NMR δ 1.42–1.96 (m, 24 H), 1.93 (s, 4 H), 3.44 (s, 2 H, OH); IR (KBr) 3325 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 266 (M$^+$, 18), 248 (100). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.83; H, 11.33.

**3a,7a-*cis*-3a,4,7,7a-Tetrahydroisobenzofuran-3(3*H*)-one (38).** This lactone was prepared by $LiAlH_4$ reduction of the corresponding anhydride **7**, according to the method of Bloomfield and Lee:[36] bp 69–71 °C (0.01 mmHg); 74% yield; $^1$H NMR δ 1.78–3.02 (br m, 7 H), 4.31 (m, 1 H), 5.75 (m, 2 H); IR (neat) 1775, 1660 cm$^{-1}$.

**1-[1,2-*cis*-(2-Hydroxymethyl)cyclohex-4-enyl]cyclopentanol (39).** This diol **39** was prepared from spirolactone **24**, as described above for compound **35**: recrystallized from ether/ligroin; mp 86–87 °C; 83% yield; $^1$H NMR δ 1.72 (m, 9 H), 2.22 (m, 4 H), 2.38 (m, 1 H), 3.43 (dd, 1 H, AMX, $J_{AM}$ = 10, $J_{MX}$ = 3 Hz, 2′-methylenic H), 3.67 (br m, 2 H, OH), 3.89 (t, 1 H, AMX, $J_{AM}$ = $J_{AX}$ = 10 Hz, 2′-methylenic H), 5.61 (m, 2 H); IR (KBr) 3210, 3025, 1660 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 196 (M$^+$, 16), 178 (25), 150 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.39.

**3′a,7′a-*cis*-3′a,4′,7′,7′a-Tetrahydrospiro[cyclopentane-1,1′(3′*H*)-isobenzofuran] (40).** This spiroether was prepared from diol **39** as described above for compound **36**: bp 70–72 °C (0.01 mmHg); 84% yield; $^1$H NMR δ 1.46 (m, 8 H), 2.04 (m, 4 H), 2.59 (dd, 2 H, *J* = 9 Hz), 3.46 (t, 1 H, *J* = 8 Hz), 3.80 (t, 1 H, *J* = 8 Hz), 5.69 (m, 2 H); IR (neat) 1045 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 178 (M$^+$, 100). Anal. Calcd for $C^{12}H^{18}O$: C, 80.85; H, 10.18. Found: C, 80.69; H, 10.19.

**1-[1,2-*cis*-(2-Hydroxymethyl)cyclohex-4-enyl]cyclohexanol (41).** This diol **41** was prepared from spirolactone **25**, a described above for compound **35**: recrystallized from ether/ligroin; mp 93–93.5 °C; 85% yield; $^1$H NMR δ 1.54 (m, 11 H), 2.00 (m, 4 H), 2.24 (m, 1 H), 3.39 (dd, 1 H, AMX, $J_{AM}$ = 10, $J_{MX}$ = 3 Hz, 2′-methylenic H), 3.84 (t, 1 H, AMX, $J_{AM}$ = $J_{AX}$ = 10 Hz, 2′-methylenic H), 3.89 (br m, 2 H, OH), 5.60 (m, 2 H); IR (KBr) 3230, 3030, 1660 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 210 (M$^+$, 11), 192 (29), 164 (100). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.21; H, 10.45.

**3′a,7′a-*cis*-3′a,4′,7′,7′a-Tetrahydrospiro[cyclohexane-1,1′-(3′*H*)-isobenzofuran] (42).** This spiroether was prepared from diol **41** as described above for compound **36**: bp 66–68 °C (0.01 mmHg); 82% yield; $^1$H NMR δ 1.51 (m, 10 H), 2.01 (m, 4 H), 2.64 (d, 2 H, *J* = 9 Hz), 3.53 (t, 1 H, *J* = 8 Hz), 3.89 (t, 1 H, *J* = 8 Hz), 5.71 (m, 2 H); IR (neat) 1050 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 192 (M$^+$, 100). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.28; H, 10.35.

**1-(4-Hydroxy-2-methylbutyl)cyclohexanol (43).** This diol **43** was prepared from spirolactone **17**, as described above for compound **35**. After fractional distillation, it had bp 98–100 °C (0.01 mmHg): 92% yield; $^1$H NMR δ 0.98 (d, 3 H, *J* = 6 Hz), 1.05–1.96 (m, 15 H), 2.78 (br m, 2 H, OH), 3.67 (2 H, t, *J* = 6 Hz); IR (KBr) 3335, 1360, 1110 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 186 (M$^+$, 12), 168 (29), 140 (100). Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.91. Found: C, 70.78; H, 12.08.

**4-Methyl-1-oxaspiro[5.5]undecane (44).** This spiroether was prepared from diol **43** as described above for compound **36**: bp 75–77 °C (8 mmHg); 84% yield: $^1$H NMR δ 1.00 (d, 3 H, *J* = 6 Hz), 1.21–1.91 (m, 15 H), 3.42 (2 H, t, *J* = 7 Hz); IR (neat) 1255, 1050 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 168 (M$^+$, 100). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.45; H, 12.12.

**1-(4-Hydroxy-2-methylbutyl)cyclopentanol (45).** This diol **45** was prepared from spirolactone **16**, as described above for compound **35**. After fractional distillation, it had bp 95–97 °C (0.01 mmHg): 93% yield; $^1$H NMR δ 0.97 (d, 3 H, *J* = 7 Hz), 1.25–1.91 (m, 13 H), 2.33 (br s, 2 H, OH), 3.46 (2 H, t, *J* = 6 Hz); IR (KBr) 3315, 1360, 1100 cm$^{-1}$; mass spectrum (70 eV), *m/e* (relative intensity) 172 (M$^+$, 16), 154 (38), 126 (100). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 66.79; H, 11.79.

**Acknowledgment.** We thank the National Research Council of Canada and le Ministère de l'éducation du Gouvernement du Québec for support of this work and Professor R. H. Burnell for helpful discussions.

**Registry No.** **1**, 108-30-5; **2**, 108-55-4; **3**, 4166-53-4; **4**, 14166-21-3; **5**, 13149-00-3; **6**, 2426-02-0; **7**, 85-43-8; **8**, 5662-95-3; **9**, 85-44-9; **10**, 716-39-2; **11**, 81-84-5; **12**, 33448-80-5; **13**, 699-61-6; **14**, 20127-07-5; **15**, 4481-78-1; **16**, 77520-32-2; **17**, 77520-33-3; **18**, 73090-08-1; **19**, 73090-10-5; **20**, 73090-07-0; **21**, 73090-09-2; **22**, 74279-79-1; **23**, 74279-81-5; **24**, 74279-80-4; **25**, 74279-82-6; **26**, 77520-34-4; **27**, 77520-35-5; **28**, 73090-06-9; **29**, 5651-49-0; **30**, 77520-36-6; **31**, 77520-37-7; **32**, 77520-38-8; **34**, 77520-39-9; **35**, 77520-40-2; **36**, 77520-41-3; **37**, 77520-42-4; **38**, 2744-05-0; **39**, 77520-43-5; **40**, 77520-44-6; **41**, 77520-45-7; **42**, 77520-46-8; **43**, 77520-47-9; **44**, 62809-36-3; **45**, 77520-48-0; 1,4-dibromobutane, 110-52-1; 1,5-dibromopentane, 111-24-0; 1,6-dibromohexane, 629-03-8.

(36) J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **32**, 3919 (1967).
(37) M. J. Bogdanowicz, T. Ambelang, and B. M. Trost, *Tetrahedron Lett.*, 923 (1973).

# Synthesis of Carboxylic Acids and Esters Using Polymer-Bound Oxazolines

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2,4-Dimethyl-4-(hydroxymethyl)-2-oxazoline was attached to cross-linked polystyrene, giving the polymer-bound oxazoline **3**. Alkylation of **3**, followed by hydrolysis or ethanolysis, provided α and α,α′ mono- and dialkylated acetic acids or their ethyl esters in 68–81% yields. The recovered polymer-bound amino alcohol was recycled to **3** with some reduced capacity. The chiral polymer-bound oxazoline **10** was prepared for use in the asymmetric synthesis of optically active carboxylic acids and other functional derivatives. Although chemical and optical yields similar to those of solution reactions were obtained, the insensitivity of α-substituted 2-oxazolines to hydrolysis greatly reduces the promise of the solid-phase method.

Asymmetric synthesis with chiral polymer-bound templates is an important topic for study for economic reasons and because of possible similarities with enzyme-directed synthesis. Leznoff[1] recently described the asymmetric solid-phase synthesis of 2-alkylcyclohexanones claiming demonstration of the practical reality of this approach. Independently, we have sought to demonstrate the feasibility of using solid supports for binding substrates for use in the asymmetric synthesis of some simple organic functional types.

Meyers[2] has shown that the oxazoline ring system possesses considerable utility in synthesis. By careful defi-

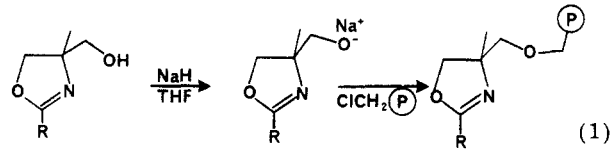
(1) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221.
(2) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375.

0022-3263/81/1946-3097$01.25/0 

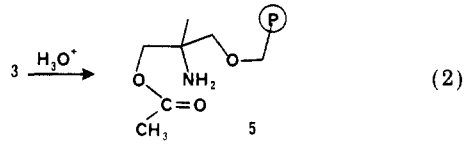
nition of the steric and electronic factors which affect stereoselectivity, Meyers and co-workers[2] have developed asymmetric syntheses for (*R*)- and (*S*)-dialkylacetic acids, (*R*)- and (*S*)-2-alkylbutyrolactones and -valerolactones, (*R*)- and (*S*)-3,3-dialkylpropanoic acids, 3-substituted valerolactones, thiiranes, diols, alcohols, esters, and alkenes. All of these asymmetric syntheses allow for regeneration of the chiral oxazoline starting materials which come from a common chiral amino alcohol. Our interest in enzyme-like synthons prompted us to study oxazoline-based asymmetric syntheses on solid supports. In addition to the economic advantages from recovering the chiral oxazoline, it was of interest to ascertain if the steric bulk of the polymer chain, when properly situated, may have a positive effect on enantiomeric selectivity. As the first step toward realization of these goals, synthesis of achiral[3] and chiral[4] 2-alkylalkanoic acids and their esters by use of polymer-bound oxazolines was chosen for our demonstration. Simultaneously, the practicality of recovering the chiral polymer-bound amino alcohol for regeneration of the polymer-bound oxazoline was investigated.

## Results and Discussion

**Demonstration of the Synthetic Concept of a Recyclable Resin-Bound Oxazoline.** The oxazolines 1 and 2 were attached to thoroughly washed,[5] swollen, chloromethylated poly(styrene-*co*-divinylbenzene) (1.7 mmol of Cl/g) by using the standard solution reaction.[6] The

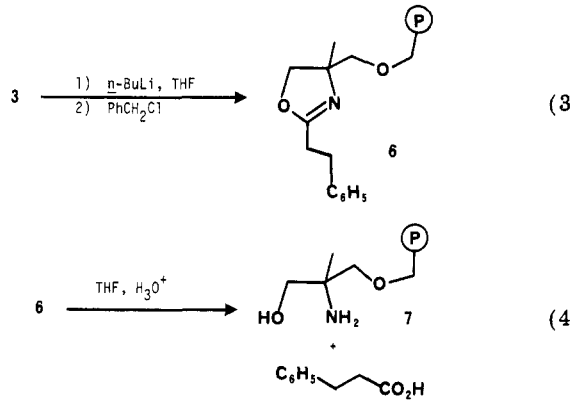



displacement reaction was very sluggish, apparently owing primarily to poor phase transfer.[7] The IR data from the first sample of **3** revealed significant amounts of the respective amino ester **5** (IR 1735 $cm^{-1}$ (C=O) vs. 1660 $cm^{-1}$

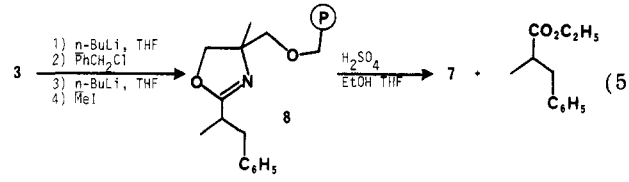



(C=N)), the expected product of acid-catalyzed hydrolysis. Impure and wet solvents were the suspected causative agents. The use of purified, dry solvents and shorter washing times, with a specially constructed pressure filter, allowed for the formation of pure **3** and **4** without noticeable hydrolysis. On the basis of elemental analysis (C, H, N, and Cl), **3** and **4** contain some residual chlorine groups (5–10% of the original amount). Since these residual benzylic chlorides potentially could lead to undesirable reactions, they should be removed prior to alkylation.[1] We used excess *n*-butyllithium to remove them by coupling.

By an adaption of the solution procedure of Meyers and Temple,[3] the polymer-bound oxazoline **3** was swollen in THF and metalated with *n*-butyllithium at −43 °C. Treatment with excess benzyl chloride[10] provided the alkylated oxazoline derivative **6** in quantitative yield, based on the weight uptake. Hydrolysis by heating **6** in THF–3 N aqueous HCl (10:1) to 60 °C for 48 h gave pure hydrocinnamic acid in 81% yield (distilled).




In another experiment **3** was double alkylated prior to hydrolysis. Thus, **3**, swollen in THF, was metalated and treated with benzyl chloride to produce **6**, which, in turn, was metalated and alkylated with methyl iodide, giving **8** (eq 5). The product **8** was identical by IR with a sample




obtained by alkylating the polymer-bound 2-ethyloxazoline derivative **4** with benzyl chloride. Hydrolysis of the dialkylated product provided ethyl 2-methyl-3-phenylpropanoate in 68% yield (by GLC analysis). By comparison, the yields reported in solution were 88–95%.[3]

The recovered polymer-bound amino alcohol **7** from the above experiments showed IR evidence of some residual amino ester (e.g., **5** or that from **6** or **8**). Accepting some lost capacity, treatment of the recovered polymer-bound amino alcohol (**7**) with ethyl iminoacetate hydrochloride afforded the oxazoline **3**. The recycled oxazoline was metalated, benzylated, and cleaved to the ethyl ester as before. By GLC analysis ethyl hydrocinnamate was obtained in 51% yield, thus demonstrating **3** to be a recyclable polymer-bound reagent which could be used to synthesize functionalized acetic acid derivatives. However, there is no advantage over the solution procedure for achiral compounds since the reported yields of the solution procedure are better, and the cost of the amino alcohol is not high.

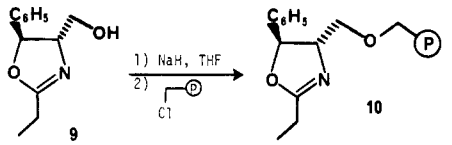
**Asymmetric Synthesis of Esters.** On the basis of the high cost of a chiral amino alcohol, the chemical yields

(3) Meyers, A. I.; Temple, D. L., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6644.
(4) Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *96*, 268.
(5) Farrall, M. J.; Frechet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.
(6) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 1186.
(7) Phase-transfer catalysis is said to greatly facilitate these reactions: cf. ref 1, 8, and 9.
(8) N'Guyan, T. D.; Boileau, S. *Tetrahedron Lett.* **1979**, 2651.
(9) Frechet, J. M. J.; deSmet, M. D.; Farrall, M. J. *J. Org. Chem.* **1979**, *44*, 1774.

(10) It was initially found that metalation was more efficient when *n*-BuLi was used in excess. There was subsequently no effort made to optimize amounts of reactants or yields. Nevertheless, an excess of alkyl halide was used to provide a sufficient amount to react with both the metalated oxazoline and any remaining *n*-BuLi. In practice automation techniques (cf.: Merrifield, R. B.; Stewart, J. M.; Jernberg, N. *Anal. Chem.* **1966**, *38*, 1905) could be used to prevent waste of metalating agent and alkylating agent. For example, the polymer could be metalated in a bath containing excess metalating agent, automatically filtered, rinsed with solvent, and then alkylated in a bath of excess alkylating agent in a sequence similar to that used in peptide synthesis.

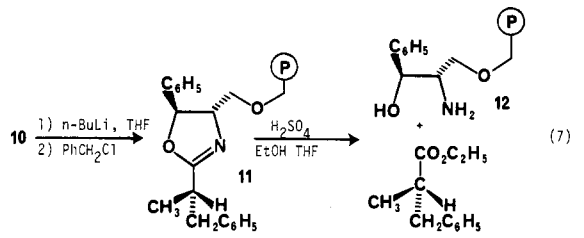
obtained above would be suitable if products of high enantiomeric excess (ee) were obtained and if the polymer-bound chiral oxazoline could be regenerated efficiently.

*trans*-(4*S*, 5*S*)-2-Ethyl-4-(hydroxymethyl)-5-phenyl-2-oxazoline (**9**) was converted to its sodium salt and attached to 2% cross-linked polystyrene,[11] using the chloromethylated polymer (1.67 mmol of Cl/g), giving the chiral polymer-bound oxazoline **10** containing 1.22 mmol of ox-



(6)

azoline/g. The alkylation of **10** with benzyl chloride was carried out at two different temperatures in an attempt to observe any temperature dependence on the chemical or optical yields. Thus, metalation with *n*-butyllithium at −78 °C followed by alkylation at −43 or at −78 °C provided the oxazoline **11** and, after acid-catalyzed ethanolysis, pure (*S*)-(+)-ethyl 2-methyl-3-phenylpropanoate in 56% optical yield but only in 43–48% chemical yield.



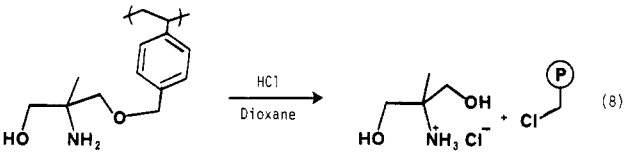
(7)

By comparison, Meyers et al. reported[4] unoptimized chemical yields of 54–59% and optical yields of 60–67%.[12] Our lower chemical yields undoubtedly resulted from incomplete hydrolysis, as witnessed by the IR spectrum of the recovered polymer which showed, in addition to bands for the amino alcohol, **12**, a medium-intensity band at 1645 $cm^{-1}$ (C=N, oxazoline **11**) and a less intense band at 1730 $cm^{-1}$ (C=O, amino ester).

Incomplete hydrolysis of the bulky chiral oxazolines was a problem which was anticipated based on studies of **3** and **4** and their alkylation products.[13,14] In that study, it was found that the relative rate of hydrolysis of **3** (R variable) to amino alcohol and carboxylic acid is Me ≥ Et > $PhCH_2CH_2$ > $PhCH_2C(CH_3)H$. Also, the yield of amino ester increased in the opposite order. Thus, the problem appears to be hydrolysis of the amino ester. Meyers et al.[4] observed similar steric problems in their studies and attributed these effects to their low chemical yields which occurred in a few of their examples (e.g., 22% for $PhPrCHCO_2H$ and 30% for $PhCH_2CH(Et)CO_2H$).

In one attempt each, polymer **10** was alkylated with *n*-propyl iodide, giving ethyl 2-methylpentanoate (33%), and with *n*-butyl iodide, giving ethyl 2-methylhexanoate (35%) after ethanolysis. These alkylations (by weight increase) and ethanolyses (by IR analysis) appeared to be incomplete.[15]

We were unable to effectively improve the chemical yields of carboxylic acids or esters from alkylation of **10**[13] because it was found that longer hydrolytic reaction times or otherwise more acidic conditions caused damaging side effects. For example, when the polymer-bound oxazoline was allowed to stir with aqueous or ethanolic acid for extended periods of time, cleavage of the amino alcohol residue from the polymer occurred by hydrolysis of benzylic ether linkage[13] (eq 8). While this loss could be decreased by using a less reactive attachment site,[16] less severe hydrolysis conditions would be more desirable.



(8)

Under the conditions used for ethanolysis of **11**, a higher boiling impurity accompanied distillation of the desired ester, thus requiring preparative GLC in order to obtain the pure ester. On the basis of its IR and NMR spectrum, the impurity is tentatively identified as ethyl 4-hydroxybutyl ether, the ethanolysis product of THF.

**Promise of the Method.** The major disadvantage of this procedure is the insensitivity of the alkylated oxazolines to hydrolysis. While the achiral polymer **8** produced a 68% yield of achiral ethyl 2-methyl-3-phenylpropanoate, the chiral polymer **11** only gave 43–48% of chiral ethyl 2-methyl-3-phenylpropanoate. Thus, the same phenyl group that leads to a high stereospecificity[2] apparently greatly slows hydrolysis. Furthermore, the polymer attachment, which could possibly give enhanced stereospecificity, apparently does not greatly affect stereoselectivity, but it seems to slightly reduce yield. The latter effect, however, may be a phase-transfer problem rather than a steric problem. The poor phase transfer, which produced very long reaction times, has now been corrected by others.[1,8,9] The long periods of time required for the wash sequences remain a disadvantage. This may be partially remedied by automation, but this would only be feasible if many similar procedures are to be accomplished.

Some workers seem to prefer the macroreticular (nonswelling) polymer to the microreticular gel-like beads of the Merrifield polymer.[17,18] We used the microreticular resin in the present study and found that the swelling and shrinking of the polymer may be unnecessarily restrictive especially with respect to the choice of solvents.

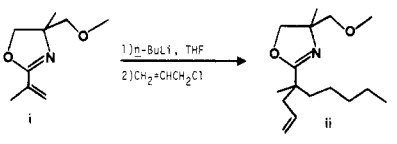
Despite the problems described here, the use of chiral polymer-bound substrates in asymmetric synthesis is a worthwhile approach. Although we had adequate experience in handling soluble polymers and in handling low molecular weight oxazolines, this was our first experience with solid-phase synthesis; therefore, the results here may, in part, be a result of that inexperience. The hydrolysis problems with oxazolines make recycling the spent polymer

(11) The 2% cross-linked polymer was found to be much easier to work with than the 1% cross-linked polymer, which proved to be rather fragile.

(12) Optical yields of the acid were optimized to ca. 80% by Meyers et al. with LDA as the base and by using techniques to prevent racemization of the acid upon hydrolysis (ref 4).

(13) Colwell, A. R. Masters Thesis, The University of Alabama in Huntsville, May 1978.

(14) In another study (McManus, S. P.; Lian, J.-S., unpublished results), oxazolines i and ii were prepared in high yields but ii was very resistant to hydrolysis, being nearly completely recovered after exposure to stronger hydrolysis conditions that were previously used successfully for less hindered oxazolines (cf. ref 4).




(15) Brooks, R. Senior Thesis, The University of Alabama in Huntsville, Spring 1978.

(16) McManus, S. P.; Olinger, R. D. *J. Org. Chem.* **1980**, *45*, 2717.

(17) Weinshenker, N. M.; Crosby, G. A.; Wong, J. Y. *J. Org. Chem.* **1975**, *40*, 1966.

(18) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

inefficient and lead to complex mixtures in subsequent cycles. For this reason alone, solid-phase synthesis using chiral polymer-bound oxazolines cannot be recommended unless the efficiency of the hydrolysis step can be greatly improved.

## Experimental Section

**General Methods.** Elemental analyses were preformed by Galbraith Laboratories, Inc. All infrared spectra were obtained on a Beckman Acculab I. NMR spectra were obtained in $CDCl_3$ solutions with an internal $Me_4Si$ reference on a 90-MHz Bruker HFX-10 and a 60-MHz Varian EM-360. Gas–liquid chromatography (GLC) was performed on a Varian Aerograph Series 1800 instrument equipped with flame-ionization detector and Honeywell recorder fitted with Model 201-13 disc chart integrator. All GLC analysis utilized a 0.25 in. × 4 ft aluminum column of 5% SE-30 on Chromosorb P. Optical rotations were obtained on a Rudolph Model 51B polarimeter equipped with sodium lamp and 589-nm filter.

**Solvent and Reagent Purification and Drying.** Except as described below, all reagents and solvents were used as obtained without further purification. Poly(styrene-*co*-divinyl benzene) (Bio-Rad SX-1 or SX-2) was chloromethylated[18] or the chloromethylated polymer (2% DVB) was purchased (Polysciences). In either instance, it was found necessary to subject the commercially available polymers to a wash cycle[5] prior to use.

Tetrahydrofuran was dried over $LiAlH_4$ and distilled just prior to use. Both methylene chloride and chloroform were distilled prior to use and stored over 4-Å molecular sieves. Sodium hydride, as an oil dispersion, was washed with dry benzene to remove the oil. Benzyl chloride was vacuum distilled, stored over 4-Å molecular sieves, and used within 14 days. Oxazolines were either prepared by the method of Billman and Parker[19] or as described by Meyers et al.[4] and were purified prior to use.

**Filtration of the Polymer Beads.** Filtration of the swollen polymer beads was a problem with both the 1% and, to a lesser extent, the 2% cross-linked polymer beads. Application of ordinary techniques such as gravity or suction filtration on a fritted glass filter proved either useless or extremely time consuming. This problem was minimized by the use of a pressure filter system which minimized clogging of the frit. The filtrations or washings were carried out at a pressure of only 1–5 psi (using air or nitrogen). The system was designed to operate safely at 50 psi.

The system consists of a large fritted glass filter of medium porosity fused to the cylinder section of the lower part of a two-piece polymerization flask. The top of the system was fitted with a pair of stopcocks, one for a gas inlet and the other to allow for rapid addition of wash solvents. The two piece flask, mated at a flat ground-glass joint, was held together by a clamp provided with the polymerization flask. The solvent inlet was designed to be large enough (710 mm) to allow passage of a long rod for stirring the mixture. A sketch of the system is shown in Figure 1.

**Preparation of Poly(styrene-*co*-divinylbenzene) Functionalized with a 2,4-Dimethyl-2-oxazoline Moiety.** In a typical reaction, sodium hydride (4.8 g, 220 mmol) was dissolved in dry THF (150 mL) in a dry $N_2$-flushed 500-mL three-necked flask, equipped with 250-mL addition funnel, condenser, and drying tube. 4-(Hydroxymethyl)-2,4-dimethyl-2-oxazoline (1; 21 g, 170 mmol) in dry THF (150 mL) was added to the stirred mixture of sodium hydride and THF at a rate to maintain a mild evolution of hydrogen. When addition was complete the reaction, now a light gray to cream color, was allowed to stir for approximately 15 min. The solution was then heated at 50–60 °C for 1.5 h and cooled to room temperature. To the solution, now containing the sodium salt of 1, was added 10 g of chloromethylated polystyrene beads (1.7 mmol of Cl/g), which was previously swollen by standing in dry THF (150 mL) for 0.5 h. The $N_2$ was removed and the reaction was stirred at room temperature with a drying tube attached for 336 h. A tenfold excess (recoverable) of the oxazoline salt was used to maximize reaction of "reactive" chloride groups. The reaction mixture was poured into the pressure filter apparatus for washing. On addition of 50–100 mL of 1:1 THF–water a mild reaction due to unreacted NaH was observed. This initial wash also removed sodium chloride. The polymer beads were then washed twice with 200 mL of THF and twice with 3:1 THF–water (300 mL) followed by a sequence of nine washes (each ~300 mL) which changed gradually from water to nearly pure THF to pure methanol. The ratio of water–THF–methanol used for each wash was as follows: 9:1:0, 7:3:0, 1:1:0, 3:7:0, 1:8:1, 0:7:3, 0:1:1, 0:3:7, pure MeOH. Drying overnight under vacuum at 50 °C gave 11.8 g of the polymer-bound oxazoline **3** (theoretical yield 11.5 g based on 1.7 mmol of Cl/g chloromethyl polymer). This additional weight appeared in many of the reactions of the polymers and is probably a result of incomplete washing since additional drying caused no additional weight loss; IR (KBr) 3020, 2910, 1665 (C=N), 1600, 1485, 1440, 1380, 1290, 1075–1085, 975, 805, 745, 685 $cm^{-1}$. Elemental analysis of selected oxazoline polymers revealed a range of N incorporation from 0.84 to 1.31 mmol of N/g (from polymer with 1.16 to 1.67 mmol of Cl/g).

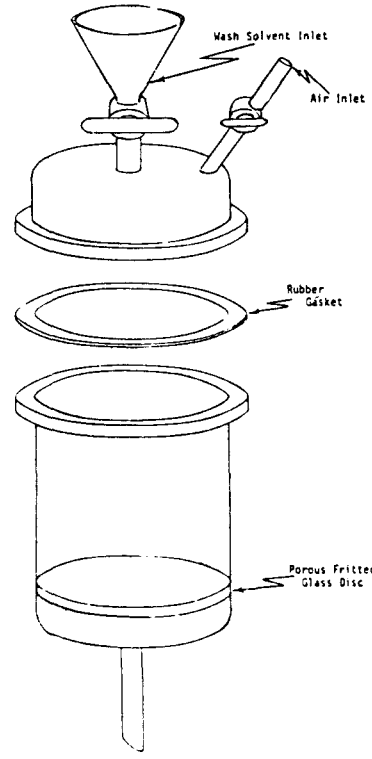



**Figure 1.** Pressure filter system for washing swollen polymer.

**Preparation of Poly(styrene-*co*-2% divinylbenzene) Functionalized with the 2-Ethyl-4-methyl-2-oxazoline Moiety.** The polymer was prepared according to the procedure given for **3**. The oxazoline salt was obtained by using sodium hydride (4.8 g, 200 mmol) in dry THF (150 mL) and 4-(hydroxymethyl)-2-ethyl-4-methyl-2-oxazoline (23 g) dissolved in 150 mL of dry THF. Adding 10 g of chloromethylated polymer (1.7 mmol of Cl/g) swollen in 150 mL of dry THF and reacting for 336 h gave 11.7 g (theory 11.6 g) of the 2-ethyl-2-oxazoline functionalized polymer **4**; IR (KBr) 3030, 2930, 1665 (C=N), 1600, 1490, 1450, 1350–1360, 1150, 1080–1090, 1000, 810, 750, 690 $cm^{-1}$.

**Alkylation of Polymer-Bound 2-Alkyloxazolines. General Procedure: Alkylation of 3 with Benzyl Chloride.** The following alkylation procedure is typical of that used throughout this work. Polymer **3** (3.5 g, 1.43 mmol of oxazoline/g) was swollen with dry THF (150 mL) in a 500-mL three-necked flask equipped with addition funnel, rubber septum, and drying tube. The system was continuously purged with dry $N_2$ and cooled to −43 °C with dry ice–monochlorobenzene. *n*-Butyllithium (12 mL, 2.5 M in hexane, a 5-fold excess[10]) was added to the addition funnel by injection through a rubber septum and then added dropwise over a period of approximately 15 min to the swollen oxazoline polymer. After addition was complete, the dark orange solution was allowed to stir at −43 °C for 1.75 h to ensure complete formation of the lithium salt. Benzyl chloride (10.0 g, 0.079 mol, a 13-fold excess)

(19) Billman, J. H.; Parker, E. E. U.S. Patent 2 556 791; *Chem. Abstr.* **1952**, *46*, 525.

in 40 mL of dry THF was added dropwise over a period of about 40 min and the solution gradually turned a light orange color. Upon complete addition of benzyl chloride solution, the reaction was stirred for 30 min at −43 °C after which it was warmed up to −20 °C and stirred at that temperature for an additional 20 min. All cooling was then removed, thus allowing a gradual warming to room temperature. The reaction, now a cream color, was left stirring for 24 h and pressure filtered. The polymer beads were washed twice with 200 mL of THF and twice with 300 mL of 3:1 THF–$H_2O$, followed by a sequence of nine washes (each wash ~300 mL) which changed gradually from water to pure THF to 100% methanol. Drying under vacuum at 50 °C gave the 2-phenethyl-4-methyl-2-oxazoline functionalized polymer (6; 3.9 g, theoretical weight 3.9 g); IR (KBr) 3030, 2925, 1665 (C=N), 1600, 1492, 1448, 1350–1360, 1140, 1080–1090, 985, 808, 745, 690 $cm^{-1}$.

**Alkylation of the 2-Ethyl-4-methyl-2-oxazoline Functionalized Polymer (4) with Benzyl Chloride.** By use of the procedure described above, polymer 4 (3.5 g, 1.43 mmol of N/g of polymer) was converted to its lithium salt, using 12 mL of *n*-butyllithium (a 5-fold excess), and alkylated, using benzyl chloride (10.0 g, 0.079 mol), giving the 2-(1-phenyl-2-propyl)-4-methyl-2-oxazoline functionalized polymer (8; 3.9 g, theoretical weight 3.9 g); IR (KBr) 3030, 2920, 1660 (C=N), 1600, 1492, 1450, 1350–1370, 1080–1090, 1010, 810, 740, 690 $cm^{-1}$.

**Double Alkylation of 3.** The first alkylation of 3 to produce 6 was carried out as described above. After the product was washed and dried under vacuum at 50 °C, 3.9 g of 6 (3.8 g, theoretical, based on 1.02 mmol of N/g) was obtained. The IR spectrum of this sample of 6 appeared identical with that obtained above.

Alkylation of 6 was accomplished by using a procedure identical with that above. Employing 3.85 g of the 2-phenethyl-4-methyl-2-oxazoline functionalized polymer (6), 12 mL of *n*-butyllithium (a 5-fold excess), and 11.0 g (0.078 mol) of methyl iodide gave 3.9 g of the purified 2-(1-phenyl-2-propyl)-4-methyl-2-oxazoline functionalized polymer (8; theoretical weight 3.8 g). The IR spectrum of this sample of 8 appeared identical with that obtained from alkylation of 4 with benzyl chloride.

**Preparation of Hydrocinnamic Acid by Hydrolysis of 6.** To 2-phenethyl-4-methyl-2-oxazoline functionalized polymer (6; 3.98 g, 1.42 mmol of N/g) swollen in THF (250 mL) was added 28 mL of 3 N HCl (0.084 mol). The resulting suspension was heated to 60 °C with stirring for 48 h after which the reaction mixture was cooled to room temperature and pressure filtered. The beads were rinsed with two 50-mL portions of ethyl ether, the combined yellow filtrate was placed in a separatory funnel, and the resulting aqueous layer was separated. The ether/THF solution was concentrated (without drying) in vacuo. The aqueous layer from the original filtrate was extracted twice with 25-mL portions of ether, which were then combined with the other organic solution and evaporated as before. The two-phase solution which resulted was made basic with 40% NaOH and the aqueous layer was extracted twice with 15-mL portions of ether. The resulting basic aqueous layer was placed in an ice bath and acidified by dropwise addition of 6 N HCl. Seeding the cloudy solution with a small crystal of hydrocinnamic acid gave crude hydrocinnamic acid (0.7 g). Dissolving the crude crystals in a small amount of ether and distilling at 145 °C (18 mm) gave a colorless oil which crystallized on agitation to give 0.6 g of pure hydrocinnamic acid (81%), mp 45–47 °C, which was identical (melting point, IR, NMR) with an authentic sample.

The polymer beads which resulted from the hydrolysis were washed with 200 mL of THF followed by 100 mL each of solutions containing 4:1, 2:2, 1:4, and 0:1 THF–dioxane. The polymer was washed with 200 mL of 3:1 dioxane–$H_2O$ followed by 300 mL each of a sequence of nine washes which gradually changed from water to pure dioxane to 100% methanol. Drying under vacuum at 50 °C for 24 h gave the amino alcohol functionalized polymer (7) which was set aside for recycling (see below); IR (KBr) 3300–3380 (br, OH), 3030, 2910, 1730 (w, C=O, amino ester), 1600, 1485, 1445, 1060–1100, 860, 805, 740, 680 $cm^{-1}$. Anal. Found: 1.31 mmol of N/g.

**Preparation of Esters by Alcoholysis of 2-Alkyloxazoline Polymers.** To the 2-(1-phenyl-2-propyl)-4-methyl-2-oxazoline functionalized polymer (8; 4.0 g, 1.42 mmol of N/g) swollen in THF (100 mL) was added 100 mL of ethanolic $H_2SO_4$, prepared by adding 4 mL of concentrated sulfuric acid and 5 mL of water to 50 mL of 95% ethanol and bringing the total volume to 100 mL by adding additional ethanol. The suspension was heated to reflux for 168 h, cooled to ambient temperature, and pressure filtered. The yellow filtrate was concentrated to approximately 25 mL in vacuo. This solution was mixed with 200 mL of diethyl ether. The resulting two-phase solution was separated and the organic phase was washed with saturated sodium chloride solution (4 × 50 mL). The ether layer was dried ($K_2CO_3$) and concentrated in vacuo yielding a light yellow liquid containing ethyl 2-methyl-2-phenylpropanoate along with impurities. The product yield (0.65 g, 68%) was obtained by GLC analysis using ethyl phenylacetate as the internal standard.

Distillation of the sample gave two fractions, the first boiling at 50 °C (1.5 mm) and the second (containing the product) at 95–105 °C (2.4 mm) [lit.[20] bp 76–79 °C (0.75 mm)]; IR (KBr) of fraction two 3440–3450 (OH, due to impurity from fraction one), 2990, 2950, 2880, 1740 (C=O), 1610, 1460, 1385, 1290, 1260, 1180, 1118, 745, 700 $cm^{-1}$. The NMR was consistent with the structure of the product and gave the following proton signals: NMR ($CD_3COCD_3$) δ 7.11 (s, 5 H, Ar H), 3.99 (q, 2 H, $OCH_2CH_3$), 1.1 (t, 3 H, $OCH_2CH_3$); proton signals from the impurity were located at δ 3.25 (m) and 1.56 (m) and are tentatively assigned as those from a hydrolysis product of THF (see below).

The resulting polymer beads were washed and dried as for the sample of 7 from above. The IR analysis showed these samples to be essentially identical. These beads were set aside for recycling.

**Preparation of Recycled 2,4-Dimethyl-2-oxazoline Functionalized Polymer (3).** The amino alcohol functionalized polymer (7; 3.2 g) from the hydrolysis reactions above was swollen in 1:1 chloroform–toluene (180 mL) and ethyl iminoacetate hydrochloride[21] (3.15 g, 0.026 mol, 5-fold excess) in dry 1:1 chloroform–toluene (180 mL) was added. The reaction flask was then fitted with a condenser with drying tube and a magnetic stirrer and was heated to reflux with stirring for 336 h. The reaction mixture was cooled to room temperature and pressure filtered. The resulting beads were washed twice with 200 mL of 1:1 toluene–chloroform followed by 200 mL each of 4:4:3, 1:1:2, and 1:1:4 chloroform–toluene–THF solutions. This was followed by 200 mL of THF and 200 mL of 3:1 THF–$H_2O$. The beads were finally treated with a sequence of nine washes as described in procedures above. Drying the support under vacuum at 50 °C gave the 2,4-dimethyl-2-oxazoline functionalized polymer (3) which by IR analysis appeared identical with the original polymer except for a small peak at 1745 $cm^{-1}$ (amino ester).[22]

**Use of Recycled Polymer 3 for Preparation of Ethyl Hydrocinnamate.** By the same procedure used for this conversion with virgin 3, recycled 3 (3.2 g, 0.92 mmol of oxazoline/g) was metalated with *n*-butyllithium and alkylated with benzyl chloride, giving 3.5 g (theoretical weight 3.5 g) of the washed and dried alkylation product, the 2-phenethyl-4-methyl-2-oxazoline functionalized polymer. The infrared spectrum of the product was identical with that obtained from the procedure with virgin 3.

Ethanolysis of a sample of the alkylated polymer (3.4 g) provided ethyl hydrocinnamate (0.26 g, 51%, by GLC).

The resulting polymer beads were subjected to the multisolvent wash and dried (vacuum oven, 50 °C), giving the amino alcohol polymer (7). The infrared spectrum of recycled 7 was identical with that of 7 obtained from virgin 3.

**Preparation of Polymer-Bound Chiral Oxazoline 10.** By a procedure similar to that described for preparation of 3, *trans*-(4*S*,5*S*)-2-ethyl-4-(hydroxymethyl)-5-phenyl-2-oxazoline[4] (9; 35.0 g, 170 mmol) in dry THF (150 mL) was converted to its sodium salt (NaH, 4.8 g, 200 mmol) and then reacted 336 h with

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(22) The presence of the amino ester, which may result from wet washes or, in the case of the recycled polymer, from a previous incomplete hydrolysis step, caused us to look for ways to remove it. Dicyclohexylcarbodiimide was not successful in cyclizing it back to oxazoline, but it was observed that alkylated polymer no longer contained any amino ester. This is thought to be the result of butyllithium extraction of a proton from the free amino group to give an anion that cyclizes.

chloromethylated polymer (10 g, 1.67 mmol of Cl/g) (2) in dry THF (150 mL), giving, after washing and drying, the *trans*-(4*S*,5*S*)-2-ethyl-5-phenyl-2-oxazoline functionalized polymer (10); IR (KBr) 3030, 2910, 1665 (C=N), 1600, 1490, 1450, 1360, 1250, 1180, 1115, 985, 870, 910, 740, 680 $cm^{-1}$. Anal. Calcd for 90% displacement of Cl and 26% of the repeating units functionalized: C, 85.20; H, 7.30; N, 2.09; Cl, 0.62. Found: C, 85.48; H, 7.65; N, 1.71; Cl, 0.49.

**General Procedure for Preparation of Chiral Ester from 10. Preparation of *S*-(+)-Ethyl-2-methyl-3-phenylpropanoate.** By use of a procedure identical with that used for alkylation of the achiral oxazolines 3 and 4, the *trans*-(4*S*,5*S*)-2-ethyl-5-phenyl-2-oxazoline functionalized polymer (10; 3.5 g, 1.22 mmol of oxazoline/g) in dry THF (150 mL) was treated stepwise with 12 mL of *n*-butyllithium at -78 °C (in dry ice-acetone) or at -43 °C (in dry ice-monochlorobenzene) and benzyl chloride[10] (10.0 g, 0.79 mol) in dry THF (40 mL), giving the alkylated polymer 12 (3.9 g, theoretical weight is 3.9 g); IR (KBr) 3030, 2910, 1652 (C=N), 1600, 1490, 1445, 1360, 1245, 1170, 1105, 975, 865, 740, 675 $cm^{-1}$.

By the procedure described for ethanolysis of 6, the sample of optically active benzylated oxazoline polymer (12; 3.7 g) from the -40 °C alkylation was swollen in 100 mL of THF and reacted with 100 mL of ethanolic sulfuric acid at 58 °C for 120 h. Workup provided 2.7 g of a light yellow liquid which contained (by GLC) 0.24 g (48%) of *S*-(+)-ethyl 2-methyl-3-phenylpropanoate. Distillation gave the purified ester: bp 70-80 °C (1.5 mm) [lit.[23] bp 90 °C (4.5 mm)]; $[\alpha]^{22.2}_{589}$ +15.0° (*c* 2.836, EtOH) [lit.[23] $[\alpha]^{18}_{589}$ +26.93° (neat)]; IR (KBr, neat) 3410-3440 (OH, due to impurity), 2980, 2940, 2880, 1730 (C=O), 1600, 1490, 1452, 1375, 1175, 1105, 1055, 735, 690 $cm^{-1}$; NMR ($CD_3COCD_3$) $\delta$ 7.11 (s, 5 H, Ar H), 3.99 (q, 2 H, $OCH_2CH_3$), 1.1 (t, 3 H, $OCH_2CH_3$), 3.75 (m), 1.56 (m). The latter two peaks were tentatively identified as arising from the ethanolysis product of THF, which codistilled with the product (20% by GLC). Subsequent experiments showed that the product could be obtained free of the impurity by preparative GLC. The polymer support which resulted was washed and dried, giving the amino alcohol polymer (13) along with unhydrolyzed or partially hydrolyzed oxazoline polymer; IR (KBr) 3200-3400 (br, OH), 3020-3600, 2920, 1720-1730 (C=O, amino ester), 1660 (C=N, oxazoline), 1660, 1490, 1450, 1362, 1070, 902, 810, 745, 685 $cm^{-1}$.

**Ethanolysis of Tetrahydrofuran.** A sample of ethanolic sulfuric acid in THF was prepared identically with the solution used to cleave the oxazoline polymer sample. Refluxing this solution for 336 h, neutralization ($Na_2CO_3$), and distillation provided a complex mixture collected over the range 30-65 °C (1.85 mm), with the bulk of the material having a boiling range of 54-63 °C (1.85 mm). The principal component, tentatively identified as ethyl 4-hydroxylbutyl ether, had the same IR and NMR spectral characteristics and an identical GLC retention time as the impurity from the ethanolysis experiments above.

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**Registry No.** 1, 39986-37-3; 2, 53416-48-1; 9, 51594-33-3; (*S*)-(+)-ethyl 2-methyl-3-phenylpropanoate, 70878-24-9; polystyrene, 9003-53-6; benzyl chloride, 25168-05-2; methyl iodide, 74-88-4; hydrocinnamic acid, 501-52-0; ethyl 2-methyl-2-phenylpropanoate, 2901-13-5; ethyl hydrocinnamate, 2021-28-5.

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# Biomimetic Polyene Cyclizations. Asymmetric Induction during the Acid-Catalyzed Cyclization of Chiral Imines

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This paper reports the details of a basic study showing that an imino function is suitable to initiate acid-catalyzed cyclizations of polyenes, affording high yields of cyclized products. The additional advantage of such a function is to introduce very easily a chirality on the polyene skeleton by the way of a chiral group linked to nitrogen. The extent of asymmetric induction by a chiral phenethyl group on nitrogen is from 36% to 65%, according to the monocyclic or bicyclic nature of the substrate.

The results obtained during the study of the biogenetic synthesis of sterols[1-3] and the stereospecificity of the enzymatic cyclization of epoxysqualene to lanosterol[4] allowed the development of a new strategy for the total synthesis of polycyclic natural products, particularly the steroids and polycyclic triterpenoids usually prepared through step by step annelations.

After a first unsuccessful attempt by Eschenmoser,[5] several biomimetic polyene cyclizations, involving the production of a number of rings stereospecifically in a single step by the ring closure of an acyclic chain having oppositely placed trans olefinic bonds, were reported and demonstrated the aptitude of several functions such as aldehyde,[6-9] carboxylic acids,[10,11] epoxide,[12] or allylic alcohol[13-21] to induce acid-catalyzed cyclizations.

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