Synthesis, Reactions, and ^{13}C FT NMR Spectroscopy of Polymer-Bound Steroids[1]

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Dehydrocholic acid (3,7,12-trioxo-5β-cholanoic acid) and cholic acid (3α,7α,12α-trihydroxy-5β-cholanoic acid) were attached, via their carboxyl groups, to chloromethylated poly(styrene–2% divinylbenzene) to form the polymers **1** and **6**, respectively. Synthetic transformations of the bound steroids containing the carbonyl and hydroxyl groups and esterification of hydroxyl functions was obtained by ^{13}C NMR spectra of solvent swollen polymer gels. The ^{13}C NMR spectra of the bound steroids represents a major advance in the analysis of polymer-supported species, permitting structural assignments to be made, on a qualitative basis, of the intact polymer without resorting to cleavage reactions of the bound material.

Polymer-supported synthesis of peptides are well documented for over two decades,[2-4] and, more recently, the syntheses of a number of oligodeoxyribonucleotides have been reported.[5] Polymeric catalysts and reagents have also been developed.[6] However there few reports[7-9] of synthetic transformations of polymer-bound steroids. Specific use of site isolation on polymers is demonstrated[6] for retardation or enhancement of bimolecular processes. A major impediment to the development of polymer-supported transformations of organic molecules has been the lack of adequate analytical data. The acute need for adequate characterization of polymer-supported reagents and catalysts, particularly NMR and UV–vis spectroscopy, has long been recognized.[7]

Results and Discussion

This investigation involves the synthesis of polymer-bound cholic acid derivatives containing keto and hydroxyl functionalities and the reaction of these compounds for synthetic purposes with the long-term goal of examining stereochemical effects, if any, exerted by the support. In addition, we examined the influence of the polymer support[10] and spacer groups upon the synthetic transformations of the bound functional groups. An important aspect of the investigation is the use of ^{13}C FT NMR spectroscopy to detect, on a qualitative basis, synthetic changes in functional groups of the polymer-supported steroid. Of the spectroscopic methods that are available for the direct examination of reactive polymers, few have offered much in the way of good qualitative or quantitative data. Various polymer-bound dehydrocholates were prepared (see Table I) according to procedures similar to those employed in solid-phase peptide synthesis.[2-4,7,11,12] For example, the polymeric 3,7,12-trioxocholanoate (**1**) was prepared by reaction of a chloromethylated (1.25 mequiv/g) poly(styrene–2% divinylbenzene) with dehydrocholic acid (3,7,12-trioxocholanionic acid) in DMF with potassium fluoride[13,14] in 93% yield. An alternative method of preparation[15] makes use of the cesium salt of the carboxylic acid and the chloromethylated polystyrene in DMF. The polymer–dehydrocholate, **1**, could be cleaved by the action of sodium hydroxide/triethylamine in methanol–*p*-dioxane to yield, after neutralization, a 87% yield of dehydrocholic acid, identical in all respects with an authentic sample. The tris-3,7,12-ketal (**2**) was prepared from **1** by reaction with ethylene glycol (1,2-ethanediol) and *p*-toluenesulfonic acid in benzene quantitatively. In contrast, the reaction of **1** with (2,4-dinitrophenyl)-hydrazine (containing phosphoric acid, ethanol, and water) with ethanol as a solvent gave a poor yield of the polymer–bound hydrazone derivative **3**. The low yield was, in part, due to the poor solvent swelling characteristics of ethanol and cleavage of the steroid from the polymer by the acidic reaction conditions.

A spacer, *p*-alkoxybenzyl group, was used in conjunction with a cross-linked polystyrene support[16] and dehydrocholic acid to prepare **4** in 48% yield. Treatment of **4** with (*p*-tolylsulfonyl)hydrazine in glacial acetic acid gave a polymeric product with a ^{13}C NMR spectrum that contained no recognizable steroidal features, including either keto or hydrazone functionality. The minimum detection level of the NMR spectrum was estimated to be 4.8%, based on the signal-to-noise level. The spectrum did show strong signals characteristic of cross-linked polystyrene containing hydroxymethyl groups at 65 ppm.[17] This

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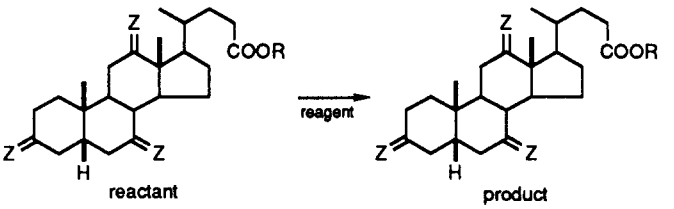
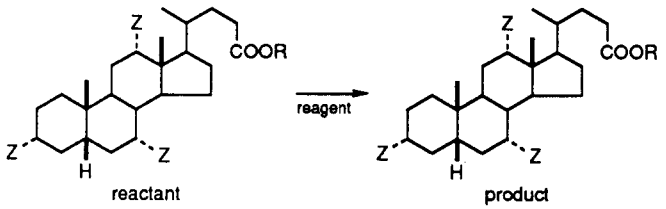
Table I. Polymer-Bound Dehydrocholates[a]



Z	R	DF	reagent	Z	R	DF	yield, %	product
O	H	–	ⓟCH_2Cl (DF = 0.15)	O	CH_2ⓟ	0.14	93	**1**
O	CH_2ⓟ	0.13	$HOCH_2CH_2OH$	$O(CH_2)_2O$	CH_2ⓟ	0.13	100	**2**
O	CH_2ⓟ	0.14	$NH_2NHPh(NO_2)_2$-2,4	NNHPh-2,4-$(NO_2)_2CH_2$ⓟ	CH_2ⓟ	0.04	28	**3**
O	H	–	$HOCH_2PhOCH_2$ⓟ (DF = 0.12)	O	CH_2PhOCH_2ⓟ	0.06	48	**4**
O	CH_2PhOCH_2ⓟ	0.06	$CH_3PhSO_2NHNH_2$	?	?	–	0	–

[a] See the Experimental Section for details.

Table II. Polymer-Bound Cholates[a]



Z	R	DF	reagent	Z	R	DF	yield, %	product
OH	H	–	$ClCH_2$ⓟ (DF = 0.13)	OH	CH_2ⓟ	0.12	89	**6**
OH	CH_2ⓟ	0.12	3,5-$(NO_2)_2PhCOCl$, py	mono-DNB	CH_2ⓟ	0.12	100	**7**
				di-DNB	CH_2ⓟ	0.08	69	–
				tri-DNB	CH_2ⓟ	0.05	42	–
OH	CH_2ⓟ	0.12	DMSO, $(COCl)_2$, TEA THF, −10 °C	O	CH_2ⓟ	0.12	100	**1**

[a] See the Experimental Section for details.

polymeric product was apparently derived from cleavage of the benzylic ester bond (C-24) linking the dehydrocholate moiety to the spacer–polymer support by the hydrazine/acetic acid combination.

Table II records the data regarding the synthesis of polymer-bound cholic acid derivatives. The 3α,7α,12α-trihydroxycholanoate **5** was prepared in high yield from the cross-linked, chloromethylated polystyrene and the sodium salt of cholic acid in DMF in 65 °C. This polymer could be quantitatively monofunctionalized by reaction with 3,5-dinitrobenzoyl chloride in pyridine (also accompanied by some di- and trifunctionalization). The ^{13}C NMR spectrum (see Figure 3b) of the resulting **6** does not permit assignment of the location of each dinitrobenzoate group on the steroidal framework, nor is there any quantitative analysis of the NMR spectrum to give the percent mono- or di- or trireaction at carbon positions 3, 7, and 12. Elemental nitrogen analysis of this product shows 100% monoesterification (probably at position 3) and 69% di- and 42% triesterification. Work is in progress to define such reaction conditions using less than an excess of 3,5-dinitrobenzoyl chloride with the polymer–cholate **5**. Oxidation of **5** with the Swern reagent[18,19] (DMSO–oxalyl chloride–triethylamine) gave quantitative oxidation of all three hydroxyl groups of **5** to yield the triketo polymer–dehydrocholate **1**. Conditions are also under investigation that would permit a study of the regioselectivity of Swern reagent and **5**.

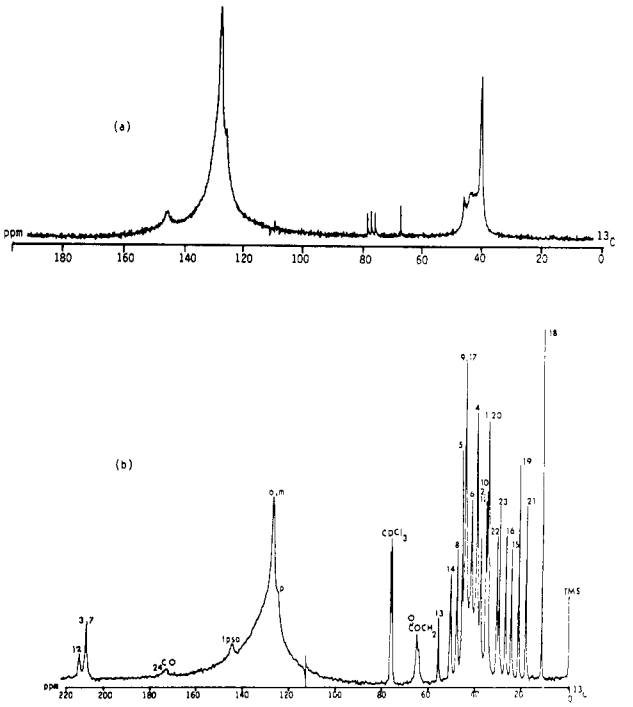


Figure 1. ^{13}C NMR spectra in $CDCl_3$ of (a) 0.7 mmol chloromethylated poly(styrene-2% divinylbenzene) at 25.4 MHz and (b) polymer **1** at 75.4 MHz.

^{13}C NMR Spectra

Confirmation of the synthetic transformations performed on polymer supports was obtained by use of ^{13}C

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Table III. ^{13}C NMR Spectral Assignments and T_1 and NOE Values

carbon	δ CH_3[a]	δ 1	1 T_1[b]	1 NOE	2 T_1[b]	2 NOE
18	11.7	11.8	0.94	1.80	0.68	2.02
21	18.5	18.6	0.39	2.20	0.46	2.35
19	21.5	21.8	0.61	1.98	0.56	2.20
15	25.1	25.1	0.17	2.13	0.21	2.63
16	27.5	27.6	0.18	2.21	0.14	2.48
23	30.4	30.4	0.18	2.30	0.17	2.55
22	31.3	31.4	0.19	2.21	0.18	2.33
1	35.2	35.4	0.18	2.00	0.26	2.10
20	35.4	35.4	0.18	2.00	0.26	2.10
10	36.0	35.9		1.63	0.16	2.51
2	36.4	36.4	0.23	2.13	0.13	2.80
11	38.6	38.6	0.19	2.02	0.18	2.72
4	42.7	42.7	0.15	1.85		1.60
6	44.9	44.9	0.26	2.01		1.99
17	45.6	45.4	0.26	1.85		
9	45.7	45.4	0.26	1.85		
5	46.7	46.7	0.21	1.85		1.29
8	49.0	48.9	0.30	1.88	0.40	1.91
CH_3	51.3					
14	51.8	51.7	0.32		0.33	2.63
13	56.9	56.8		1.54		
COO	174.3	174.1				
7	208.4	209.0				
3	208.6	209.0				
12	211.6	211.8				

[a] Methyl ester chemical shift values as reported in ref 12. Polymer-dehydrocholate was determined in $DCCl_3$. The polystyrene support was a 2% DVB copolymer with a 1.3 mequiv of CH_2Cl/g. The spectrum was obtained with a pulse width of 12.0 Hz, pulse delay, D1 = 1.0 s, and 45 000 acquisitions at 75.4 MHz. [b] T_1 values are in seconds. Both T_1 and NOE values are subject to error due to overlapping peaks.

NMR spectra of solvent swollen gels[20] at either 75 or 25 MHz (see the Experimental Section for details). The structual assignments for each chemical shift value were made by comparison between solution spectrum of the corresponding methyl ester and a spectrum[17] of cross-linked (2%) chloromethylated polystyrene [0.7 mmol/g CH_2Cl] (Figure 1a). The spectra of polymers 1–3 have relatively broad resonances for the methylene, methine, and aromatic carbons due to the polymer support, yet it is possible to observe up to 25 different chemical shift values assignable to the attached cholic acid derivatives as shown in Figures 1b, 2a, and 2b, respectively. Table III correlates the chemical shift assignments for methyl dehydrocholate[21] and polymer-bound dehydrocholate 1. (see Figure 1b). Most assignments are within ±0.3 ppm and no assignment exchanges position with other adjacent carbons, indicating that the chemical shift values of the steroid attached to the solvent-swollen polymer are the same as those of the homogeneous solution spectrum of the corresponding methyl ester. There is slight line broadening of the 3- and 7-carbonyl carbons in 1, superimposing the two chemical shift values that are resolved in the methyl ester under solution conditions.

Ketalization of 1 with ethylene glycol was verified by ^{13}C NMR spectrum (Figure 2a) of the product, 2, by an absence of any resonances in the 207–212 ppm range, indicating the lack of keto functions, and the appearance of new bands in the region of 63–66 ppm corresponding to methylene carbons of the ketal and 108–110 ppm of the ketyl carbons.[22] In similar fashion, (2,4-dinitrophenyl)-hydrazone formation from 1 was revealed in the spectrum

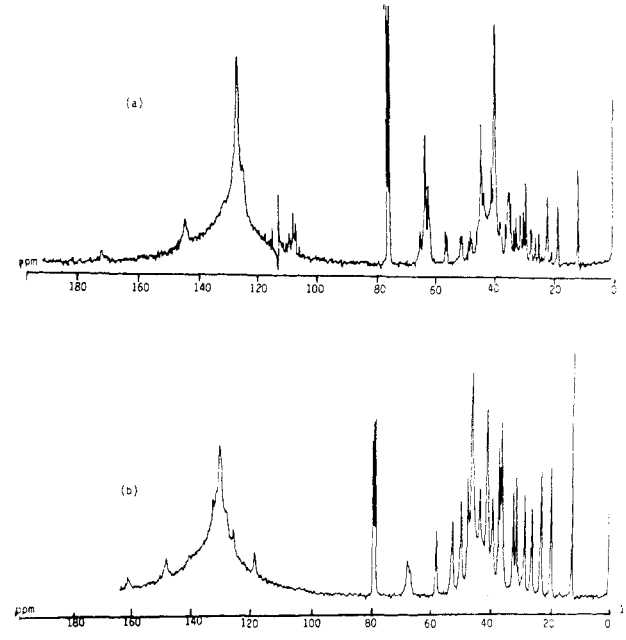

Figure 2. ^{13}C NMR in $CDCl_3$ at 75.4 MHz of (a) polymer 2 and (b) polymer 3.

of 3 (Figure 2b) where new aromatic carbons are seen at 116, 124, 130, and 159 ppm,[22] corresponding to the ring carbons of the phenylhydrazone. Some loss by acid-catalyzed cleavage of the steroid from the polymer is seen in the increased peak height at 65 ppm due to the hydroxymethylene group of the polymer.[17] Reaction of 1 with (*p*-tolylsulfonyl)hydrazine under acidic conditions[23] resulted in a polymeric product that had no discernible steroidal features in its ^{13}C NMR spectrum. The reaction conditions were apparently sufficiently acidic to cause cleavage of the benzylic ester bond that attached the steroid to the polymer. The T_1 and NOE values for most

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Table IV. Cholates

carbon	^{13}C PFT NMR, δ (ppm) methyl ester[a]	polymer 6	carbon	^{13}C PFT NMR, δ (ppm) methyl ester[a]	polymer 6
18	12.3	12.4	20	35.3	35.3
21	17.4	17.1	4	39.4	39.5
19	22.3	22.5	8	39.4	39.8
15	23.1	23.0	5	41.4	41.5
9	26.2	26.2	14	41.4	41.5
16	27.4	27.4	13	46.3	46.1
11	28.0	28.3	17	46.8	46.4
2	30.1	30.3	7	68.3	67.3
22	31.0	30.4	3	71.7	71.1
23	31.0	30.8	12	73.0	72.1
6	34.7	34.6	24-COO	174.7	174.0
10	34.7	34.8	CH_3	51.4	0
1	35.3	35.1			

[a] Reference 16.

of the steroidal carbons of polymers **1** and **2** are recorded at 75.43 MHz in Table III. With the exception of the methyl carbons, the T_1 values for ring methylenes and methine carbons are in the range 0.13–0.26 s, which are only slightly less than the values reported by Roberts[24] (methylene, 0.25 s; methine, 0.40 s; and quaternary, 2.0 s) for desoxycholic acid under homogeneous conditions. The T_1 values for **1** and **2** are consistent with a steroidal portion of the polymer being in an environment much like that of the corresponding methyl esters in homogeneous solution, suggesting that the polymer-bound steroidal framework is highly swollen with solvent.

Figure 3, parts a–c, shows the spectra for the polymeric cholates **6** and **7**. Again there is good agreement between the literature values for solution spectrum of methyl cholate[25] and polymer-bound cholate **6** recorded in this study as shown in Table IV. Figure 3a shows a clear resolution of the hydroxyl-bearing carbons at positions 3, 7, and 12. Dinitrobenzoylation of **6** with 3,5-dinitrobenzoyl chloride gave a product in which there appears to be mono-, di-, and triesterification from analytical data and the ^{13}C NMR spectrum (Figure 3b), with separation of chemical shift values for each of the carbons bearing the ester groups (3-, 7-, and 12-positions). Oxidation of the polymer cholate **6** with DMSO–oxalyl chloride (Swern oxidation)[18,19] gave a quantitative yield of the triketo derivative **1** as shown in the spectra, with a disappearance of the hydroxyl-bearing carbons at 67–70 ppm and the appearance of carbonyl carbons in the 208–212 ppm range (Figure 3c, compare with Figure 1b). The spectrum in this case clearly demonstrates the analytical power of ^{13}C NMR spectroscopy and its application to the interpretation of reactions performed on polymer supports.

Experimental Section

Chloromethylated polystyrene was obtained from the Bio-Rad (S-X1, 1.25 mmol Cl/g, 4.43% Cl), Fluka (1.16 mmol Cl/g, 4.11% Cl), and Calbiochem (1.34 mmol Cl/g, 4.75% Cl). Merrifield peptide resin (*p*-alkoxybenzyl) was obtained from Chemical Dynamics Corp. (1.0 mmol CH_2OH/g).

All solvents were reagent grade and stored over 4-Å molecular sieves. THF was distilled from calcium hydride. DMF was 99 mol % and was tested for dimethylamine content prior to use.[4] All experiments were performed under an atmosphere of nitrogen or argon. Steroids were purchased from Sigma Chemical Co. and azeotropically dried prior to use.

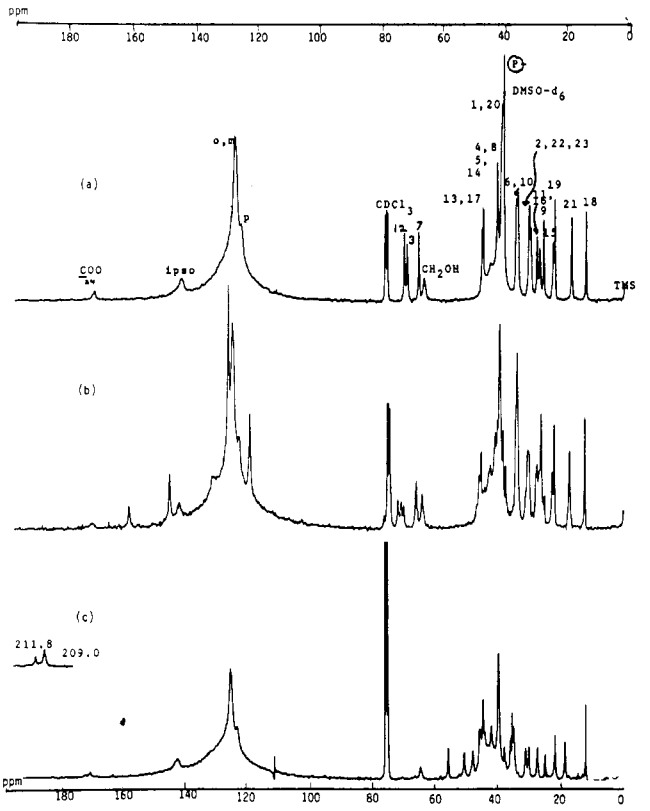

Figure 3. ^{13}C NMR spectra at 75.4 MHz of (a) polymer **6** in 50% $CDCl_3$–50% DMSO-d_6, (b) polymer **7**, and (c) oxidation of polymer **6**.

IR spectra of KBr pellets of polymers were recorded either on Beckman IR-20, Hilger-Watts 1200, Perkin-Elmer 710B, or Perkin-Elmer 681 spectrophotometers. ^{13}C NMR spectra of solvent-swollen polymer gels ($CDCl_3$ or 50/50 $CDCl_3$–DMSO-d_6) were obtained on either a Varian XL-100-15 instrument equipped with a Nicolet TT-100 PFT accessory operating at 25.2 MHz or a Varian XL-300 spectrometer at 75.43 MHz. Minimum detection level was estimated to 4.8% based on median signal-to-noise level. Elemental analyses were obtained from MicAnal (Tucson, AZ) or Midwest Micro Lab, Ltd. (Indianapolis, IN).

Polymer–Dehydrocholate 1. To a suspension of 5.00 g (1.34 mmol Cl/g, DF = 0.15) of chloromethylated polystyrene (Bio-Rad) in 50 mL of dry dimethylformamide (DMF) was added 4.04 g (10.1 mmol) of dehydrocholic acid and 1.90 g (20.2 mmol) of potassium fluoride dihydrate,[13,14] and the mixture was stirred at 60 °C for 16 h. The polymer beads were recovered by filtration, thoroughly washed with methanol–water (1:1), water, methanol–water (1:1), methanol, methanol–dichloromethane (1:1), and dichloromethane. The solid was vacuum dried overnight to yield 7.24 g (93%) of light-brown polymer **1**: DF = 0.137; IR 3400–3200, 1710, 1610, 1460, 1170, 760, 700, 570 cm^{-1}; ^{13}C NMR data in Figure 1b.

An alternative method involved heating (50 °C) and stirring 2.00 g (1.16 mmol Cl/g, DF = 0.13) chloromethylated polystyrene with 1.70 g (4.0 mmol) of sodium dehydrocholate for 27.5 h to yield 2.92 g of **1** (DF = 0.13, based on gravimetric analysis) after washing and drying described above.

Cleavage of Polymer–Dehydrocholate 1. To a solution of 44 mL of methanol, 44 mL of *p*-dioxane, 5 mL of 0.1 N sodium hydroxide, and 7 mL of triethylamine was added 1.05 g of polymer–dehydrocholate **1**. Nitrogen gas was bubbled through the mixture for 5 min, and the flask was stoppered and stirred at room temperature of 16 h. The polymer was removed by filtration, and the filtrate was evaporated to yield 1.00 g of semisolid residue. The residue was partitioned between 5% hydrochloric acid and a mixture of ether–chloroform (1:1). The organic layer was washed with water and saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Evaporation of the organic solvents produced 0.46 g (87% yield) of white solid, mp 238–240 °C, identical with dehydrocholic acid by TLC comparison ($CHCl_3$–

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(25) Iida, T.; Tamura, T.; Matsumoto, T.; Chang, F. C. *Org. Magn. Reson.* **1983**, *21*, 305–309.

EtOAc-HOAc, 45:45:10) and mixed melting point.

Polymer-Dehydrocholate Ketal 2. A mixture of 1.00 g of 1 (1.16 mmol/g, DF = 0.13), 17.8 mmol of ethylene glycol, 50 mg of *p*-toluenesulfonic acid monohydrate, and 50 mL of benzene was slowly distilled over a period of 16 h. After washing and drying (as above), 0.86 g (100%) of white polymer 2 (DF = 0.13) was produced: IR 1740 (ester), 1190-1150 (ketal), 960, 920, 840, 760, 700 cm^{-1}; ^{13}C NMR data, see Figure 2a.

Polymer-Dehydrocholate 2,4-DNP 3. Polymer-dehydrocholate 1, 1.00 g (DF = 0.14) in 50 mL of absolute ethanol was treated with 6.0 mL of 0.25 M (2,4-dinitrophenyl)hydrazine in 51:38:11 (v/v/v) 85% phosphoric acid-95% ethanol-and water. The mixture was stirred at room temperature for 20 h, filtered, washed with 95% ethanol, and Soxhlet extracted with 95% ethanol for 18 h. After drying in a vacuum oven overnight the yellow polymer 3 weighed 1.01 g (28%, DF = 0.04): ^{13}C NMR data, see Figure 2b. Anal.: N, 1.71 (corresponds to 0.31 mmol of p-$CH_3PhSO_2NHN{=}$/g polymer).

Polymer-Spacer-Dehydrocholate 4. A mixture of 2.50 g of Merrifield peptide resin (*p*-alkoxylbenzyl, 1.0 mmol CH_2OH/g, DF = 0.24)[16] was stirred at room temperature with 2.01 g (5.0 mmol) of dehydrocholic acid, 0.61 g (5.0 mmol) of 4-(*N,N*-dimethylamino)pyridine, and 1.20 g (5.8 mmol) of *N,N*-dicyclohexylcarbodimide (DDC) in 35 mL of dichloromethane for 18 h. The resulting mixture was filtered and washed with ethanol, water, methanol, and dichloromethane. Vacuum drying of the polymer at 53 °C for 1.5 h gave 2.68 g (48%) of white polymer (DF = 0.12); IR 3400 (br d, wk), 1740 (shl), 1730 (strong), 1608, 820, 744, 695, 550 cm^{-1}; ^{13}C NMR data, see Figure 1b.

Polymer-Spacer-Dehydrocholate 4 + *p*-Tosylhydrazine. To a solution of 0.93 g (5 mmol) of (*p*-tolylsulfonyl)hydrazine in 10 mL of glacial acetic acid was added 1.00 g of 4 (DF = 0.12). The mixture was placed on a wrist shaker for 37 h at room temperature. The polymer was recovered by filtration, washed with methanol and dichloromethane, and dried in vacuo at 1 Torr at room temperature for 24 h to yield 1.09 g: IR 1390, 1355, 1170, 760, 700 cm^{-1}; ^{13}C NMR showed no resonances due to a steroid or a polymer described by the structure 5. Anal.: N, 2.74; S, 2.70.

Polymer-Cholate 6. To a mixture of 1.00 g (1.16 mmol Cl/g, DF = 0.13) of chloromethylated polystyrene in 50 mL of DMF was added 0.65 g of sodium cholate. The mixture was stirred at 65 °C for 21 h, filtered, washed thoroughly, and dried for 2 h at 1 Torr to give 1.39 g (89%) of 6 (DF = 0.12): IR 3500, 1740 cm^{-1}; ^{13}C NMR data, see Figure 3a.

Polymer-Cholate 6 + 3,5-Dinitrobenzoyl Chloride. A mixture of 6 and 0.93 g (4 mmol) of 3,5-dinitrobenzoyl chloride (recrystallized) in 20 mL of pyridine was stirred at room temperature in a sealed flask for 3 days. The polymer was washed with THF, THF-water (1:1), and THF and dried at 56 °C at 1 Torr overnight to produce 1.16 g (some polymer lost in transfers). Anal.: N, 2.73. DF for monoesterification, 0.12 (100%); diesterification, 0.08 (69%); and triesterification, 0.05 (42%) of hydroxyl groups; ^{13}C NMR data, see Figure 3b.

Swern Oxidation of Polymer-Cholate 6. A solution of 0.5 mL (5.2 mmol) of oxalyl chloride and 6 mL of dichloromethane was cooled to -50 to -60 °C (dry ice-$CHCl_3$). The addition of 0.81 mL (11.4 mmol) of DMSO in 2 mL of dichloromethane proceeded over a period of 2 min via a pressure-equalizing funnel. The reaction flask was then transferred to a salt-ice bath (-10 °C), and the mixture was stirred for 5 min. Polymer 6, 1.50 g (DF = 0.12), in 10 mL of dichloromethane was added to the flask, and stirring was continued for 1.5 h. The mixture was reacted with 1.7 mL of triethylamine and allowed to warm to room temperature over a period of 0.5 h. The polymer was filtered and washed thoroughly with dichloromethane, methanol, water, methanol, and dichloromethane. The polymer was dried overnight at 2 Torr/40 °C, weighed 1.17 g (some loss in transfer), DF = 0.12, and was identical in all spectroscopic respects with polymer 1: ^{13}C NMR data, see Figure 3c and compare to that of Figure 1b.

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Synthesis of Streptazolin: Use of the Aza-Ferrier Reaction in Conjunction with the INOC Process To Deliver a Unique but Sensitive Natural Product

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The total synthesis of the unique alkaloid natural product streptazolin is described. The synthetic route makes use of the Ferrier-like reaction of a Δ^2-piperidinol with allyltrimethylsilane in combination with the INOC reaction to create the ring skeleton of this product. The extension of the aza-Ferrier reaction to other nucleophiles is discussed. The transformation of isoxazolines with peracids to β-hydroxy ketones or diol monoacetates discovered during the course of these studies is also presented.

Streptazolin (1) is a lipophilic, neutral compound first isolated from cultures of *Streptomyces viridochromogenes* strain Tü 1678 by Drautz and Zähner in 1981.[1] The purification of streptazolin was made rather difficult because of its tendency to undergo partial polymerization in concentrated form. In dilute solution, however, streptazolin proved to be stable for several days.

A culmination of spectroscopic investigations, chemical degradation,[1] and an X-ray analysis[2] carried out by Kupfer and Keller-Schierlein established the major features of the streptazolin structure, including its absolute stereochemistry. However, since the X-ray analysis had been carried out on dihydrostreptazolin acetate (2), and due to a lack of suitable reference compounds, the configuration[1] of the C8-C9 exocyclic olefin was not assigned unambiguously.

(1) Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752.

(2) Karrer, A.; Dobler, M. *Helv. Chim. Acta* **1982**, *65*, 1432.

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