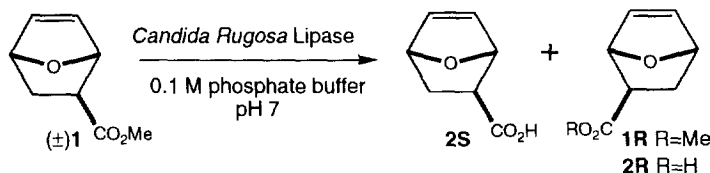


Preparation of (*R*)-(+)-7-Oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid, a Precursor to Substrates for the Ring Opening Metathesis Polymerization

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Abstract: (*R*)-(+)-7-Oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid (**2R**), which can be transformed into carbohydrate-substituted monomer **5** appropriate for ring opening metathesis polymerization (ROMP) was prepared by an enzymatic kinetic resolution of 7-oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid methyl ester [(±)**1**] with the lipase from *Candida Rugosa*. Copyright © 1996 Elsevier Science Ltd

7-Oxanorbornene derivatives are readily accessible intermediates that have been used in the synthesis of both natural and non-natural biologically active molecules.¹ With the advent of new developments in ring opening metathesis polymerization (ROMP) chemistry,² substituted oxanorbornenes have emerged as important precursors for the synthesis of new materials.^{3,4} For example, ROMP of 7-oxanorbornenes displaying carbohydrate residues^{3,4} results in materials that potently inhibit the function of saccharide-binding proteins.³ To continue our studies of multivalent protein-carbohydrate interactions, we required a 7-oxanorbornene derivative to which saccharides could easily be appended. Consequently, we have developed conditions for the synthesis of the non-racemic carboxylic acid **2R** and its conversion to a suitable substrate for ROMP.



Scheme 1. Strategy for generating oxanorbornenes for display of chiral, non-racemic ligands.

Several features of target **2R** render it a utile precursor for the synthesis of carbohydrate-substituted polymers by ROMP. The strained alkene in 7-oxanorbornene systems makes them excellent substrates for metathesis because their reactions are virtually irreversible. In addition, bicyclic [2.2.1] systems are readily constructed through Diels-Alder reactions. For our studies, the saccharide attachment point for the bicyclic core must be in the *exo* orientation because ROMP of carbonyl-containing norbornene templates of the *endo* configuration fails. This failure is presumably due to unfavorable chelation of the carbonyl oxygen with the metal catalyst.⁵ Monomers generated from coupling of a saccharide to 7-oxanorbornene templates such as **2R** can be used to synthesize carbohydrate-substituted polymers. Neoglycopolymers derived from these substrates will have a density of one saccharide residue per repeat unit, and these derivatives can possess superior biological activities relative to those materials derived from monomers bearing two saccharide units.^{3c} Although norbornene derivatives have been employed in some studies, we prefer to use the more hydrophilic oxanorbornene core because its increased

water solubility affords polymers more suitable for biological studies.

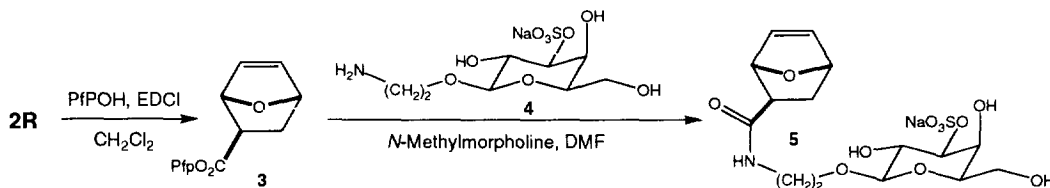
ROMP reactions using ruthenium catalysts generally produce structurally complex polymers.⁶ The relationship between two repeat units in the polymer can differ by the stereochemistry of the double bond, tacticity of the backbone, and head-tail isomerism for the substituents in adjacent rings. In our initial studies, we employed diastereomeric mixtures of monomers as substrates in ROMP,^{3c} thereby generating materials that display saccharide residues in a range of different orientations. The relationship between the structural variability afforded by the use of diastereomeric mixtures of monomers and the potent activity of these neoglycopolymers is not known. To begin to dissect the various structural features of the neoglycopolymers, we sought to decrease the structural heterogeneity of the polymers by preparing a single monomer isomer. In previous studies, the attachment of a single saccharide residue to a bicyclic [2.2.1] system afforded inseparable mixtures of diastereomers;^{3c,4} therefore, a method for generating a chiral, non-racemic oxanorbornene template prior to saccharide attachment was devised. Chiral, non-racemic 7-oxanorbornene derivatives have been generated by a variety of methods,⁷⁻⁹ but no practical method was available for the production of derivatives to which saccharides or other recognition elements could easily be tethered. Therefore, we developed conditions for the synthesis of such a compound, **2R**.

Three criteria were important in developing a procedure to generate the target bicyclic template: the method should be highly enantioselective, amenable to large scale, and convenient to perform. Enzymatic kinetic resolutions meet these criteria,¹⁰ but previous workers have had little success resolving the related norbornene ester.^{8d} Despite these reported difficulties, the advantages of a kinetic resolution spurred us to examine this strategy. The substrate for resolution, compound **1**, is readily produced by a zinc iodide-catalyzed Diels-Alder reaction of furan and methyl acrylate,¹¹ which affords a 3:1 mixture of separable *exo* to *endo* diastereomers. A variety of enzymes were screened for their ability to hydrolyze **1** enantioselectively.¹² Our survey identified a lipase isolated from *Candida Rugosa* (also referred to as *Candida Cylindracea*) supplied by Meito Sangyo as a suitable candidate. When the hydrolysis reaction was run to 60% completion, an enantiomeric excess of 92% was obtained for the remaining methyl ester **1R**.^{12,13} The progression of the hydrolysis reaction was monitored by comparing the intensities of the methyl ester singlets arising from (\pm)**1**, as these signals could be separated using Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] in a ¹H NMR-shift experiment¹⁴ The kinetic resolution can be run on multigram scale, and the ester **1R** can easily be isolated by extraction with dichloromethane; therefore, this protocol provides a convenient method for production of the desired compound although the enzyme is only moderately enantioselective (the enantiomer ratio for the lipase is calculated to be 11^{10a}). The desired acid was generated by saponification of **1R** with lithium hydroxide in THF to afford **2R** in 84% yield.^{8d,15}

The absolute configuration of **2R** was assigned by its conversion to the known compound (*S*)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid.⁷ The resolved oxanorbornene derivative, **1R**, was treated with sodium methoxide to epimerize the center bearing the ester group. After isolation of the *endo* isomer, the resulting ester was saponified to afford (*S*)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid as determined by its optical rotation.^{7,16} The observed preference for hydrolysis of the **1S** enantiomer by the *Candida rugosa* lipase is consistent with the empirical rule advanced by Ahmed *et al.*¹⁷

Chiral acid **2R** serves as a precursor for the synthesis of neoglycopolymers, as demonstrated by its efficient transformation into the carbohydrate appended ROMP substrate **5** (Scheme 2). Attempts to directly couple **4** to

carboxylic acid **2R** were complicated by the insolubility of **4** in non-polar solvents at low temperatures. When **2R** was activated with 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) at room temperature, the desired product was contaminated with those derived from retro Diels-Alder reaction. To circumvent this difficulty, **2R** was activated and trapped at low temperature using pentafluorophenol to yield activated ester **3**.¹⁸ Further purification of **3** could be achieved by crystallization, which resulted in material with an enantiomeric excess greater than 99%.¹⁹ Subsequent, amide bond formation with **4**²⁰ proceeded smoothly to obtain **5**.²¹ Template **5** can be used for the synthesis of a unique class of materials, which display sulfated saccharide residues in a multivalent array.



Scheme 2. Synthesis of carbohydrate-substituted ROMP substrate for the production of neoglycopolymers. Abbreviations are: PfpOH, pentafluorophenol; EDCI, 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride)

We have developed a method to synthesize a single enantiomer of 7-oxanorbornene derivatives, such as **3**, to which chiral non-racemic recognition elements can be appended. The resulting compounds can serve as useful precursors to natural and non-natural products.¹ For example, compound **5**, which bears a sulfated galactose residue, can be used to synthesize neoglycopolymers using ROMP. Materials derived from the reaction of these monomer units will facilitate the elucidation of structure/function relationships in multivalent protein – carbohydrate interactions.

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 12. Several lipases were found to be inactive or afford low enantioselectivity in the hydrolysis of (\pm)-**1**. Lipases derived from *Aspergillus niger*, *Mucor miehei*, *Pseudomonas* sp. were obtained from Amano and found to be unsuitable, as were lipases supplied by Aldrich Chemical Co. from *Porcine Pancreas* and *Candida Rugosa*.
 13. Resolution of (*R*)-(+)-7-oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid methyl ester, **1R**. Racemic 7-oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid methyl ester (300 mg, 1.95 mmol) and *Candida Rugosa* lipase (300 mg) were dissolved in 0.1 M pH 7.0 phosphate buffer (45 mL), and the mixture was stirred at 32 °C for 7 hours. The reaction was cooled to room temperature and solid sodium bicarbonate was added until the pH of the solution was approximately 8. The unreacted ester was extracted from the reaction mixture with dichloromethane (4 x 50 mL). The reaction mixture was acidified with 1 M HCl and the carboxylic acid was extracted with ethyl acetate (6 x 50 mL). The dichloromethane extracts were dried with anhydrous magnesium sulfate and concentrated under reduced pressure to yield **1R** (110 mg, 37% yield, 92% ee). The ethyl acetate extracts were dried with anhydrous magnesium sulfate and concentrated under reduced pressure to afford **2S** (169 mg, 62% yield).
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 15. Spectroscopic data for (*R*)-(+)-7-oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid, **2R**: ¹H NMR (300 MHz, CDCl₃): δ 6.40 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.38 (dd, *J* = 16.0, 1.5 Hz, 1H), 5.23 (br s, 1H), 5.11 (br d, *J* = 4.0 Hz, 1H), 2.48 (dd, *J* = 8.5, 3.9 Hz, 1H), 2.17 (ddd, *J* = 11.6, 4.0, 3.9 Hz, 1H), 1.60 (dd, *J* = 11.6, 8.5 Hz, 1H).
 16. Ogawa *et al.* report [α]_D²² = -111.8° (EtOH) for the *S* *endo* carboxylic acid⁷ which is comparable to the optical rotation determined for *endo* carboxylic acid derived from **1R**, [α]_D²² = -98.0° (EtOH). Absolute optical rotations were determined for the precursor *exo* ester **1R** [α]_D²² = +23.9° (EtOH) and the *exo* acid **2R** [α]_D²² = +27.6° (EtOH).
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 18. (*R*)-(+)-7-oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid pentafluorophenyl ester, **3**. Resolved 7-oxabicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid (50 mg, 0.36 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (84 mg, 0.44 mmol) and pentafluorophenol (82 mg, 0.44 mmol) were dissolved in dichloromethane (0.50 mL) at 0 °C. This mixture was warmed to room temperature overnight. The reaction mixture was filtered through silica (diethyl ether eluent) to afford **3** (115 mg, 0.376 mmol), which was contaminated with residual pentafluorophenol and the acrylic ester product derived from retro Diels-Alder reaction (ratio of **3** to acrylic ester derivative = 20:1). Crystallization of **3** from the mixture using hexane (-20 °C) afforded the purified product (67 mg, 0.22 mmol, 61% yield). ¹H NMR (300 MHz, CDCl₃): δ 6.48 (dd, *J* = 17, 2 Hz, 1H), 6.46 (dd, *J* = 17, 2 Hz, 1H), 5.35 (bs, 1H), 5.18 (d, *J* = 4 Hz, 1H), 2.79 (dd, *J* = 8, 4 Hz, 1H), 2.29 (dt, *J* = 12, 4 Hz, 1H), 1.75 (dd, *J* = 12, 8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 170.0, 142.8, 141.1, 139.5, 137.5, 136.1, 134.4, 125.2, 81.0, 78.1, 42.6, 29.6; IR (KBr): 3145, 3100, 3016, 2971, 2871, 2667, 2459, 1778, 1656, 1529 cm⁻¹; mass spectrum (LSIMS, 3-NBA): *m/z* 307.1 [M + H⁺, calcd for C₁₃H₈O₃F₅ 307.0].
 19. The enantiomeric excess of the pentafluorophenyl ester **3** was determined to be greater than 99% by chiral HPLC using a Regis (R,R)-WHELK-O column, 20 cm x 4.6 mm I.D. (0.3% isopropanol in hexane eluent).
 20. The synthesis of **4** will be described elsewhere: D. D. Manning, L. L. Kiessling, in preparation.
 21. Oxabicyclic [2.2.1] derivative **5**. 3-*O*-sulfo(β -2-aminoethyl)galactoside, **4**, (45 mg, estimated as 0.16 mmol as sodium counterion) and activated ester **3** (48 mg, 0.16 mmol) were dissolved in amine-free *N,N*-dimethylformamide (410 μ L) and *N*-methylmorpholine (30 μ L) was added. After 5 h, the reaction was diluted with water (1 mL), and the resulting amide product was purified by anion exchange chromatography [DEAE Cellulose (fast flow), 0 to 0.25 M Et₃NH₂CO₂ linear gradient] to afford **5** (76 mg, 0.15 mmol, 93%) as a white solid. Yield: 93%; ¹H NMR (300 MHz, D₂O): δ 6.00 (dd, *J* = 16, 2 Hz, 1H), 5.99 (dd, *J* = 16, 2 Hz, 1H), 4.68 (d, *J* = 4 Hz, 1H), 4.64 (dd, *J* = 2, 1 Hz, 1H), 4.06 (d, *J* = 8 Hz, 1H), 3.86 (dd, *J* = 10, 3 Hz, 1H), 4.83 (dd, *J* = 3, 1 Hz, 1H), 3.57-3.50 (m, 1H), 3.38-3.26 (m, 4H), 3.22 (dd, *J* = 10, 8 Hz, 1H), 3.03-2.98 (m, 2H), 1.98 (dd, *J* = 9, 4 Hz, 1H), 1.45 (dt, *J* = 12, 4 Hz, 1H), 1.22 (dd, *J* = 12, 9 Hz, 1H); ¹³C NMR (75 MHz, D₂O): δ 178.5, 137.9, 135.8, 103.6, 82.3, 81.4, 79.1, 75.8, 69.9, 69.6, 68.0, 62.0, 43.8, 40.4, 30.6; IR (KBr): 3454, 2951, 2891, 2515, 1658, 1541 cm⁻¹.

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