

The additional contribution may be attributable to the Mo⁴-Re bond, by analogy with the very large diamagnetic anisotropies of Mo⁴-Mo bonds.^[16] However, whereas the Mo⁴-Mo unit has a *deshielding* effect on the *endo* groups (corresponding to a negative magnetic anisotropy), the Mo⁴-Re moiety in **1** apparently causes *shielding* of the *endo* protons. This may reflect different electronic properties of heteronuclear and homonuclear quadruple bonds.

Experimental Section^[17]

All operations were performed under strictly anaerobic and anhydrous conditions. A mixture of [Mo(tpp)(py)₂] **2** (25 mg, 30 μmol) and [Re(oep)-(PEt₃)₂] **3** (8 mg, 8.4 μmol) was lyophilized by rapid removal of the solvent (C₆H₆, 2.5 mL). The resulting amorphous solid was pyrolyzed at 220 °C under vacuum (2 μTorr) for 8 h. The pyrolysis was repeated five times, the solids from these five batches were combined (ca. 150 mg),^[18] dissolved in C₆H₆ (10 mL), and the solution was filtered through a celite plug on to [Cp₂Fe]PF₆ (20 μmol, obtained by evaporating 800 μL of a 25 mM stock solution in acetonitrile in the reaction vial) and the mixture was stirred overnight. The precipitate of [Re(oep)(PEt₃)₂]PF₆ (and some **1**) was filtered, and the filtrate was treated with another 20 μmol portion of [Cp₂Fe]PF₆ to yield after 12 h, crude **1** as a dark-brown solid (the C₆H₆ filtrate contained mostly [Mo₂(tpp)₂] and a small amount (<10%) of [OMo(tpp)] along with [Cp₂Fe] and some [(oep)ReMo(tpp)]). The precipitate was treated with [Cp₂Co] (18 μmol, 40 mM stock solution in C₃H₆) in C₆H₆ for 24 h. The remaining solids ([Cp₂Co]PF₆ and an unidentified Re(oep) species) were separated, and the filtrate (mostly [(tpp)MoRe(oep)]) was subjected to two cycles of oxidation with [Cp₂Fe]⁺ followed by reduction with [Cp₂Co] exactly as described above. The main impurity isolated in these subsequent redox cycles was an unidentified Re(oep) species. Recrystallization of the precipitate of the final oxidation from CH₂Cl₂/toluene (1/3) yielded **1** (12 mg, 7.2 μmol, 17% yield based on [Re(oep)(PEt₃)₂]). ¹H NMR (500 MHz, CDCl₃, TMS): δ = 10.10 (s, 4H; *meso*-H, Re(oep)), 9.86 (d, ³J(H,H) = 7 Hz, 4H; *ortho-endo*-H_{ph}, Mo(tpp)), 8.51 (t, ³J(H,H) = 8 Hz, 4H; *meta-endo*-H_{ph}, Mo(tpp)), 8.47 (s, 8H; β-pyrrolic, Mo(tpp)), 7.97 (t, ³J(H,H) = 8 Hz, 4H; *p*-H_{ph}, Mo(tpp)), 7.50 (m, 4H; *meta-exo*-H_{ph}, Mo(tpp)), 6.82 (d, ³J(H,H) = 7.5 Hz, 4H; *ortho-exo*-H_{ph}, Mo(tpp)), 4.35 (m, 8H; CH₂, Re(oep)), 4.14 (m, 8H; CH₂, Re(oep)), 0.86 (t, ³J(H,H) = 7.5 Hz, 24H; CH₃, Re(oep)).

Crystal data for **1**·3 C₆H₅CH₃ (C₁₀₁H₉₆F₆MoN₈PRE): *M*_r = 1848.97, orthorhombic, space group *Pmma*, *a* = 26.350(5), *b* = 15.516(3), *c* = 9.802(2) Å; *V* = 4007.6(14) Å³, *Z* = 2 (imposing *mm2* symmetry on **1**), ρ_{calcd} = 1.532 g cm⁻³, absorption coefficient 1.757 mm⁻¹, *F*(000) = 1888, reflections collected 18484, independent reflections 3642, GOF = 1.132, *R* = 0.05457, *wR*₂ = 0.1344. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149919. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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- [17] See Supporting Information for syntheses of the intermediates and the details of the crystallographic studies.
- [18] The exact composition of this mixture could not be determined quantitatively due to paramagnetism of [(oep)ReMo(tpp)] and unreacted [Re(oep)(PEt₃)₂]. A small sample of the mixture was oxidized stepwise by adding small portions of [Cp₂Fe]PF₆ until mostly diamagnetic NMR spectra were observed. These indicated that the major species in the sample were [(oep)ReMo(tpp)], [Re(oep)-(PEt₃)₂], and [Mo₂(tpp)₂] in ca. 1:(<1):(<3) ratio.

Synthesis of the Globo H Hexasaccharide Using the Programmable Reactivity-Based One-Pot Strategy**

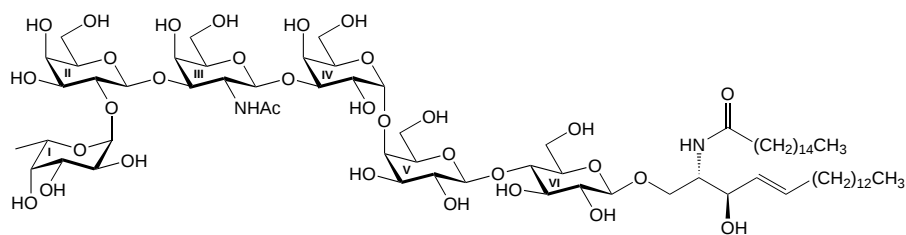
Fred Burkhart, Zhiyuan Zhang, Shirley Wacowich-Sgarbi, and Chi-Huey Wong*

Dedicated to Professor Horst Kunz on the occasion of his 60th birthday

Carbohydrate antigens are the most abundantly expressed antigens on the surface of most cancer cells.^[1] Globo H (Scheme 1), a glycosyl ceramide, was isolated and identified as an antigen on prostate and breast cancer cells.^[2] Its immunofunction has been characterized by Mênard et al.^[3] and Kuryashov et al.^[4] The use of this molecule as a vaccine for breast and prostate cancer has been studied by Danishefsky and co-workers.^[5]

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Scheme 1. The Globo H glycolipid.

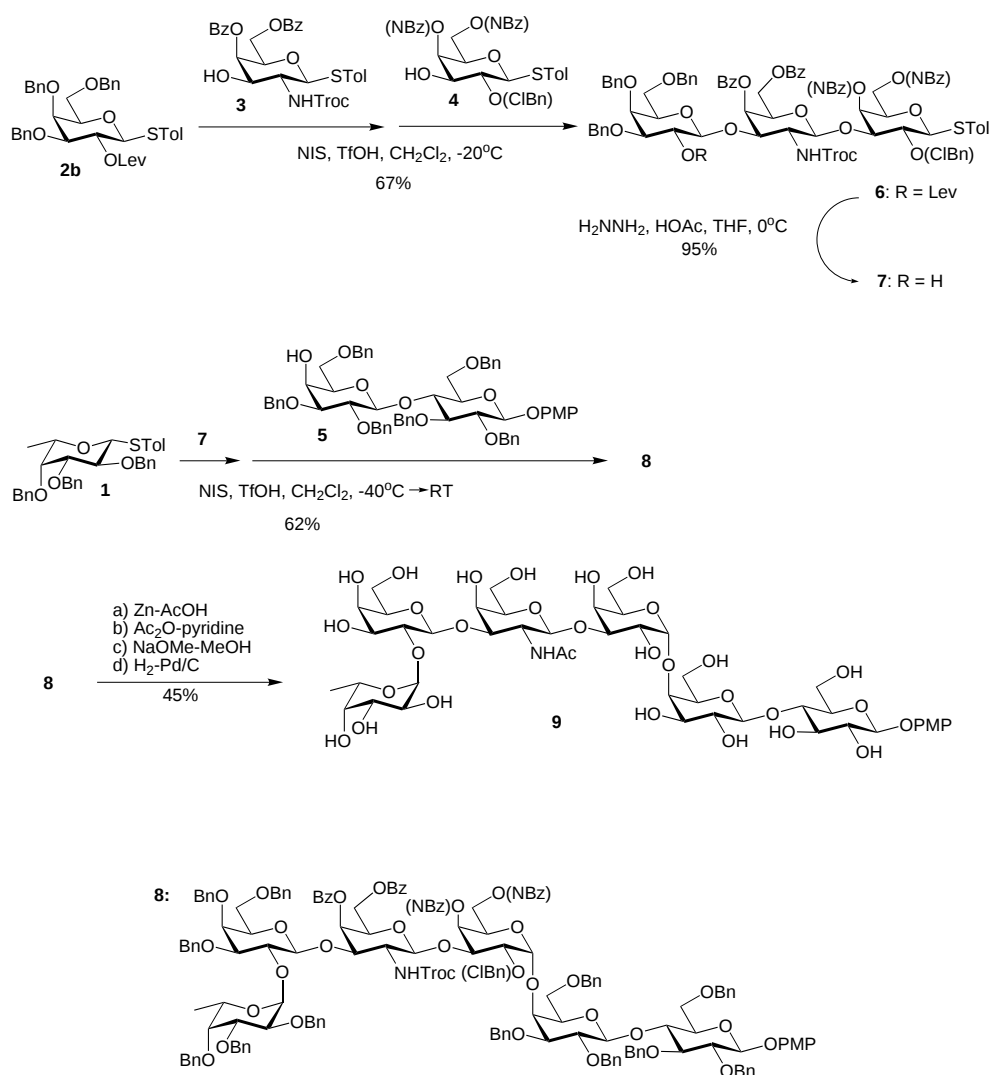
The first synthesis of the saccharide moiety of Globo H was reported by Danishefsky and co-workers using the glycal assembly strategy.^[6] Lassaletta and Schmidt synthesized the Globo H hexasaccharide with the trichloroacetimidate methodology.^[7] Another very effective synthesis of the saccharide moiety of Globo H was published by Zhu and Boons.^[8] However, controlling the β -selectivity of the coupling between rings II and III was a problem.

Herein we present a new method for the synthesis of the Globo H hexasaccharide using the anomeric reactivity-based one-pot strategy developed by Ley and co-workers^[9] and this group.^[10] Our programmable one-pot approach uses a computer program called “OptiMer” to guide the selection of appropriate tolylthioglycoside building blocks from a large pool for the one-pot synthesis.^[10] With this strategy, oligosaccharides containing three to six monosaccharides are rapidly assembled in minutes or hours by mixing the selected building blocks in sequence, with the most reactive one first. No intermediate work-up and purification is required except for the final deprotection/isolation step. The “relative reactivity” (against peracetyltolylthiomannoside) of each building block serves as an “identity tag” to identify or decode the structure of the target oligosaccharide. This approach thus represents a new method of combinatorial chemistry suitable for the synthesis of single-molecule libraries. Currently there are 80 building blocks in the database; expansion of the database (to approximately 300 building blocks) is necessary to cover the synthesis of most oligosaccharides.

Control of the stereoselectivity of each glycosylation

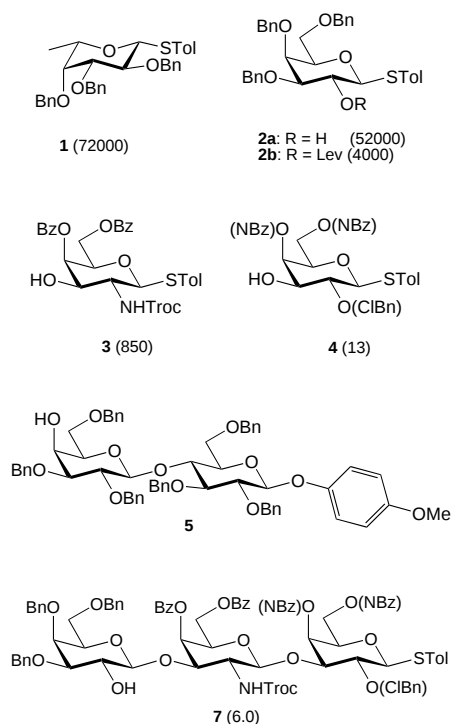
and the generation of a significant reactivity difference between the thio-glycosides are crucial for the successful synthesis of an oligosaccharide with the one-pot strategy. Our strategy for the Globo H saccharide synthesis involved the use of two one-pot reactions separated by a selective deprotection step to fully control the α and β selectivities (Scheme 2). The

first one-pot reaction was to build the two β -linkages connecting rings II, III, and IV to form **6**, which would then be converted into the trisaccharide building block **7**. The second one-pot reaction was to build the two α -linkages, between rings I and II and between rings IV and V, to form the protected Globo H saccharide **8**, through the sequential reaction of **1**, **7**, and **5**. We decided to use a levulinate as a temporary protecting group on the 2-position of galactose II (that is, **2b**), which would be removed selectively after the first one-pot reaction. Based on the knowledge of what affects the reactivity of a building block,^[10] compounds **1–5** were



Scheme 2. One-pot synthesis of the Globo H hexasaccharide. Bn = benzyl, Bz = benzoyl, ClBn = *ortho*-chlorobenzyl, Lev = levulinate, NBz = *para*-nitrobenzoyl, NHTrac = 2,2,2-trichloroethylcarbamate, NIS = *N*-iodosuccinamide, PMP = *para*-methoxyphenyl, Tf = triflate = trifluoromethanesulfonyl, Tol = *para*-methylphenyl.

designed and synthesized (Scheme 3). The reactivities were mainly tuned by using electron-donating groups (benzyl ether and 2,2,2-trichloroethylcarbamate) and electron-withdrawing groups (benzoyl, *p*-nitrobenzoyl, and *o*-chlorobenzyl ethers).



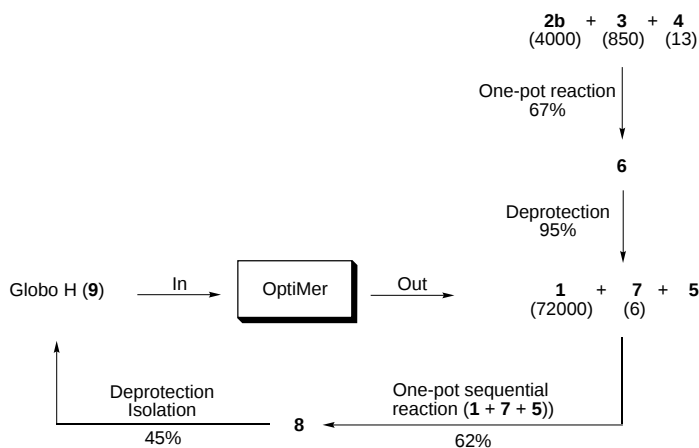
Scheme 3. The building blocks **1**–**5** and **7** were designed for the synthesis of the Globo H hexasaccharide. The relative reactivity values (against peracetyltolylthiomannoside, as determined by HPLC^[10]) are given in brackets.

Compounds **1**^[10] and **5**^[11] have been described previously. Thioglycosides **2a** and **2b** were prepared with the procedure analogous to that described by Sinaÿ and co-workers.^[12] The syntheses of glycosyl donors **3** and **4** were straightforward and required standard protecting group manipulations. Reactivities of those compounds were determined by HPLC as described previously.^[10] As shown in Scheme 3, the reactivity differences of the designed compounds are in a suitable range for a successful one-pot synthesis.

The three-step-synthesis of fully protected Globo H derivative **8** is outlined in Scheme 2. The first one-pot reaction built up the two β -linkages from compounds **3** (1 equiv), **2b** (1.5 equiv), and **4** (1.5 equiv). *N*-iodosuccinimide and triflic acid were used as promoters. The desired trisaccharide **6** was isolated in 67% yield. Deprotection of the levulinate using hydrazine in a mixture of THF and acetic acid at 0°C gave building block **7** in 95% yield.^[13] The reactivity of this compound relative to peracetyltolylthiomannoside is 6.0, similar to that of building block **4**. The second one-pot reaction formed the two α -linkages of Globo H. Thus, the fully protected Globo H derivative **8**^[13] was assembled in 62% yield, using donor **1** (1.8 equiv), compound **7** (1 equiv), and acceptor **5** (2.5 equiv). It is worth pointing out that all glycosyl linkages were built stereoselectively, and the overall yield after two one-pot assemblies and one deprotection step was 41% yield. Finally, the protecting groups on compound **8** were removed to give the deprotected Globo H hexasaccharide **9** in

45% yield.^[13] The *p*-methoxyphenyl group (PMP) was used in order to give us the possibility to independently deprotect the reducing end to further functionalize for biological purposes.

We have demonstrated the stereoselective synthesis of the hexasaccharide moiety of the tumor-associated antigen Globo H through the programmable one-pot synthesis strategy (Scheme 4). The building blocks developed for the synthesis



Scheme 4. Overall strategy for the programmed one-pot synthesis of the Globo H hexasaccharide. The numbers in parenthesis are the relative reactivities (against peracetyltolylthiomannoside).

contain mono-, di-, and trisaccharides and have been entered into the OptiMer database. They were assembled in two separate one-pot reactions performed stereoselectively in good overall yields. We believe that this new synthetic strategy has potential for use in the rapid synthesis of Globo H and analogues, including the aglycon moiety, for identification of the optimal structure to be used in vaccine development. The programmable one-pot strategy should also be applicable to the structure–activity relationship study of other complex oligosaccharides. Work is in progress to develop another one-pot synthesis of the Globo H saccharide using the disaccharide of rings II and III as a building block to react with **1**, followed by **4** and **5**. The result will be published in due course.

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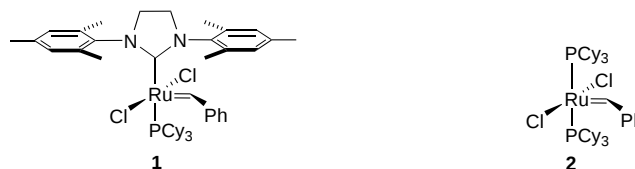
Synthesis of α,β -Unsaturated Amides by Olefin Cross-Metathesis**

Tae-Lim Choi, Arnab K. Chatterjee, and Robert H. Grubbs*

Dedicated to Professor Gilbert Stork on the occasion of his 80th birthday

Over the past few years, olefin metathesis has become a useful reaction in organic,^[1] polymer^[2] and bioorganic chemistry.^[3] Among olefin metathesis reactions, ring-closing metathesis (RCM) and ring-opening metathesis polymerization

(ROMP) have received the most attention. However, cross-metathesis (CM) is also of increasing utility in C=C bond formation under mild conditions.^[4, 5] The synthesis of trisubstituted^[6] and functionalized alkenes^[7] by cross-metathesis has become possible due to the development of the more active and more stable catalyst **1**, containing the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand.^[8] Catalyst **1** not only has



activity comparable to early transition metal catalysts, but also retains the functional group tolerance comparable to catalyst **2**.^[9] Herein, we report a versatile cross-coupling reaction of various α,β -unsaturated amides with terminal olefins and styrene, and that the CM efficiency is affected by the substituents on the amide nitrogen.

Several unsaturated amide substrates were screened for CM with terminal olefins (Table 1). Initially, dimethylacryl-

Table 1. Cross-metathesis reactions with terminal olefins^[a] and styrene.^[b]

Entry	Acrylamide	Terminal olefin ^[c]	Isolated yield of CM [%] ^[d] Terminal olefin Styrene (<i>E/Z</i>)
1a		I	3 : 39 (25:1) 4 : 25
1b ^[e]		I	3 : 83 (25:1)
2		I	5 : 77 6 : 57
3		II	7 : 80 8 : 62
4		II	9 : 89 (60:1) 10 : 66
5		III	11 : 89 12 : 69
6		II	13 : 90 14 : 69
7		II	15 : 97 (28:1) 16 : 83
8		II	17 : 100 (40:1) 18 : 87
9		I	19 : 87 (60:1) 20 : 40 ^[d]
10		II	21 : 100 22 : 63

[a] Reaction with 5 mol % catalyst **1** and 1.25 equiv terminal olefin (0.2 M in CH_2Cl_2) at 40 °C for 15 hours. [b] Reaction with 5 mol % catalyst **1** and 1.9 equiv styrene (0.2 M in CH_2Cl_2) at 40 °C for 15 hours. [c] See Scheme 1 for the chemical formulas. [d] Isolated ratio or no *cis* product observed by ^1H NMR spectroscopy. The compound numbers are used in the Supporting Information. [e] Reaction with 10 mol % catalyst **1** and 1.5 equiv terminal olefin. [f] Yield determined by ^1H NMR spectroscopy.

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Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.