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A POLYMER-SUPPORTED C_2-SYMMETRIC CHIRAL AUXILIARY: PREPARATION OF NON-RACEMIC 3,5-DISUBSTITUTED-γ-BUTYROLACTONES.

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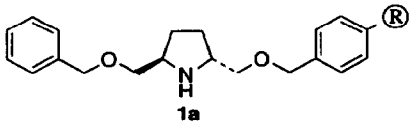
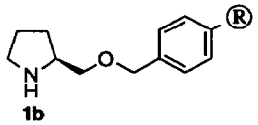
Abstract: *A polymer-bound "C_2-symmetric" pyrrolidine-based auxiliary is reported and shown to serve an effective control element for a three-step process consisting of N-acylation, Cα-alkylation, and subsequent iodolactonization to deliver optically active 3,5-disubstituted-γ-butyrolactone.*

Recent interest in the preparation of libraries of molecularly diverse compounds[1] has led to the development of a number of intriguing polymer-supported strategies for the synthesis of peptide[2] (combinatorial) and, to a lesser extent, small organic molecule[3] (analogous) collections. Inherent to these strategies are the benefits of polymer-supported synthesis which include, but are not limited to, increased ease of product isolation and modified reaction selectivity. Unlike "combinatorial synthesis" where polymer-supported reaction types are quite limited (i.e., peptide formation), extension of Merrifield's pioneering polypeptide work[4] to organic synthesis problems[5,6] has the potential to deliver analogue libraries (analogous organic synthesis[3c]) which arise from and encompass an impressive array of reagent and chemical reaction diversity. In that context, interest in analogous synthesis commissions the further development of polymer-based, enantioselective methodologies for organic synthesis. We report herein a polymer-bound "C_2-symmetric" (i.e., functional but not truly C_2-symmetric) pyrrolidine-based auxiliary which can be used as an efficient chiral controller in amide alkylation and iodolactonization reactions.[7]

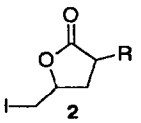
The reduced number of competing diastereomeric transition states available to C_2-symmetric auxiliaries often results in higher stereoselectivity.[8] This, coupled with the documented advantages of polymer-bound auxiliaries,[9] led us to consider resin-bound auxiliary **1a** as a promising candidate for a three-step process consisting of *N*-acylation, *C*α-alkylation, and subsequent iodolactonization to deliver optically pure 3,5-disubstituted-γ-butyrolactone **2**.



1a



1b



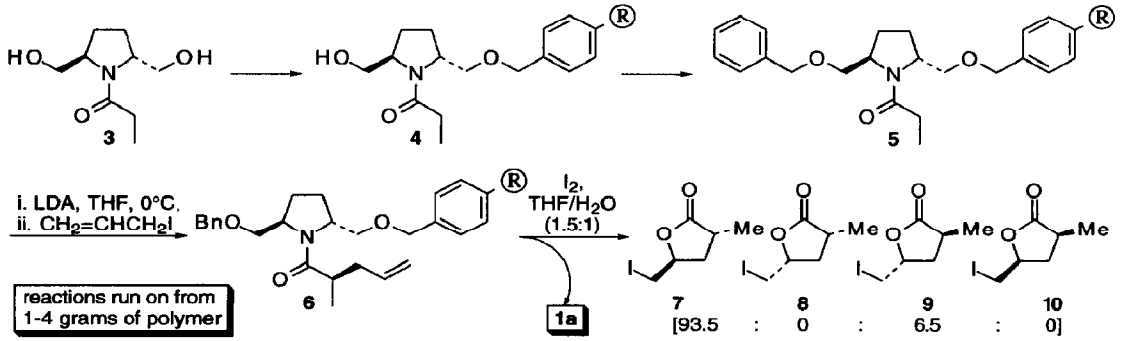
2

® = styrene/2% divinyl benzene copolymer

The C_2-symmetric pyrrolidine-based auxiliary required to launch this study, *trans*-(2*R*,5*R*)-(*N*-propionyl)-2,5-bis(hydroxymethyl)pyrrolidine (**3**), is readily available from 1,2:5,6-di-*O*-isopropylidene-D-mannitol by adaptation of chemistry developed by Marzi.[10] Taking advantage of the effective site isolation afforded by polymer attachment,[11] a THF solution of the potassium alkoxide of pyrrolidine **3** was directly coupled to DMF swollen Merrifield's resin (® = polystyrene/2% divinyl benzene co-polymer; 1 meq. Cl/g) containing catalytic 18-crown-6. Incubation of this mixture at 90°C for five days followed by filtration and thorough washing of the resulting resin delivered **4** as evidenced by the appearance of an FTIR (KBr) bands for the resulting hydroxyl and amide moieties (1647 and 3440 cm^{-1}, respectively). Attempted Cα-alkylation of amide **4** was complicated by competing alkoxide alkylation, so **4** was first converted to C_2-symmetric pyrrolidine **5** (1-methyl-2-pyrrolidone swollen resin treated with sodium hydride and benzyl bromide; 100°C, 2 d; disappearance of the 3440 cm^{-1} FTIR band).

Treating THF swollen resin **5** with lithium diisopropylamide (2 eq., 0°C, 30 min) presumably gives the highly favored *Z*-enolate[12] which, upon treatment with allyl iodide (3 eq.; 0°C → r.t., 24 h), produced Cα-alkylated resin **6**. While the stereoselectivity of this transformation could not be established at this stage, final iodolactone ratios established this Cα-alkylation selectivity to be 93.5:6.5 (*vide infra*).

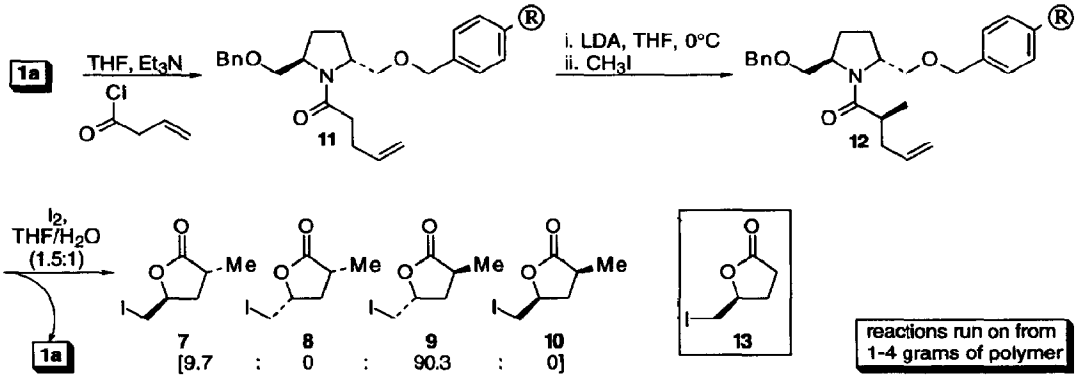
Subsequent iodolactonization of **6** was effected by treating a THF/H_2O (1.5:1) suspension of this resin with iodine for three days at room temperature. Filtration and ether washing of the resin delivered only γ-butyrolactones **7** and **9**[13] (93.5:6.5 ratio; 34% overall yield from **3**); no trace of lactones **8** or **10** were detected in the crude reaction mixture. These lactone product ratios establish the polymer-supported selectivity of both the alkylation (>14:1) and electrophilic cyclization (>99:1) steps. When contrasted with the L-prolinol derived auxiliary **1b**, C_2-symmetric pyrrolidine **1a** is a great deal more selective in both the Cα-alkylation step (**1b** affords 2:1 selectivity) and, suprisingly, the iodolactonization step (**1b** affords 92:8 selectivity).[6e] While consistent with previous reports of the *N*,*N*-dimethylamino moiety directing face selectivity,[14] A(1,3) strain[15] in polymeric amide **6** is apparently even more pronounced which forces the α-alkyl substituent to adopt a quasi-axial orientation favoring *trans*-selective iodolactonization.



Transformation **6** → **7** also liberates chiral resin **1a** as evidenced by disappearance of the FTIR amide band at 1647 cm^{-1}; this chiral auxiliary is trivial to isolate by simple filtration of the crude reaction mixture.

Moreover, we were pleased to find that reuse of resin **1a** is eminently practical and, by *N*-acylation, *Cα*-alkylation, and iodolactonization, again leads to chiral γ-butyrolactones.

Thus, by swelling recovered **1a** [washed sequentially with DMF, H_2O, CH_3OH, dioxane, acetone, THF, and Et_2O; dried overnight under vacuum (0.8 torr)] in THF and treating the resulting resin with 4-pentenoyl chloride and triethylamine (2 eq.'s each; r.t., 2 d), we obtain 4-pentenoylamide **11** (C=O FTIR absorbance at 1639 cm^{-1}. Enolate formation of THF swollen **11** (2 eq. LDA, THF, 0°C) followed by *Cα*-alkylation with methyl iodide (3 eq.) delivers resin **12**. While we anticipated that resin **12** was the *Cα* epimer of resin **6**, we were indeed gratified to find that iodolactonization (I_2, THF:H_2O::1.5:1, r.t., 3d) delivered γ-butyrolactone **9** as the major product (35% overall yield from **1a**). The reduced enantioselectivity from **11** (81% ee) relative to **5** (87% ee) most probably reflects the reduced steric requirements of methyl versus allyl iodide.[16] Again, *cis*-lactones **8** and **10** were not detected in the crude reaction mixture from **12**. It is also interesting to note that nor-methyl lactone **13**, which would arise by electrophilic cyclization of **11**, was not detected in the crude iodolactonization reaction mixture, indicating that the polymer-supported *Cα*-methylation of **11** is an efficient process. Finally, resin **1a** can again be recovered by filtration and washing [washed sequentially with DMF, H_2O, CH_3OH, dioxane, acetone, THF, and Et_2O; dried overnight under vacuum (0.8 torr)]. If care has been taken to avoid mechanical damage to the resin, this chiral auxiliary can be reused with no loss of chemical yield or stereoselectivity.



In summary, we find that polymer-supported C_2-symmetric pyrrolidine **1a** is an effective chiral auxiliary which is easily recovered and reused. The three-step process presented here promises to be an excellent route to chiral, *trans*-2,5-disubstituted-γ-butyrolactones.

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