JOC *Article*

Comparison of Solid-Phase and Solution-Phase Chiral Auxiliaries in the Alkylation/Iodolactonization Sequence to γ-Butyrolactones

Michael D. Price, Mark J. Kurth, and Neil E. Schore*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616

neschore@ucdavis.edu

Received June 17, 2002

Five prolinol-based chiral auxilaries have been compared for the stereoselective synthesis of γ-butyrolactones via the sequence of N-acylation, C_α-allylation, and iodolactonization under both solution-phase and solid-phase conditions. Comparisons of stereoselectivity of both the C_α-allylation and iodolactonization processes indicate that incorporation of a non-C_2-symmetric auxiliary as a polymer cross-link gives results superior to those obtained either in solution or with other non-C_2-symmetric auxiliaries and comparable to those observed using a polymer-supported pseudo-C_2-symmetric auxiliary.

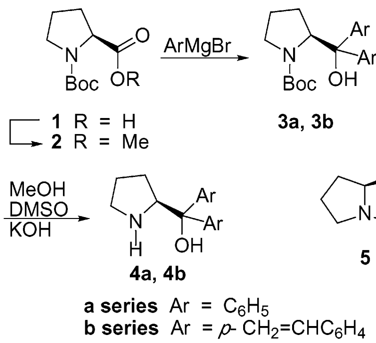
Introduction

In recent years, we have explored several approaches to the transfer of resident stereochemistry in the synthesis of 3,5-disubstituted γ-butyrolactones via an alkylation−iodolactonization protocol.[1] We have examined both non-C_2-symmetric prolinol-based auxiliaries and their pseudo-C_2-symmetric counterparts, both in solution and polymer supported.[2−4] Non-C_2-symmetric auxiliaries in general provide modest C_α-allylation stereoselectivity and good but incomplete stereocontrol of the subsequent electrophilic cyclization. Use of a polymer-supported pseudo-C_2-symmetric auxiliary improves the selectivity of both processes, but its synthesis is laborious. We describe herein a reexamination of the more readily accessible prolinol-based auxiliaries, modified by increasing steric bulk. We also describe the use of a novel strategy in which the auxiliary is incorporated as a cross-linker for the polymer matrix itself.

Results and Discussion

Chiral Auxiliary Synthesis. We chose to prepare auxiliaries **4a** and **4b** for solution- and solid-phase applications, respectively. We followed Corey's general procedure,[5] slightly modified, rather than alternatives utilizing phosgene or phosgene analogues.[6,7] We began by converting *N*-(*t*-BOC)-L-proline **1** into its methyl ester **2**, followed by addition of excess phenylmagnesium bromide. Several standard methods for deprotection of the amine were discarded because ring closure to the bicyclic oxazolidinone **5** interfered. Hydrolysis with KOH in methanolic DMSO proved successful, affording **4a** in 50% overall yield for the three steps on a large scale. Once this route was established, it was repeated using (*p*-vinylphenyl)magnesium bromide, providing **4b** in similar overall yield (Scheme 1).

SCHEME 1. Synthesis of Auxiliaries 4a and 4b



Amide Synthesis. Addition of propionic acid and DCC to solutions of DMAP containing **4a** and **4b** gave rise to amides **6a** and **6b** in yields of 71% and 88%, respectively. There was no interference by O-acylation in either process (Scheme 2).

In contrast, and as we had earlier found in some related situations,[4] attempts at C_α-allylation in the presence of the unprotected tertiary alcohol functionality did not succeed. We chose therefore to block the alcohol

---

[1] For reviews of the halolactonization reactions, see: (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171−197. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1983; Vol. 3, pp 411−454. (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321−3408.

[2] Najdi, S.; Reichlin, D.; Kurth, M. J. *J. Org. Chem.* **1990**, *55*, 6241−6244.

[3] Moon, H.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6088−6089.

[4] Moon, H.; Schore, N. E.; Kurth, M. J.; *Tetrahedron Lett.* **1994**, *35*, 8915−8918.

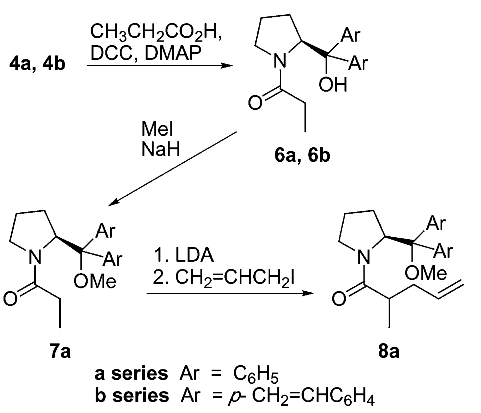
[5] (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861−2863.

[6] Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751−762.

[7] Kaufman, T. S.; Ponze, V. L.; Zinczck, J. *OPPI Briefs* **1996**, *28*, 487−490.

10.1021/jo0260692 CCC: $22.00

SCHEME 2. Preparation of Iodolactonization Precursors

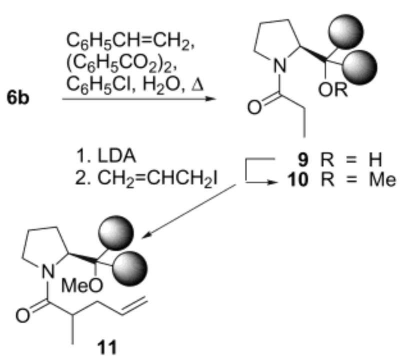


by methylation prior to C-alkylation. Thus, we obtained amide **7a** for direct determination of stereoselectivity under solution-phase conditions. Consistent with spectroscopic observations of other prolinol-derived amides,[2−4,10c] the ^{1}H NMR spectra of **6a** and **6b** indicated the presence of only a single amide rotamer, presumably the one in which intramolecular hydrogen bonding is present between the hydroxy and carbonyl moieties. In contrast, the NMR of **7a**, in which the hydroxy oxygen has been alkylated, displays two rotamers in a ca. 1:1 ratio.

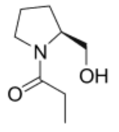
Polymer Preparation. The potential for undesired involvement of a terminal allyl double bond of an allylated derivative of **6b** under radical polymerization conditions prompted us to delay incorporation of this moiety until after polymer preparation. We therefore proceeded with the suspension polymerization of mixtures of amide **6b** with styrene to furnish polymer **9**, which displayed a broad IR absorption at 3312 cm^{-1} and was found to have a loading of 0.33 mequiv/g on the basis of elemental analysis. The analysis corresponds to ca. 12 wt % or 4 mol % incorporation of the auxiliary in the polymer. That this polymer was found to be insoluble in all solvents confirmed that **6b** had indeed been incorporated in a cross-linking role. O-Methylation was achieved by reaction of the polymer in THF with excesses of both NaH and MeI under reflux for 2 h. Disappearance of the O−H absorption in the IR confirmed that conversion to **10** had succeeded. Subsequent C$_\alpha$-allylation was effected by treatment of **10** in THF with 1 equiv of LDA followed by a 4-fold excess of allyl iodide to give polymer **11** (Scheme 3).

Iodolactonization Reactions. As described for polymer **11**, above, solution-phase C$_\alpha$-allylation of **7a** was carried out to give **8a**, which was used immediately in crude form. Iodolactonizations were carried out by the addition of iodine in THF to both a THF/H_2O solution of **8a** and a similar suspension of **11**, followed by stirring at rt for 3d. The expected 3,5-disubstituted γ-butyrolactones **15**−**18** were isolated as mixtures of stereoisomers in 42% and 45% yields, respectively, from **7a** (via **8a**) and **9** (via **10** and **11**).

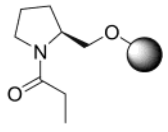
SCHEME 3. Preparation of Polymer-Supported Iodolactonization Precursor



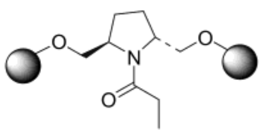
The stereochemistry of the lactone obtained from this sequence reflects the stereoselectivity of two independent processes. The enantioselectivity of the alkylation is transmitted to the α-carbon of the lactone, while the face selectivity of the iodolactonization determines the cis or trans disposition of the two substituents in the lactone ring. The C$_\alpha$-alkylation of chiral amides has been studied by several groups;[8−10] in particular, they report that stereoselectivity drops and the sense of the enantioselection is reversed upon O-alkylation of the prolinol OH. Our earlier observations using solution phase **12** (R/S = 81:19 = 4:1) and pendant-polymer-bound **13** (S/R = 66:34 = 2:1) concurred (Table 1). We additionally found that the pseudo-C_2-symmetric auxiliary **14** gave the best control over stereoselection in this step (R/S = 93.5:6.5 = 14:1; reversed because the auxiliary is 2R rather than 2S), higher even than did free prolinol-derived **12**.



12



13



14

The solution-phase diaryl amide ether **7a** provided superior enantioselection upon allylation to give **8a** (S/R = 72:28 = 2.5:1) than did the simpler polymer-bound

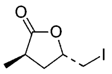
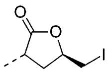
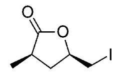
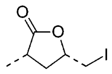
---

[8] Prolinol-based auxiliaries: (a) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137−3139. (b) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233−4236. (c) Mori, K.; Ito, T.; Tanaka, K.; Honda, H.; Yamamoto, I. *Tetrahedron* **1983**, *39*, 2303−2306. (d) Schultz, A.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. *Tetrahedron Lett.* **1985**, *26*, 4575−4578. (e) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290−5313.

[9] 2,5-Disubstituted pyrrolidine (C_2-symmetric) auxiliaries: (a) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857−860. (b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015−6016. (c) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 1343−1344.

[10] Other auxiliaries: (a) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.* **1978**, 3961−3964. (b) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5−15. (c) Guoqiang, L.; Hjalmarsson, M.; Hoegberg, E.; Jernstedt, K.; Norin, T. *Acta Chem. Scand., Ser. B* **1984**, *B38*, 795−801. (d) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771−2773. (e) Tamion, R.; Marsais, F.; Ribereau, P.; Queguiner, G. *Tetrahedron*: *Asymmetry* **1993**, *4*, 2415−2418. (f) Kanemasa, S.; Ueno, K.; Onimura, K.; Kikukawa, T.; Yamamoto, H. *Tetrahedron* **1995**, *51*, 10453-10462. (g) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428−2440.

TABLE 1. Product Ratios from C_α-Allylation/ Iodolactonization Reaction Sequences

lactone product →				
starting amide	**15** (3*R*, 5*S*)	**16** (3*S*, 5*R*)	**17** (3*R*, 5*R*)	**18** (3*S*, 5*S*)
12 (2*S*, –OH)	75	17	6	2
13 (2*S*, –OR)	33	62	1	4
14 (2*R*, –OR)	93.5	6.5	0	0
7a (2*S*, –OR)	28	72	0	0
10 (2*S*, –OR)	11	89	0	0

benzylic ether **13**, but the selectivity using cross-link-bound **10**, giving **11** ($S/R = 89{:}11 = 8{:}1$)/ surpassed that of **12** as well. This latter result is remarkable because there is no obvious reason based upon the local environment about C_α alone to have expected any significant difference in behavior in allylation between **7a** and **10**, let alone a 3-fold selectivity enhancement. We demonstrated earlier that bulky functional groups at *cross-links* experience a relatively constrained environment with respect to molecular motion, e.g., freedom of rotation.[11] Our results correspond to a $\Delta G^\ddagger$of ~0.65 kcal mol^{-1}; it is impossible to say how much of this is due to conformational constraints imposed by the cross-link environment and how much arises from other effects of the microenvironment such as modifications in solvation in the polymer interior. Without a better understanding of the effects, it can only be considered fortuitous that in this case selectivity is enhanced. By way of comparison, cross-link-bound Mn(III)–salen complexes gave comparable or better chemical yields but considerably *poorer* enantioselectivity in asymmetric olefin epoxidation than their solution-phase analogues.[12] In those cases, increasing the spacing between the auxiliary and the polymer chain *improved ee* values, implying that the microenvironment in the vicinity of the polymer chain reduced differentiation between the relevant diastereomeric transition states. Clearly, more data need to be gathered comparing pendant- vs cross-link-bound functional behavior before any sort of generalizations, much less predictions, become possible.

We were pleased to find the total absence of any cis isomers (**17** and **18**) in the iodolactonization products derived from both solution-phase **7a** (via **8a**) and cross-link-bound **10** (via **11**). Thus, the bulkier diarylprolinol-derived auxiliary is comparable with the pseudo-C_2-symmetric system and surpasses the allylated derivatives of both **12** and **13** in the face selectivity of iodolactonization. This result is also somewhat surprising in that the models that have been used to rationalize the trans selectivity in the halolactonization of such pentenamides show no direct interaction between a *single* bulky N-substituent and the relevant structural elements in the cyclization transition state.[13] We presume that the added steric bulk affects the dihedral angle about the carbonyl C–N partial double bond, thereby influencing the free energy difference between the pre-trans and pre-cis transition state structures enough to give rise to this effect.

Conclusions

We have shown that diarylprolinol methyl ethers have synthetic potential as chiral auxiliaries in the formation of 3,5-disubstituted γ-butyrolactones. Furthermore, the cross-linked polymer-supported version of the auxiliary gave appreciably higher ee values upon C_α-allylation than did its solution-phase counterpart. In contrast to all other non-C_2 symmetric systems we have studied, both diaryl-based allylated amides underwent iodolactonization with complete trans selectivity.

Experimental Section

General Methods. All reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen or argon. Chromatography was carried out on a silica gel column using an ethyl acetate–hexane mixture as the eluent unless specified otherwise. NMR spectra were recorded on a 300 MHz instrument in $CDCl_3$. FTIR spectra of liquids were recorded neat; of solids either as KBr pellets or using ATR. Optical purities were determined using a Shimadzu capillary GC with a 25 m Chirasil column (β-cyclodextrin on OV-1701).

(*S*)-Pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester [*N*-(*tert*-Butoxycarbonyl)-L-proline Methyl Ester] (2).[14] A solution of 1-hydroxybenzotriazole (HOBT, 12.74 g, 0.083mol) and *N*-(*tert*-butoxycarbonyl)-L-proline **1** (17.67 g, 0.082mol) in 176 mL of CH_2Cl_2 and 20 mL of MeOH was cooled to 0 °C, and 1,3-dicyclohexylcarbodiimide (DCC, 18.73 g, 0.091mol) in 44 mL of CH_2Cl_2 was added via cannula. The mixture was stirred for 12 h at rt. Dicyclohexylurea was removed by filtration, and the filtrate was washed with water, saturated $NaHCO_3$, and brine. Drying (Na_2SO_4), evaporation of solvent, and flash chromatography furnished 15.39 g (82%) of *N*-(*t*-BOC)-L-proline methyl ester **2** as a yellow oil: IR 1751, 1700, 1162 cm^{-1}; ^{1}H NMR δ 4.2–4.1 (m, 1H), 3.6 (m, 3H), 3.4–3.3 (m, 2H), 2.1–2.0 (m, 1H), 1.8–1.7 (m, 3H), 1.3 (s, 9H); ^{13}C NMR δ 173.3, 173.0, 153.9, 153.2, 79.5, 79.4, 58.8, 58.5, 51.8, 51.7, 46.3, 46.1, 30.7, 29.7, 28.2, 28.1, 24.1, 23.5; $[\alpha]^{21}_{589}$ −57.5 (c = 0.3, MeOH) [lit.[14] $[\alpha]_{589}$ = −61.5 (c = 0.34, MeOH)].

2-[Hydroxy(diphenyl)methyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3a).[5,6] To 141 mL of a 1.0 M solution of PhMgBr in THF (0.141mol) was added a solution of *N*-(*t*-BOC)-L-proline methyl ester **2** (19.26 g, 0.040 mol) in 243 mL of THF slowly via addition funnel. The solution was stirred for 4 h at 25°C and then cooled to −78 °C. After slow addition of 10 mL of water, the solution was slowly warmed to rt with stirring. Decantation and washing of precipitated salt with ether gave a solution that was washed with brine, dried (K_2CO_3), and evaporated to an oil that was subjected to flash chromatography to yield 11.68 g, 82% of **3a** as a white crystalline solid: mp 101–103 °C; IR 3370 (br), 1655 cm^{-1}; ^{1}H NMR δ 7.5–7.2 (m, 10H), 6.4 (s, 1H), 4.9 (dd, J = 8.9, 3.7 Hz, 1H), 3.4–3.2 (m, 1H), 3.0–2.9 (m, 1H), 2.2–2.0 (m, 1H), 2.0–1.8 (m, 1H), 1.6–1.4 (m, 10H), 0.8 (s, 1H); ^{13}C NMR δ 146.3, 143.6, 128.1, 127.7, 127.5, 127.2, 127.1, 127.0, 126.9, 126.9, 81.6, 80.6, 65.6, 47.8, 29.8, 28.4, 22.9; $[\alpha]^{23}_{589}$ −154.8 (c = 0.025, MeOH) [lit.[5,6] $[\alpha]^{21}_{589}$ −154.3 (c = 0.261, MeOH)].

---

[11] Wilson, M. E.; Wilson, J. A.; Kurth, M. J. *Macromolecules* **1997**, *30*, 3340–3348.

[12] (a) De, B. B.; Lohray, B. B.; Sivaram, S.; Dhal, P. K. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2105–2108. (b) Minutolo, F.; Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2293–2302.

[13] Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079–1085.

[14] Yuste, F.; Ortiz, B.; Carrasco, A.; Peralta, M.; Quintero, L.; Sánchez-Obregón, R.; Walls, F.; García Ruano, J. L. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3079–3090.

2-[Hydroxy[bis(4-vinylphenyl)]methyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (3b). Freshly cut Mg ribbon (3.43 g, 0.141mol) was flame dried under vacuum and stirred for 24 h. A solution of 4-bromostyrene (24.29 g, 0.133mol) in 243 mL of THF was added. The solution was refluxed for 30 min, and 1,2-dibromoethane (1.52 g, 8.1 mmol) was added followed by 30 min of additional refluxing. The solution was cooled to 0 °C, and *N*-(*t*-BOC)-L-proline methyl ester **2** (9.26 g, 0.040 mol) in 20 mL of THF was added. Workup and purification as for **3a**, above, gave 10.71 g (75%) of **3b** as a white crystalline solid: mp 101−103 °C; IR 3310 (br), 1659, 1169, 839 cm−^{1}; ^{1}H NMR δ 7.3−7.2 (m, 8H), 6.7 (ddd, $J =$ 17.6, 10.9, 2.6 Hz, 2H), 5.8 (dd, $J =$ 17.6, 5.2 Hz, 2H), 5.3 (d, $J =$ 10.6 Hz, 2H), 4.9 (dd, $J =$ 9.1, 3.6 Hz, 1H), 3.4−3.2 (m, 1H), 3.0−2.8 (m, 1H), 2.2−2.0 (m, 1H), 2.0−1.8 (m, 1H), 1.6−1.4 (m, 10H), 0.9 (s, 1H); ^{13}C NMR δ 145.8, 143.3, 136.4, 136.3, 136.2, 136.1, 128.3, 127.7, 125.6, 125.1, 113.7, 113.6, 81.5, 80.6, 65.6, 47.9, 29.7, 28.4, 23.1; $[\alpha]^{23}_{589}$ −166.9 ($c =$ 0.025 MeOH). Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.01; H, 7.70; N, 3.45. Found: C, 76.83; H, 7.74; N, 3.39.

Diphenyl[(*S*)-pyrrolidin-2-yl]methanol (4a).[6] A solution of 6.33 g of **3a** (17.9 mmol), 10.04 g of KOH (0.179mol), 17 mL of MeOH, and 84 mL of DMSO was heated at 65 °C for 4 h. Water (100 mL) was added, the solution was extracted with 5 × 30 mL of hexane, and the extracts were dried (K_2CO_3). Evaporation and flash chromatography yielded 3.32 g (73%) of **4a** as a white solid: mp 79−80°C from hexane (lit.[6] mp 79−79.5 °C); IR 3600−3300(br), 3057 cm^{-1}; ^{1}H NMR δ 7.7−7.5 (m, 4H), 7.4−7.1 (m, 6H), 4.7 (s, 1H), 4.3 (t, $J =$ 7.4 Hz, 1H), 3.1−2.9 (m, 2H),1.9−1.5 (m, 5H); ^{13}C NMR δ 148.2, 145.4, 128.2, 128.0, 126.5, 126.4, 125.9, 125.6, 77.1, 64.4, 46.7, 26.3, 25.5; $[\alpha]^{26}_{589}$ −66.5 ($c =$ 0.03, MeOH) [lit.[6] $[\alpha]^{24}_{589}$ −58.8 ($c =$ 3.0, MeOH)].

Bis(4-vinylphenyl)[(*S*)-pyrrolidin-2-yl]methanol (4b). In a similar manner, 1.07 g of **3b** (3.02 mmol), 1.69 g of KOH (0.030 mol) in 5.0 mL of MeOH, and 14.2 mL of DMSO were reacted to yield 0.59 g (64%) of **4b** as a white solid: mp 85−86 °C; IR 3352 (br), 3084, 1630 cm^{-1}; ^{1}H NMR δ 7.5−7.4 (m, 4H), 7.4−7.3 (m, 4H), 6.7 (dd, $J =$ 17.4, 10.9 Hz, 2H), 5.7 (d, $J =$ 17.6 Hz, 2H), 5.2 (d, $J =$ 10.9 Hz, 2H), 4.3 (t, $J =$ 7.7 Hz, 1H), 3.1−2.8 (m, 2H), 1.8−1.5 (m, 4H); ^{13}C NMR δ 147.6, 144.8, 136.4, 136.2, 135.7, 135.6, 126.0, 125.9, 125.8, 125.5, 113.5, 113.3, 77.0, 64.3, 46.8, 26.3, 25.6; $[\alpha]^{23}_{589}$ −55.6 ($c =$ 0.03 MeOH). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59. Found: C, 82.48; H, 7.61.

1-[2-[Hydroxy(diphenyl)methyl]pyrrolidin-1-yl]-1-propanone (6a). A mixture of 2.00 g of **4a** (7.89 mmol) and 0.044 g of DMAP (0.395 mmol) was dissolved in 17.1 mL of CH_2Cl_2 and cooled to 0 °C. A solution of 1.79 g of DCC (8.68 mmol) in 4.3 mL of CH_2Cl_2 was added by cannula, followed by 2.34 g of propionic acid (31.6 mmol). The flask was allowed to slowly warm to rt and stirred for 12 h. After removal of dicyclohexylurea by filtration, the filtrate was washed with saturated $NaHCO_3$ and brine. Additional precipitated urea was removed and the solution dried (Na_2SO_4). Flash chromatography furnished 1.73 g (71%) of **6a** as a white solid: mp 85−86 °C; IR 3248 (br), 1613 cm^{-1}; ^{1}H NMR δ 7.4−7.2 (m, 10H), 7.1(s, 1H), 5.2 (dd, $J =$ 8.9, 4.5 Hz, 1H), 3.4−3.3 (m, 1H), 2.9−2.8 (m, 1H), 2.3−2.2 (m, 2H), 2.1−1.9 (m, 2H), 1.6−1.5 (m, 1H), 1.1 (t, $J =$ 7.6 Hz, 3H), 1.0−0.8 (m, 1H); ^{13}C NMR δ 176.5, 146.3, 143.5, 128.2, 128.0, 127.8, 127.4, 127.22, 127.19, 82.1, 66.7, 48.6, 29.7, 28.7, 23.4, 9.5; $[\alpha]^{23}_{589}$ −196.9 ($c =$ 0.03, MeOH). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.56; H, 7.54.

1-[2-[Hydroxy[bis(4-vinylphenyl)]methyl]pyrrolidin-1-yl]-1-propanone (6b). In a similar way, 2.41 g of **4b** (7.89 mmol) and 0.044 g of DMAP (0.40 mmol) in 17.1 mL of CH_2Cl_2 was treated with 1.79 g of DCC (8.68 mmol) in 4.3 mL of CH_2Cl_2 and then 2.34 g of propionic acid. After similar workup, flash chromatography furnished 2.51 g (88%) of **6b** as a white solid: mp 85−86 °C; IR 3240 (br), 1614, 990, 909, 840 cm^{-1}; ^{1}H NMR δ 7.4 (s, 4H), 7.3 (s, 4H), 7.1 (s, 1H), 6.7 (dd, $J =$ 17.7, 10.9 Hz, 2H), 5.6 (dd, $J =$ 17.6, 4.9 Hz, 2H), 5.24 (dd, $J =$ 11.0, 2.8 Hz, 2H), 5.20 (dd, $J =$ 8.8, 4.4 Hz, 1H), 3.4−3.3 (m, 1H), 3.0−2.9 (m, 1H), 2.3−2.2 (m, 2H), 2.1−2.0 (m, 1H), 2.0−1.9 (m, 1H), 1.6−1.5 (m, 1H), 1.1 (t, $J =$ 7.4 Hz, 3H), 1.0−0.9 (m, 1H); ^{13}C NMR δ 176.8, 146.0, 143.3, 136.7, 136.6, 128.6, 128.1, 126.0, 125.4, 114.2, 114.0, 82.1, 66.8, 48.8, 29.8, 28.8, 23.7, 9.7; $[\alpha]^{23}_{589}$ −198.3 ($c =$ 0.03, MeOH). Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53. Found: C, 79.64; H, 7.63.

1-[2-[Methoxy(diphenyl)methyl]pyrrolidin-1-yl]-1-propanone (7a). A solution of 0.72 g of **6a** (2.33 mmol) in 10 mL of THF was added via syringe to 0.12 g of NaH (5.0 mmol), followed by addition of 0.65 g (4.58 mmol) of MeI. The mixture was heated to reflux for 5 h, cooled, and taken up in 20 mL of Et_2O. The solution was washed with saturated aq $Na_2S_2O_3$, saturated $NaHCO_3$, and brine and evaporated, and the residue was subjected to flash chromatography to yield 0.60 g of **7a** (80%) as a white crystalline solid: mp 80−81 °C; IR 1638, 1074 cm^{-1}; ^{1}H NMR δ 7.5−7.2 (m, 10H), 5.52 (dd, $J =$ 8.4, 2.3 Hz, 0.5H), 5.00 (d, $J =$ 7.7 Hz, 0.5H), 3.7−3.6 (m, 0.5H), 3.3.-3.2 (m, 0.5H), 2.99 (s, 1.5H), 2.88 (s, 1.5H), 2.7−2.2 (m, 2H), 2.1−1.9 (m, 3H), 1.5−1.4 (m, 1H), 1.1 (t, $J =$ 7.3 Hz, 3H) 1.0−0.9 (m, 1H); ^{13}C NMR 175.4, 174.1, 142.6, 140.8, 138.2, 137.4, 130.14, 130.07, 130.0, 129.6, 128.3, 128.2, 128.0, 127.9, 127.8, 127.4, 87.9, 86.3, 65.8, 59.5, 52.8, 52.0, 48.2, 46.8, 29.2, 28.6, 27.9, 27.6, 23.8, 22.3, 10.5, 9.9; $[\alpha]^{22}_{589}$ −20.43 ($c =$ 0.03, MeOH). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79. Found: C, 77.79; H, 7.89.

Dihydro-5-iodomethyl-3-methyl-2(3*H*)-furanone (Solution Phase) (15 and 16).[2] A solution of 0.31 g of **7a** (0.95 mmol) in 15 mL of THF was cooled to −78 °C and treated with 0.53 mL of 2.0 M LDA in THF. The mixture was allowed to warm to −20°C for 1 h and then cooled to −78 °C, and 0.21 g of allyl iodide (1.22 mmol) was added. After being stirred at −78 °C for 2 h, the mixture was warmed to rt and quenched with 1% aq HCl. Extraction (Et_2O), drying (Na_2SO_4), and concentration gave 0.32 g of crude **8a** as an oil that was taken up directly in 3 mL of THF and 3 mL of water. This mixture was cooled to 0 °C, treated in the dark with 0.71 g of I_2 (2.8 mmol) in 2 mL of THF, and maintained at 0 °C in the dark for 3 d, after which time 15 mL of saturated aq $Na_2S_2O_3$ and 30 mL of Et_2O were added. The aqueous layer was separated and washed with Et_2O. The combined organic layers were washed with 1% aq HCl and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography to give 0.10 g (42% yield) of *trans*-dihydro-5-iodomethyl-3-methyl-2(3*H*)-furanone as a 72:28 mixture of enantiomers **16** and **15** (44.2% ee). None of the cis isomer was detected: IR (neat) 1770 cm^{-1}; ^{1}H NMR δ 4.61 (m, 1H), 3.36 (m, 1H), 3.26 (m, 1H), 2.79 (m, 1H), 2.32 (m, 1H), 2.11 (m, 1H), 1.30 (d, $J =$ 7 Hz, 3H); ^{13}C NMR δ 178.7, 76.3, 35.2, 33.9, 15.9, 7.1.

Polymer-Supported Propionyl Amide−Alcohol (9). Into a 45/50 500 mL two-necked indented (Morton-style) flask equipped with a propeller-shaped mechanical stirrer was placed 188 mL of water and 13 g of gum Arabic, and a stir rate of 475 rpm was established. A mixture of 9.44 g (90.59 mmol) of styrene, 0.107 g (0.442 mmol) of benzoyl peroxide, 13.4 mL of chlorobenzene, and 0.67 g (1.85 mmol) of monomer **6b** was prepared and added to the stirred aqueous mixture. The reaction vessel was heated to 85 °C while maintaining the 475 rpm stir rate. After 2 h, the stir rate was lowered to 215 rpm, and 0.178 g of Al_2O_3 (1.75 mmol) was added to inhibit droplet coalescence. The temperature and stir rate were maintained at 85 °C and 215 rpm, respectively, for an additional 24 h. The newly formed resin was collected by filtration and washed in turn with water, THF, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH. The beads were dried under vacuum overnight to give 8.23 g, 81.4% yield, of resin **9**. Elemental analysis indicated the presence of 0.33 mequiv of auxiliary/gram of polymer (Anal. Calcd: N, 0.46. Found: N, 0.45, 0.46): IR 3312, 1740 cm^{-1}.

Polymer-Supported Propionyl Amide−Methoxy Ether (10). A mixture of 0.12 g of NaH (5.0 mmol) and 5.06 g of **9** (1.67 mequiv) was treated with 20 mL of THF and the mixture heated to reflux for 2 h, at which time 1.18 g of MeI (8.3 mmol) was added and reflux continued for 8 h. Resin **10** was isolated by filtration and washed with water, THF, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH. The beads were dried under vacuum overnight. IR showed the absence of any absorption in the region of 3300 cm^{-1}.

Dihydro-5-iodomethyl-3-methyl-2(3*H*)-furanone (Solid Phase) (15 and 16).[2] A mixture of 3.11 g of **10** (assumed 0.33 mequiv/g) and 12 mL of THF was cooled to −78 °C, and 0.61 mL of 2.0 M LDA in THF was added. The mixture was allowed to warm to −20 °C for 1 h and then recooled to −78 °C, at which point 0.2 g of allyl iodide (1.22 mmol) was added. After being agitated at −78 °C for 4 h, the mixture was warmed to rt and quenched with 1% aq HCl. Resin **11** was isolated by filtration and washed with H_2O, THF, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH. To this resin was added 25 mL of THF and 20 mL of H_2O. The mixture was cooled to 0°C, and in the absence of light 0.77 g of I_2 (3.06 mmol) in 5 mL of THF was added via syringe. The mixture was agitated at 0 °C for 3 d at which time 15 mL of saturated aq $Na_2S_2O_3$ and 30 mL of THF were added. The resin was isolated by filtration and washed with THF, H_2O, THF, H_2O, and THF. The filtrate was diluted with brine and extracted with Et_2O. The aqueous layer was extracted once more with Et_2O, and the combined organic layers were washed with 1% HCl and brine, dried (Na_2SO_4), filtered, and concentrated. The oily residue was purified by flash chromatography to give 0.11 g (45% yield) of *trans*-dihydro-5-iodomethyl-3-methyl-2(3H)-furanone as an 89:11 mixture of enantiomers **16** and **15** (78.4% ee).

Acknowledgment. We thank the National Science Foundation (CHE-0078191) for research support. Funding sources for the NMR instrumentation at UC Davis include the NSF CRIF program (CHE-9808183), the UC Davis Office of Research, and Office of the Dean, Division of Mathematics and Physical Sciences.

JO0260692