1730 (ester C=O), 1603 (phenyl), 1540 (NHCO), 1350, 1205, 730 cm^{-1}.

Ethyl α-Hydroxy-2-oxocycloheptaneacetate (6). Compound **3** (2.09 g, 9.77 mmol) was treated with bakers' yeast (20 g) at 32 °C for 70 h. Flash column chromatography of the crude products afforded 1.75 g of crude **6**. Purification by preparative HPLC [SA-I; hexane/ethyl acetate/ethanol (20/1/1)] gave two components. The first fraction gave 0.430 g (20.6%) of (αR,1S)-**6**: R_t 8.8 min; $[\alpha]^{26}_D$ -58.20° (*c* 1.62, $CHCl_3$); IR (neat) 3400 (OH), 1740 (ester C=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, *J* = 6 Hz, 3 H, CH_3), 1.2-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, OH), 4.00 (d, *J* = 3.5 Hz, 1 H, CHOH), 4.20 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 24.0 (t), 28.1 (t), 29.2 (t), 29.9 (t), 44.1 (t), 55.1 (d), 61.7 (t), 73.6 (d), 173.5 (s), 214.9 (s). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.69; H, 8.33.

The second fraction gave 0.287 g (13.7%) of (αR,1R)-**6**: R_t 9.4 min; $[\alpha]^{26}_D$ +48.61° (*c* 1.44, $CHCl_3$); IR (neat) 3400 (OH), 1740 (ester C=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, *J* = 6 Hz, 3 H, CH_3), 1.2-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, OH), 4.20 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$), 4.36 (d, *J* = 3 Hz, 1 H, CHOH); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 24.2 (t), 25.7 (t), 29.1 (t), 29.9 (t), 43.9 (t), 55.3 (d), 61.8 (t), 72.1 (d), 173.6 (s), 214.5 (s). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66, H, 8.47. Found: C, 61.68; H, 8.41.

Determination of Enantiomeric Excess of 6. (a) In the same manner as shown in **4**, (αR,1S)-**6** (34 mg, 0.159 mmol) was treated with 3,5-dinitrophenyl isocyanate (40 mg, 0.19 mmol) to give 58 mg (85.6%) of ethyl (αR,1S)-α-[[(3,5-dinitrophenyl)carbamoyl]oxy]-2-oxocycloheptaneacetate: ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 6 Hz, 3 H, CH_3), 1.3-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, NH), 4.20 (apparent s, 1 H, CHOCONH), 4.25 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$), 7.7-8.8 (m, 3 H, $C_6H_3(NO_2)_2$). HPLC analysis [Sumipax OA-3000; hexane/ethyl acetate (20/1/1), 1.0 mL/min] showed two peaks at 4.0 and 4.3 min (intensity ratio 56/44), 12% ee.

(b) In the same manner, (αR,1R)-**6** (25 mg, 0.12 mmol) gave 43 mg (87%) of ethyl (αR,1R)-α-[[(3,5-dinitrophenyl)carbamoyl]oxy]-2-oxocycloheptaneacetate: ^1H NMR ($CDCl_3$) δ 1.25 (t, *J* = 6 Hz, 3 H, CH_3), 1.3-2.2 (m, 8 H, 4 CH_2), 2.3-3.2 (m, 4 H, CH_2COCH, NH), 4.25 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 4.56 (d, *J* = 3 Hz, 1 H, CHOCONH), 7.7-8.8 (m, 3 H, $C_6H_3(NO_2)_2$). HPLC analysis [Sumipax OA-3000; hexane/ethyl acetate (20/1/1); 0.7 mL/min] showed two peaks at 5.6 and 6.2 min (intensity ratio 80/20); 60% ee.

Ethyl (*R*)-(-)-Hexahydromandelate (7). Dry hydrogen chloride was introduced into 13 mL of ether at -15 °C. After addition of **5b** (0.12 g, 0.6 mmol), 0.78 g (0.012 mol) of zinc powder was added with several portions. The mixture was stirred for 2 h at -5 °C and then poured into ice-water and extracted with ether. The extract was washed with dilute sodium hydrogen carbonate and water and dried ($MgSO_4$). Removal of the solvent gave 88 mg (78%) of **7**: $[\alpha]^{30.5}_D$ -6.92° (*c* 39.6, $CHCl_3$); IR (neat) 3500 (OH), 1740 (C=O), 1450, 1260, 1120 cm^{-1}; ^1H NMR (CCl_4) δ 1.35 (t, *J* = 6 Hz, 3 H, CH_3), 1.5-2.2 (m, 11 H, cyclohexyl) 4.25 (q, *J* = 6 Hz, 2 H, $CO_2CH_2CH_3$). This was used for the next step without further purification.

(*R*)-(-)-Hexahydromandelic Acid (8). A mixture of 1.1 g (6.0 mmol) of **7**, 0.5 g (8.91 mmol) of KOH, and 9 mL of water was stirred at room temperature. After 8 h, the mixture was acidified with 10% HCl and extracted with ether. The ether layer was washed with water and dried ($MgSO_4$). The solvent was evaporated to give 0.569 g (59%) of **8**: mp 127-129 °C (from benzene) (lit.[16a] mp 129 °C); $[\alpha]^{33}_D$ -12.0° (*c* 2.0, EtOH) [lit.[14] $[\alpha]^{25}_D$ +12.0° (*c* 2.0, EtOH)], $[\alpha]^{22}_D$ -25.3° (*c* 1.0, HOAc) [lit.[16a] $[\alpha]^{20}_D$ -25.5° (*c* 1.0, HOAc)].

Methyl (1*R*,5*R*)-α-[6,6-Dimethylbicyclo[3.1.1]hept-3-yl]-2,α-dioxoacetate (10). In a same manner as shown in **3**, a solution of 3.31 g (0.024 mol) of nopinone[23] and 2.83 g (0.024 mol) of dimethyl oxalate in 20 mL of THF was treated with 1.30 g (0.024 mol) of sodium methoxide. The crude product was chromatographed on silica gel (hexane/ethyl acetate, 10/1) to give 3.59 g (81.4%) of **10**: IR (neat) 1730 (ester C=O), 1700 (C=O), 1630, 1585 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (s, 3 H), 1.35 (s, 3 H), 1.5-2.7 (m, 4 H), 2.85 (d, *J* = 2.5 Hz, 2 H), 3.80 (s, 3 H), 14.1 (br s, 1 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.08; H, 7.29.

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Trifluoroacetylation of Amines and Amino Acids by Polymer-Bound Trifluoroacetylation Reagents

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Trifluoroacetylation of amino acids[1-6] and amines[7] with trifluoroacetic anhydride, *S*-ethyl trifluorothioacetate,[8] or alkyl trifluoroacetates[9-11] is a useful method for the reversible protection of the amino group, but all of these methods have certain limitations and drawbacks. Our interests in solid-phase syntheses[12,13] and protection of amino groups[7] have led us to develop an exceedingly attractive and simple method for N-trifluoroacetylation using polymer-bound *S*-benzyl trifluorothioacetate (**2a**) or polymer-bound benzyl trifluoroacetate (**2b**). Incorporation of an *S*-benzyl (instead of the *S*-ethyl group of *S*-ethyl trifluorothioacetate) on a polymer support ensures that the potentially odiferous mercaptan liberated on reaction of **2a** with amines remains attached to the insoluble support and is hence nonvolatile.

Polymer-bound benzyl thioalcohol (**1a**)[14,15] and polymer-bound benzyl alcohol (**1b**)[15,16] can be readily converted

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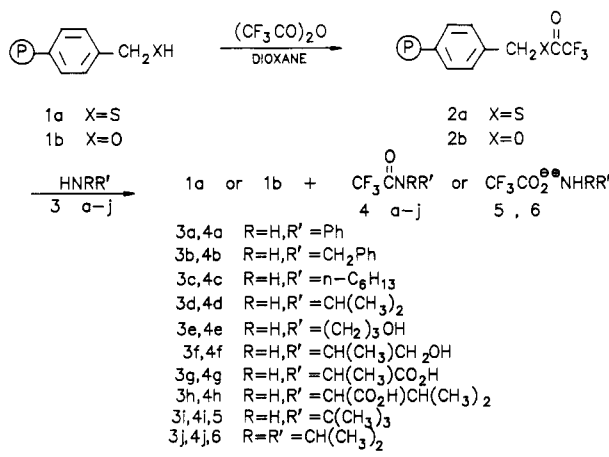
Table I. Polymer-Supported Synthesis of N-Substituted Trifluoroacetamides (CF_3CONRR^1)

compd	R	R^1	solvent	temp,[n] °C	time, h	yield, %[a] b	c	d	mp [bp], °C	lit. mp [bp], °C
4a	H	Ph	dioxane	reflux	3	80	80		88–89	89–90
4b	H	$PhCH_2$	dioxane	reflux	3	86	91	75	75–76	73.5–74.5
4c	H	n-C_6H_{13}	dioxane	reflux	3	90	93	74	[78–80 (1.5 mm)]	[120 (11 mm)]
4d	H	$(CH_3)_2CH$	dioxane	85	4	86			52–53	52–53
4e	H	$HO(CH_2)_3$	dioxane	reflux	3	90			[90–100 (1 mm)][e]	
4f	H	$HOCH_2(CH_3)CH$	dioxane	reflux	3		90[f]	93[g]	80–81[e]	
4g	H	$CH_3(CO_2H)CH$	CH_3OH[h]	rt	48		90[i]	80[j]	70–71	70–71
4h	H	$(CH_3)_2CH(CO_2H)CH$	CH_3OH[b]	rt	72	80			87–88	87–88
4i + 5	H	$(CH_3)_3C$	THF	rt	48	89[k]	90[k]	90[l]	45[e,l]	44–45
6	$(CH_3)_2CH$	$(CH_3)_2CH$	THF	rt	48	67[m]			*m*	

[a] Based on pure crystallized isolated compounds. [b] Using excess amine (Method 1) and reagent **2a**. [c] Using excess polymer **2a** (method 2). [d] Using excess polymer **2b** (method 2). [e] New compounds listed had spectral properties and mass spectral data for the molecular ion fully compatible with the assigned structures. The C, H, and N analyses were within ±0.3% of the calculated values. [f] $[\alpha]^{22}_D$ −15.3° (*c* 4, EtOH). [g] $[\alpha]^{22}_D$ −13° (*c* 5, EtOH). [h] And triethylamine. [i] $[\alpha]^{22}_D$ −60.3° (*c* 6.5, EtOH) (lit. $[\alpha]^{22}_D$ −60.3°). [j] $[\alpha]^{22}_D$ −5.3° (*c* 5, EtOH). This isolated product had 86.8% ee. [k] This figure represents the isolated yield of pure **5**, mp 180 °C, in these experiments. [l] Isolated from a 1:3 mixture with **5**, mp 180 °C. [m] An ammonium salt, **6**, mp 125 °C was isolated. [n] rt = room temperature.

Scheme I



to **2a** and **2b** by treatment of **1a** and **1b** with trifluoroacetic anhydride in dry dioxane. Polymer **2a** reacted with a large variety of unhindered primary amines (**3a–i**), including an arylamine (**3a**), alkylamines (**3b–d**), amino alcohols (**3e–f**), and amino acids (**3g,h**) to give upon simple filtration polymer **1a** and the *N*-substituted trifluoroacetamides **4a–h** in high yield (Scheme I) (Table I). The reaction of **2a** with the more hindered amines **3i,j** did not lead to the *N*-trifluoroacetyl derivatives **4i,j** but rather to the alkyl ammonium salts **5** and **6** (Table I and Experimental Section). Under reaction conditions in which the amines were in excess (method 1), recovered polymer **1a** no longer exhibited any carbonyl absorption in its infrared spectrum, indicating that polymer reagent **2a** was completely consumed in the reaction. Under conditions in which the polymer was in excess with respect to the amine (method 2), almost pure *N*-trifluoroacetyl derivatives were obtained upon direct filtration of the polymer and evaporation of the solvent. The yields quoted in Table I are based on pure product. Compound **2a** can be completely regenerated by recycling used **1a** with trifluoroacetic anhydride. Ten times recycled **2a** maintains a similar capacity and reactivity as fresh **2a**.

The formation of the alkylammonium salts **5** and **6** is likely due to low reactivity of **3i,j** with **2a,b** in refluxing tetrahydrofuran, and the resulting long times of the attempted reaction may have resulted in the admission of adventitious moisture (Table I). Under conditions of shorter reaction times, considerable starting material remained. In a control experiment pure **4j** was subjected to the workup conditions of the N-trifluoroacetylation reactions, but no hydrolysis of **4j** occurred.

Similarly, polymer **2b** reacted with amines **3b**, **3c**, **3f**, and **3g**, by using the protocol of method 2 (excess **2b**), to give recovered polymer **1b** and **4b**, **4c**, **4f**, and **4g** in high yield. The reaction of **2b** with the hindered amine **3i** again gave the ammonium salt **5a**, admixed with some of the desired **4i** (Table I). The preparation of the chiral *N*-substituted trifluoroacetamides **4g,h** via **2a** gave **4g,h** with no loss of enantiomeric purity, while the preparation using **2b** did result in the production of **4g** having a reduced ee of 87% (Table I). Polymer **2b** can be stored at room temperature without dimunition of capacity.

The use of polymer-bound *S*-benzyl trifluorothioacetate (**2a**) provides a simple method of producing *N*-substituted trifluoroacetamides in high yield, with no racemization of chiral centers, no production of disagreeable odors, and isolation of product by simple filtration and solvent evaporation of the filtrate.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM360 spectrometer at 60 MHz using deuteriochloroform ($CDCl_3$) as solvent and tetramethylsilane as the internal standard. Mass spectra (MS) were recorded at 70 eV on a VG Micromass 16F mass spectrometer in the EI mode. Optical rotations were determined with a Perkin-Elmer 141 polarimeter at 21 ± 2 °C.

Commercially available polymer-bound benzyl chloride (Merrifield's resin Sigma Chemical Co.), containing 1 mequiv of chloride per gram was used in the preparation of **1a** and **2a**.

Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

All other instrumentation and general procedures were the same as described previously.[17]

Polymer-Bound *S*-Benzyl Trifluorothioacetate (2a). To a suspension at 0 °C of 93 g of polymer-bound benzyl thioalcohol (**1a**), prepared as previously described,[14] in 650 mL of dry dioxane was added 20 mL of trifluoroacetic anhydride under an argon atmosphere. The mixture was stirred for 0.5 h at 0 °C, 18 h at room temperature, and 2 h at 45–50 °C (bath temperature). The cooled mixture was filtered and washed twice with dry dioxane, three to six times with anhydrous ethanol, three to four times with anhydrous tetrahydrofuran (THF), and five to six times with anhydrous ether until the pH of an aqueous extract of the filtrate was 7, to give resin **2a**. Resin **2a** was dried in a high vacuum at 50–60 °C for 3–5 h. The infrared spectrum of **2a** exhibited characteristic absorptions at 1720 and 1740 cm^{-1}. Resin **2a** can be stored at room temperature for several months without di-

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munition of capacity or the liberation of disagreeable odors. The minimum capacity of **2a** was determined to be 0.86 mmol/g as determined by its use in N-trifluoroacetylation reactions with benzylamine (see method 1).

Polymer-Bound Benzyl Trifluoroacetate (2b). In a manner similar to that described for **2a**, 30 g of polymer-bound benzyl alcohol (**1b**) gave 31 g of **2b**. The infrared spectrum of **2b** exhibited characteristic absorptions at 1700 cm^{-1}. The minimum capacity of **2b** was determined to be 0.75 mmol/g as determined by its use in N-trifluoroacetylation reactions with benzylamine (method 1). Resin **2b** did show some dimunition in capacity after storage for several months.

Preparation of N-Substituted Trifluoroacetamides 4a-e (Method 1). In a typical procedure, to a suspension of 3.0 g (2.7 mmol) of polymer **2a** in 25 mL of dry dioxane was added 0.75 g (7 mmol) of benzylamine (**3b**). The mixture was refluxed under an argon atmosphere for 3 h, cooled to room temperature and filtered. The recovered polymer **1a** was washed twice with 10 mL of dioxane, three times with 10 mL of ethanol, four times each with 10-15 mL of dichloromethane and ether and finally dried. The IR spectrum of recovered **1a** exhibited a weak absorbance at 2560 cm^{-1} (SH), and the carbonyl absorbance, characteristic of **2a**, had disappeared. The filtrate was evaporated to dryness. The crude product was dissolved in methylene chloride, ether, or ethyl acetate, washed with cool 5% HCl and cool brine, and dried over magnesium sulfate. Evaporation of the solvent gave 0.6 g of crude *N*-benzyl-2,2,2-trifluoroacetamide (**4b**). Flash chromatography[18] of the residue using methylene chloride as eluant gave in 86% yield 0.54 g of pure **4b**: mp 75-76 °C (lit.[4] mp 75-76 °C). From the yield of **4b**, it was calculated that polymer **2a** had a loading capacity of 0.86 mmol of *S*-benzyl 2,2,2-trifluorothioacetate groups per gram of polymer.

Similarly, 3-amino-1-propanol (**3e**) and **2a** gave as an oil in 90% yield pure *N*-(3-hydroxypropyl)-2,2,2-trifluoroacetamide (**4e**): IR (film) 3330, 3100, 2980-2890, 1720, 1570, 1180, 1060, 730 cm^{-1}; ^1H NMR δ 1.85 (q, 2), 3.3-3.8 (t of t overlapping, 4), 2.3-2.6 (m, br, 2); MS; *m/z* (relative intensity) 171 (7) (M^+), 126 (100), 114 (20), 102 (20), 84 (40), 69 (56), 41 (27).

Preparation of N-Substituted Trifluoroacetamides 4a-c,f-i (Method 2). In a typical reaction, 6 g (a two times excess, 5.3 mmol) of polymer **2a** or **2b** and 0.24 g (3 mmol) of (*S*)-2-amino-1-propanol (**3f**) was refluxed under argon for 3 h and worked up with ethyl acetate as described above for method 1 to give in 90% yield (from **2a**) after distillation 0.45 g of *N*-(*S*)-(2-hydroxy-1-methylethyl)-2,2,2-trifluoroacetamide (**4f**): bp 100-102 °C (1.2 mm); mp 80-81 °C; $[\alpha]^{22}_D$ -15.3° (*c* 4.5, EtOH); IR (Nujol) 3340, 3160, 1695, 1250, 1220, 1180, 1050, 730 cm^{-1}; ^1H NMR [$(CD_3)_2CO$] δ 1.18 (d, 3, J = 6 Hz), 2.8 (m, br, 1), 3.38 (m, 2), 3.88 (t, 2, J = 8 Hz); MS; *m/z* (relative intensity) 171 (4) (M^+), 156 (40), 140 (100), 92 (15), 69 (60), 45 (15).

Preparation of *N*-Trifluoroacetyl Amino Acids 4g,h. With method 1 described above, polymer **2a** was stirred with equivalent amounts of L-valine (**3h**) and triethylamine in anhydrous methanol for 72 h at room temperature. The resin was filtered and washed as described above and the filtrate worked-up as previously described[11] to give pure **4h**: mp 87-88 °C (lit. mp 88-89 °C).

Similarly, but with method 2 described above, polymer **2a** or **2b** was stirred with equivalent amounts of L-alanine (**3g**) and gave pure **4g**: mp 70-71 °C [after sublimation, 110-115 °C (0.01 mm)] (lit.[11] mp 70-71 °C).

Preparation of 4i,j and Salts 5 and 6. With method 1 or 2 as described above, *tert*-butylamine (**3i**) or diisopropylamine (**3j**) reacted with polymer **2a** to give *tert*-butylammonium 2,2,2-trifluoroacetate (**5**) and diisopropylammonium 2,2,2-trifluoroacetate (**6**) (Table I).

With method 2 and polymer **2b**, **3j** gave only salt **6**, but **3i** yielded a 1:3 mixture of **4i**: mp 45 °C (lit.[4] mp 44-45 °C) and **5** (Table I).

With a previously described method,[4] amine **3j** reacted with trifluoroacetic anhydride to give **4j**: mp 53 °C (lit.[4] mp 52-53 °C).

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Organopalladium Approaches to Prostaglandins. 8.[1] Ethyl (Acetoxymercurio)acetate Approach to Prostaglandin Endoperoxide Analogues

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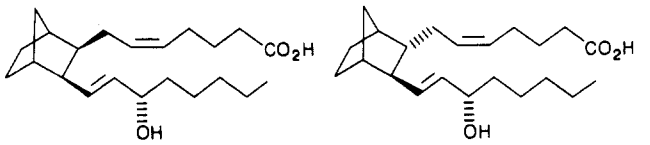
The synthesis of stable analogues of the prostaglandin endoperoxides (PGG_2 and PGH_2) has received considerable attention from organic chemists in recent years.[2,3] We have recently reported organopalladium approaches to these compounds employing π-allylic,[4] benzylic,[5,6] thienyl,[7,8] and vinylic[1] palladium intermediates. The latter approach affords easy entry to endoperoxide analogues **1** and **2**, which are effective inhibitors of blood platelet aggregation.[1]



1 **2**

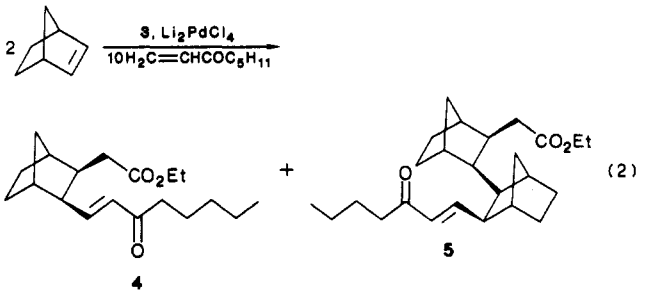
Recently, we have discovered an even more efficient synthesis of exo-exo analogues of compound **1** using an organopalladium intermediate derived from ethyl (acetoxymercurio)acetate (**3**) which we wish to report on at this time.

Results and Discussion

Ethyl (acetoxymercurio)acetate (**3**) is readily available in high yield in one step from commercially available 1,1-difluoroethylene (eq 1).[9] Reaction of compound **3** with

$$Hg(OAc)_2 + H_2C{=}CF_2 + EtOH \rightarrow \underset{\mathbf{3}}{AcOHgCH_2CO_2Et} \quad (1)$$

Li_2PdCl_4, 2 equiv of norbornene, and 10 equiv of 1-octen-3-one for 4 days resulted in an ~4:1 ratio of the desired keto ester **4** and the double insertion product **5** in 70% overall yield (eq 2). Keto ester **4** is a diastereomeric



4 **5** (2)

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