddition of (*S*)-3-alkoxypyrroline *N*-oxide to maleate and crotonate derivatives

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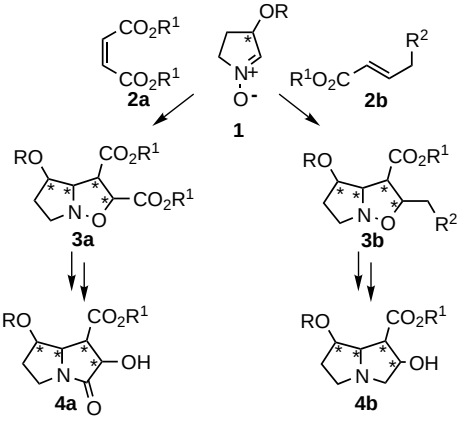
Abstract—2,7-Dihydroxyhexahydropyrrolizine-1-carboxylic acid derivatives have been prepared in solid-phase by intermolecular 1,3-dipolar cycloaddition between an immobilised maleate or 4-hydroxycrotonate and an enantiopure 3-alkoxypyrroline *N*-oxide.

Polyhydroxypyrrolizidines,[1] as well as indolizidines and imminosugars are potential inhibitors of glycosidases, a class of enzymes which hydrolyse glycosidic bonds in oligo- and polysaccharide chains. Glycosidases are involved in the biosynthesis of glycoproteins, which are responsible for cell to cell and cell to exogen molecular recognition processes. Inhibitors of these enzymes can therefore be active as antibacterial, antitumoral and antiviral agents. The great interest mounted in recent years in the synthesis of these compounds prompted the search for new general and stereoselective synthetic methods. Solid-phase synthesis[2] has recently imposed as a modern mean of synthesis particularly to produce combinatorial libraries of compounds of biological interest. We have investigated two different syntheses of 2,7-dihydroxyhexahydropyrrolizine-1-carboxylic acid derivatives either in solution and on solid-phase, based on 1,3-dipolar cycloaddition of pyrroline *N*-oxide **1**.[3] Actually the hydroxy pyrrolizidine skeleton **4** could be easily obtained by 1,3-dipolar cycloaddition[4] of an enantiopure cyclic hydroxylated nitrone **1** and a maleate **2a** or a crotonate **2b** derivative, followed by a suitable elaboration of the adducts. In particular the primary adducts **3** were transformed in the polyhydroxypyrrolizidines **4** (Scheme 1) by reductive cleavage of N–O bond followed by cyclisation.

1,3-Dipolar cycloaddition of (*S*)-3-*tert*-butoxy-1-pyrroline-*N*-oxide **5** and methylmaleate **6** in toluene at rt for 3 days,[5] gave three diastereomeric adducts in a 5:1:1 ratio in favour of the *exo–anti* isoxazolidine **7** (89% total yield). Treatment of **7** with $Mo(CO)_6$ in refluxing CH_3CN[6] afforded directly the pyrrolizidinone **8** in 82% yield, through a two-step domino process consisting of reduction of N–O bond followed by intramolecular amidation (Scheme 2).

The solid-phase version of this process was studied with the aim of obtaining a pyrrolizidine scaffold linked to a resin. Monoethyl maleate was linked to Wang resin in standard coupling conditions (DIC, DMAP, CH_2Cl_2).[7] 3-Tetrahydropyranyloxy-1-pyrroline *N*-oxide **10**[3d,e] reacted with the supported dipolarophile **9** in CH_2Cl_2 at



Scheme 1.

Keywords: solid-phase synthesis; 1,3-dipolar cycloaddition; nitrone; pyrrolizidines.

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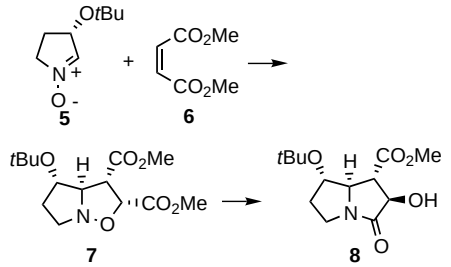
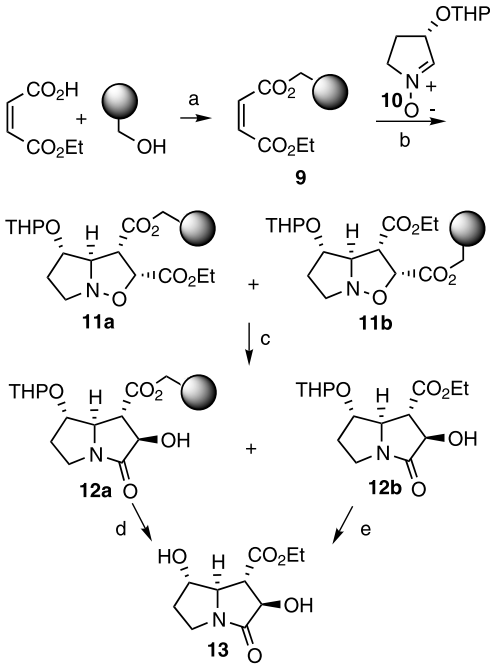


Scheme 2.

rt in 14 days. The reaction progress was monitored by cleaving small amount of products from resin and analysing the mixture by ^{1}H NMR. The spectra showed the presence of two regioisomeric isoxazolidines deriving from the adducts **11a** and **11b** in ca 1:1 ratio. Treatment of the resin with $Mo(CO)_6$ in toluene/CH_3CN/water mixture at reflux induced the reduction/cyclisation process that in the case of **11b** resulted in the concurrent cleavage of the product from the resin (Scheme 3). THP deprotection of **12b** followed by purification on silica-gel afforded the pyrrolizidinone **13**[8] in 22% yield with respect to the resin loading (1.10 mmol/g). The resin **12a**, containing the second part of the product, was left dark brown after treatment with $Mo(CO)_6$. Several attempts were made to clean the resin from traces of the metal. Only the treatment with ethylenediamine appeared to be able to clean resin, but caused also the cleavage of a significant amount of pyrrolizidinone by a transamidation reaction. The cleavage of the dark resin **12a** with TFA followed by esterification allowed the recovery of the second batch of product **13** in a 18% yield. In conclusion

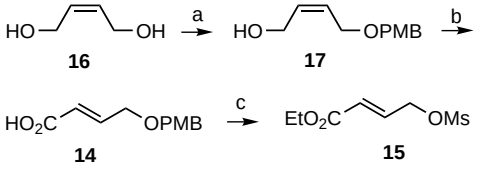


Scheme 3. *Reagents and conditions*: (a) DIC, DMAP, CH_2Cl_2, 12 h; (b) CH_2Cl_2, rt, 14 days; (c) $Mo(CO)_6$, toluene, CH_3CN, H_2O, reflux, 4 h; (d) (1) TFA, CH_2Cl_2, (2) TMSCl, EtOH; (e) EtOH, Amberlyst 15.

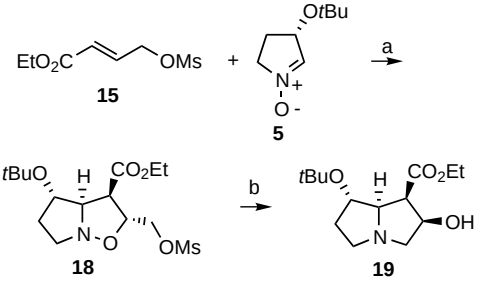
pyrrolizidine **13** was obtained in 40% total yield. Only traces of minor diastereomeric pyrrolizidinones were present in the crude mixtures, suggesting that the cycloaddition occurs with higher diastereoselectivity on solid-phase than in solution. On the contrary, no regioselectivity was observed in the reaction of **10** with the asymmetric diester **9**.

To bypass this problem, we decided to link a crotonic acid derivative to the solid support. Actually in solution, cycloadditions of cyclic nitrones with these dipolarophiles run in a regio- and stereoselective manner to give usually only one adduct.[3d,e,9] The synthesis of crotonates **14** and **15** were performed starting from commercially available *cis*-1,4-butendiol (**16**) which was protected as *p*-methoxybenzyl (PMB) ether by acetalysation[10] with *p*-anisaldehyde followed by reduction with DIBAL. Oxidation with Jones reagent furnished the *trans*-4-*p*-methoxybenzyloxy crotonic acid (**14**), that was coupled with hydroxypolystyrenic Merrifield and Wang resins in the solid-phase path. Esterification and mesylation of **14** gave **15** (Scheme 4) which was used as dipolarophiles in the solution path.

The solution-procedure used by Tufariello[9] to obtain racemic pyrrolizidines, was repeated using the optically active nitrone **5** and then adapted to the solid-phase synthesis of enantiomerically pure products. Nitrone **5** was allowed to react with ethyl 4-mesyloxy crotonate (**15**) in toluene at rt for 7 days. The regio- and diastereoselective 1,3-dipolar cycloaddition furnished **18** as a single adduct. The regioselectivity was driven by orbital interactions, while both orbital and steric factors favoured stereoselectively the *endo(COOEt)–anti* transition state. Hydrogenation of the adduct **18** followed by final base-treatment gave pyrrolizidine **19**[11] in three steps and 52% overall yield (Scheme 5).



Scheme 4. *Reagents and conditions*: (a) (1) *p*-anisaldehyde, *p*TsOH, benzene, reflux, (2) DIBAL, toluene, 0°C (87%); (b) CrO_3, H_2SO_4, acetone, rt (52%); (c) (1) *p*TsOH, EtOH, benzene, reflux (62%), (2) MsCl, TEA, CH_2Cl_2, 0°C→rt (68%).

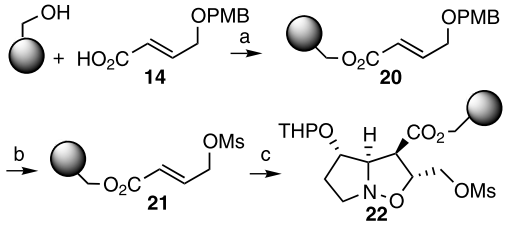


Scheme 5. *Reagents and conditions*: (a) toluene, rt, 7 days; (b) (1) $Pd(OH)_2/C$, EtOH, H_2, rt, (2) Ambersep 900 OH (52%).

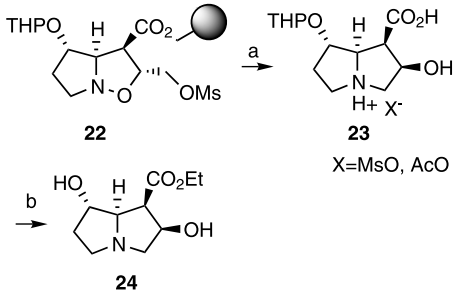
For the solid-phase synthesis of the same pyrrolizidine **19** both hydroxypolystyrenic Merrifield and Wang resins were employed and the first coupling step between the resins and the protected alcohol **14** was performed by using the standard coupling procedure (Scheme 6). Resin **20** was deprotected with DDQ and mesylated. Treatment of resin **21** with 4 equiv. of nitrone **10** for 11 days furnished resin **22** (Scheme 6), whose formation was monitored by cleaving and recording an ^{1}H NMR spectrum of the residue. As in the previous synthesis, a long time was required to complete the cycloaddition step at rt either in solid-phase and in solution. Unfortunately the reactions could not be accelerated by heating because of the thermal instability of the cycloadducts.

$Mo(CO)_6$ reduction procedure failed for substrate **22**, probably for steric hindrance of the isoxazolidine.[6a] Several other reducing agents, like SmI_2[12] and $SnCl_2$, compatible with solid-phase synthesis, were tested to cleave the N–O bond, but failed.[13] Finally the one-pot N–O cleavage/ring closure/resin-cleavage by hydrogenolysis[14] was carried out. Using $Pd(OAc)_2$, and H_2 in DMF, pyrrolizidinium salt **23** was obtained after filtration of the solid residue. Crude **23** was esterified in dry EtOH in the presence of trimethylsilylchloride (TMSCl) and treated with basic ion-exchange resin Ambersep 900 OH to furnish **24**[15] in 11% overall yield (Scheme 7) with respect to the loading of resins (Wang resin: 1.10 mmol/g, Merrifield resin: 0.68 mmol/g).

In conclusion, the solid-phase synthesis of highly functionalised enantiopure pyrrolizidines has been achieved. A selective method to reduce the N–O bond of isoxazolidine without removal from the resin is still necessary to improve the methodology and it will be object of further studies in our group.



Scheme 6. *Reagents and conditions*: (a) DIC, DMAP, CH_2Cl_2, rt; (b) (1) DDQ, H_2O, CH_2Cl_2, rt, (2) MsCl, CH_2Cl_2, rt; (c) **10**, toluene, rt, 11 days.



Scheme 7. *Reagents and conditions*: (a) $Pd(OAc)_2$, DMF, H_2, 35 atm, rt; (b) (1) TMSCl, EtOH, rt, (2) Ambersep 900 OH.

Acknowledgements

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7. All solid-phase reactions were monitored by FT-IR.
8. Ethyl (1*S*,2*R*,7*S*,7a*R*)-2,7-dihydroxy-3-oxohexahydropyrrolizine-1-carboxylate (**13**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.78 (d, J=9.9 Hz, 1H; H-2), 4.24 (q, J=7.0 Hz, 2H; CH_2CH_3), 4.15 (q, J=6.6 Hz, 1H; H-7), 3.65 (m, 2H; H_a-5, H-7a), 3.23 (m, 1H; H_b-5), 2.92 (dd, J=9.8, 8.5 Hz, 1H; H-1), 2.35–2.19 (m, 1H; H_a-6), 2.08–1.90 (m, 1H; H_b-6), 1.29 (t, J=7.0 Hz, 3H; CH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.2 (s), 171.0 (s), 75.2 (d), 74.6 (d), 64.7 (d), 61.8 (t), 54.4 (d), 40.5 (t), 33.8 (t), 14.1 (q).
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11. Ethyl (1*R*,2*R*,7*S*,7a*R*)-7-*tert*-butoxy-2-hydroxyhexahydropyrrolizine-1-carboxylate (**19**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.56 (dt, $J=6.1$, 7.7 Hz, 1H; H-2), 4.19 (q, $J=7.1$ Hz, 1H; C*H*HCH$_3$), 4.18 (q, $J=7.1$ Hz, 1H; C*H*HCH$_3$), 4.14–4.04 (m, 1H; H-7), 3.42 (dd, $J=8.5$, 3.2 Hz, 1H; H-7a), 3.35 (dd, $J=10.0$, 6.1 Hz, 1H; H$_a$-3), 3.24–3.11 (m, 1H; H$_a$-5), 2.73 (ddd, $J=11.7$, 6.1, 4.8 Hz, 1H; H$_b$-5), 2.57 (dd, $J=7.9$, 2.2 Hz, 1H; H-1), 2.52 (dd, $J=7.8$, 4.1 Hz, 1H; H$_b$-3), 2.16–1.93 (m, 1H; H$_a$-6), 1.79–1.59 (m, 1H; H$_b$-6), 1.28 (t, $J=7.1$ Hz, 3H; CH$_2$C*H*$_3$); 1.17 (s, 9H; *t*Bu); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8 (s), 76.8 (d), 75.1 (d), 73.6 (s), 73.3 (d), 60.9 (t), 60.8 (t), 56.2 (d), 53.2 (t), 33.1 (t), 28.4 (q, 3C), 14.2 (q).
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14. Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589–1592.
15. Ethyl (1*R*,2*R*,7*S*,7a*R*)-2,7-dihydroxyhexahydropyrrolizine-1-carboxylate (**24**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.63 (dt, $J=6.1$, 7.9 Hz, 1H, H-2), 4.33 (dt, $J=3.3$, 5.0 Hz, 1H; H-7), 4.23 (q, $J=7.2$ Hz, 2H, OC*H*$_2$CH$_3$), 3.56 (dd, $J=9.3$, 3.2 Hz, 1H, H-7a), 3.48 (dd, $J=10.1$, 6.1 Hz, 1H; H$_a$-3), 3.36 (dt, $J=12.7$, 6.7 Hz, 1H; H$_a$-5), 2.82 (dt, $J=12.7$, 6.3 Hz, H$_b$-5), 2.63 (dd, $J=10.1$, 7.9 Hz, 1H; H$_b$-3), 2.59 (t, $J=8.4$ Hz, 1H; H-1), 2.28–2.19 (m, 1H; H$_a$-6), 1.98–1.70 (m, 3H; H$_b$-6, OH, OH), 1.31 (t, $J=7.2$ Hz, 3H; OCH$_2$C*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.3 (s), 77.4 (d), 74.3 (d), 73.1 (d), 61.3 (t), 60.4 (t), 55.7 (d), 53.1 (t), 33.6 (t), 14.2 (q).