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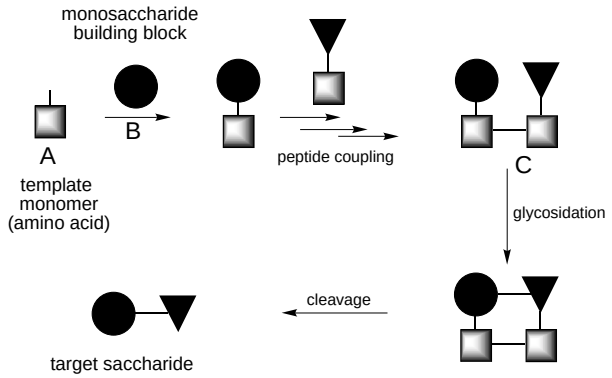
Peptide-Templated Saccharide Synthesis on a Solid Support**

David R. Greenwell, Abdel F. Ibnouzaki, and Stuart L. Warriner*

The chemical synthesis of oligosaccharides remains a major challenge in synthetic chemistry. Of particular importance is the development of new strategies for the stereoselective synthesis of oligosaccharides and the incorporation of these methods into the overall process of the assembly of target glycosides. Following the pioneering work of Hindsgaul and Barresi[1] a number of authors have investigated the use of temporary molecular tethers to control the regio- and/or stereoselectivity of glycosidation reactions.[2, 3] We were intrigued by the possibilities of extending these concepts of tethered intramolecular glycosidation reactions to an overall approach for the synthesis of saccharides. Such an approach requires the challenging construction of a molecular template bearing different monosaccharides at different points along its length. This problem is greatly simplified if the template is based upon a peptide skeleton. In following this strategy a suitably functionalized amino acid **A** is first conjugated to the monosaccharide building blocks **B** through a cleavable linker (Scheme 1). These units are then coupled by means of standard peptide synthesis protocols to provide the suitably functionalized template **C**. We then envisaged a glycosidation reaction which would "zip up" the carbohydrate with the template and thus control the steroselectivity of the glycosidation process. The product is then cleaved from the template to furnish the target saccharide.



Scheme 1. Peptide-templated saccharide synthesis.

An additional advantage of using peptide templates is that it should be possible to assemble **C** on solid support by using standard peptide synthesis protocols which opens the door to automation of the whole process. Fairbanks et al. have recently reported on independent studies on the use of peptide tethers to control the solution-phase synthesis of mannose-containing disaccharides.[4] Here we describe our initial studies of the peptide-templated synthesis of disaccharides on solid support.

The amino acid hydroxyproline (HyP) was chosen as the core of our peptide template as coupling of these units should provide a relatively rigid skeleton. Linkage of the amino acid with the monosaccharide was envisaged by means of a mixed carbonate link between the HyP hydroxy group and the 6-hydroxy group of the sugar unit. Our initial studies focussed on the synthesis of disaccharides by using this methodology, which required the preparation of a peptide template bearing a single glycosyl donor and glycosyl acceptor.

The required building block **3** was prepared in 80 % yield by formation of a mixed carbonate linkage between glucosyl donor **2**[5] and protected HyP derivative **1**[6] in phosgene solution (Scheme 2). The room-temperature NMR spectrum of building blocks such as **3** is complicated by the observation of two Fmoc group rotamers in approximately equal quantities. The acceptor unit **5** was prepared in a similar manner by selective coupling of the 6-hydroxy group of the BDA-protected[7, 8] methyl glucoside **4** with **1** in 81 % yield (Scheme 2; BDA = butanedione-2,3-diacetal). Protection of the secondary hydroxy group was not necessary.

With the required units in hand, we turned our attention to the solid-phase synthesis of the peptide template. As isolation of the final peptide was not required, the peptides were attached directly to an aminomethyl polystyrene-based resin, aminomethyl Novagel,[9] which had a nominal loading capacity of 0.74 mmol g^{-1}. Peptide synthesis was performed on a semiautomated peptide synthesizer in the presence of 1-hydroxy-7-azabenzotriazole (HOAt).[10]

The peptide template sequence was initiated by the addition of a glycine unit onto the resin backbone to minimize

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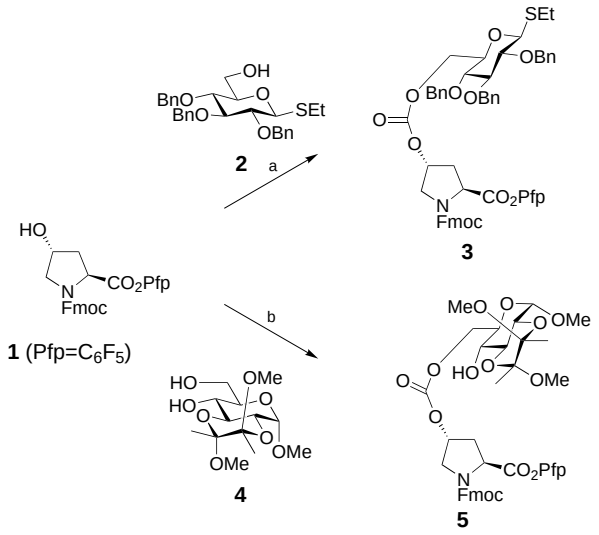
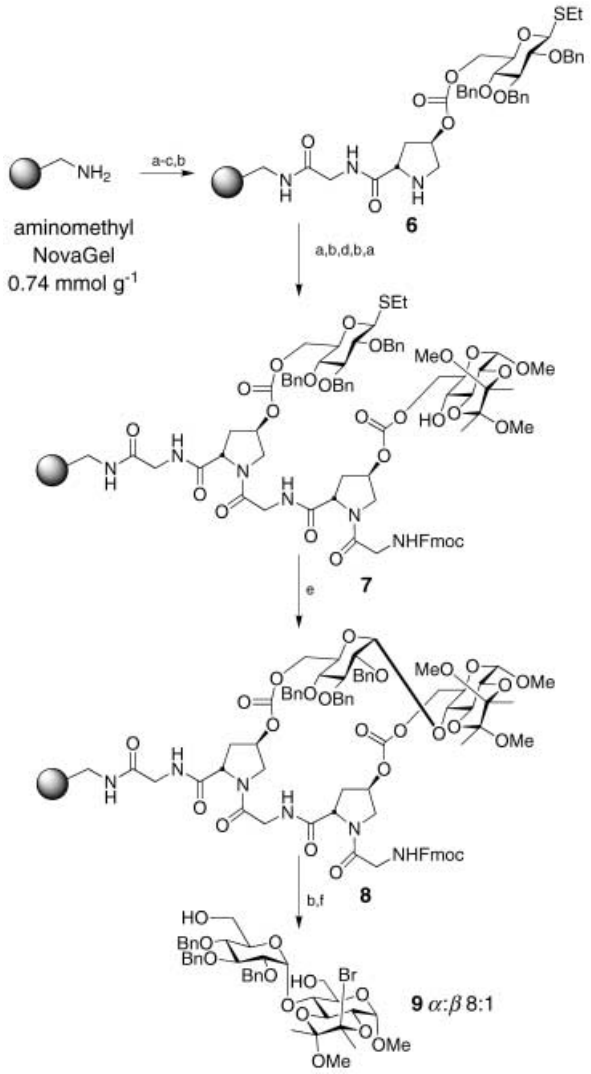


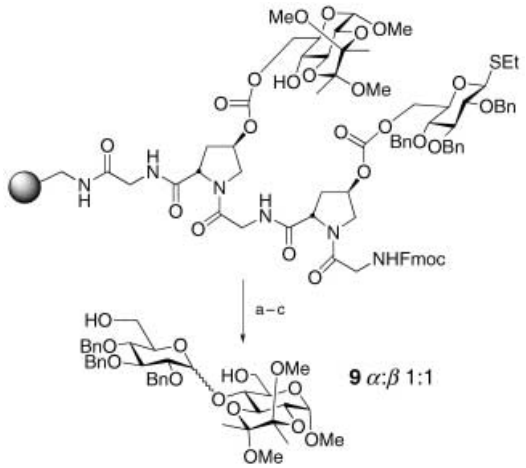
Scheme 2. Preparation of glycosyl donor **3** and glycosyl acceptor **5**. a) $COCl_2$, toluene, py, THF, $-78\,^{\circ}C \rightarrow RT$, then **2**, $-78\,^{\circ}C \rightarrow RT$, 78%; b) $COCl_2$, toluene, THF, **1**, $-78\,^{\circ}C \rightarrow RT$, then add to **4**, $-78\,^{\circ}C \rightarrow RT$, 81%. Fmoc = 9-fluorenylmethoxycarbonyl, py = pyridine.

any interactions between the sugars and the polystyrene. The hydroxyproline unit bearing the glycosyl donor building block **3** was then coupled to the resin-bound glycine to give the dipeptide **6** (Scheme 3). Unfortunately, it was not possible to directly couple the acceptor-bearing HyP unit **5** to the proline unit of **6**, presumably because of the steric hindrance of the bulky sugars; however, insertion of an intermediate glycine unit enabled subsequent addition of the acceptor unit **5** and a terminal-protected glycine. The final template structure was hence pentapeptide **7** (Scheme 3) with an alternating HyP-Gly sequence suitably functionalized to form a disaccharide. Fmoc cleavage analysis revealed a final loading of 0.39 mmol g^{-1}. As the loading of the resin is relatively low, any glycoside product must come from intramolecular glycosidation along the template backbone. The dry resin was hence treated with excess of NIS and catalytic amounts of TMSOTf for 16 h. A successful glycosidation reaction would form the 24-membered macrocycle **8**. Following removal of the excess reagents by washing, the terminal Fmoc group was then cleaved by using piperidine in dichloromethane. Cleavage of the carbonate linkage under basic conditions furnished the desired disaccharide **9** in 80% yield (based on a pentapeptide loading of 0.39 mmol g^{-1}) as almost exclusively the α isomer (Scheme 3).

To investigate the influence of the order of addition of the sugar units to the peptide on overall selectivity, the template was resynthesized with the donor and acceptor groups in the opposite order (that is, with the donor towards the N-terminus). The glycosidation reaction once again proceeded smoothly but in this case gave a 75% yield of **9** as a 1:1 mixture of anomers (Scheme 4).[11] This result clearly demonstrates the influence of the peptide template on the steroselectivity of the glycosidation process as by simply altering the order of addition the steroselectivity was dramatically changed. Clearly the conformational preferences of the peptide backbone influence the anomeric selectivity during the glycosidation process.



Scheme 3. Synthesis of disaccharide **9** on a peptide template. a) 4 equiv Fmoc-Gly-OPfP, HOAt; b) 20% piperidine, DMF; c) 2.5 equiv **5**, HOAt; d) 2.5 equiv **9** HOAt; e) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF:CH_2Cl_2 4:1, 16 h; f) NaOH, MeOH:THF 4:1, H_2O. DMF = dimethylformamide, NIS = *N*-iodosuccinimide, TMSOTf = trimethylsilyltriflate, MS = molecular sieves.



Scheme 4. Synthesis of disaccharide **9** with the reversed order of glycoside donor and acceptor. a) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF:CH_2Cl_2 4:1, 16 h; b) 20% piperidine, CH_2Cl_2; c) NaOH, MeOH:THF 4:1, H_2O.

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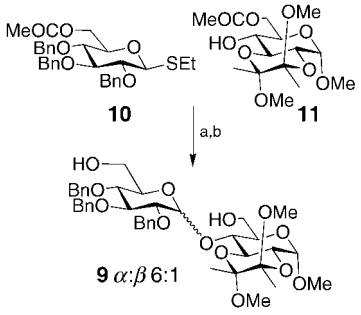
The inherent selectivity of the solution-phase intermolecular glycosidations in the absence of a template were ascertained by the coupling of methyl carbonates **10** and **11** (Scheme 5).[12] Under conditions identical to those employed in the template-based synthesis, disaccharide **9** was formed with an α/β selectivity of 6:1.[11] It therefore appears that the peptide template increases the α selectivity of the glycosidation when the donor is attached towards the C-terminus of the peptide, while more β anomer is formed when the donor is attached towards the N-terminus.



Scheme 5. Selectivity of coupling in solution. a) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF:CH_2Cl_2 4:1, 16 h; b) NaOH, MeOH:THF 4:1, H_2O.

We then explored the applicability of this methodology to the synthesis of a range of disaccharides. In each case the donor **3** remained constant. Glucose-, mannose-, and galactose-based acceptors were synthesized by procedures similar to those employed in the synthesis of **5**, and the subsequent disaccharides synthesized on the peptide template with the glycosyl donor attached at either the N- or C-terminus of the template. Solution-phase glycosidations of the model 6*O*-methoxycarbonyl compounds were also performed to ascertain the inherent selectivities of the glycosidation reactions (Scheme 6).

In all cases, the model solution studies displayed a selectivity of approximately 6:1 in favor of the α isomer (Table 1). In the case of acceptors with the free hydroxy group at the 2-position (to form glucoside **16** and mannoside **17**) the selectivity was more in favor of the β isomer when the reaction

Table 1. Comparison of the yields and selectivities for the synthesis of disaccharides **16**–**18** according to Scheme 6.

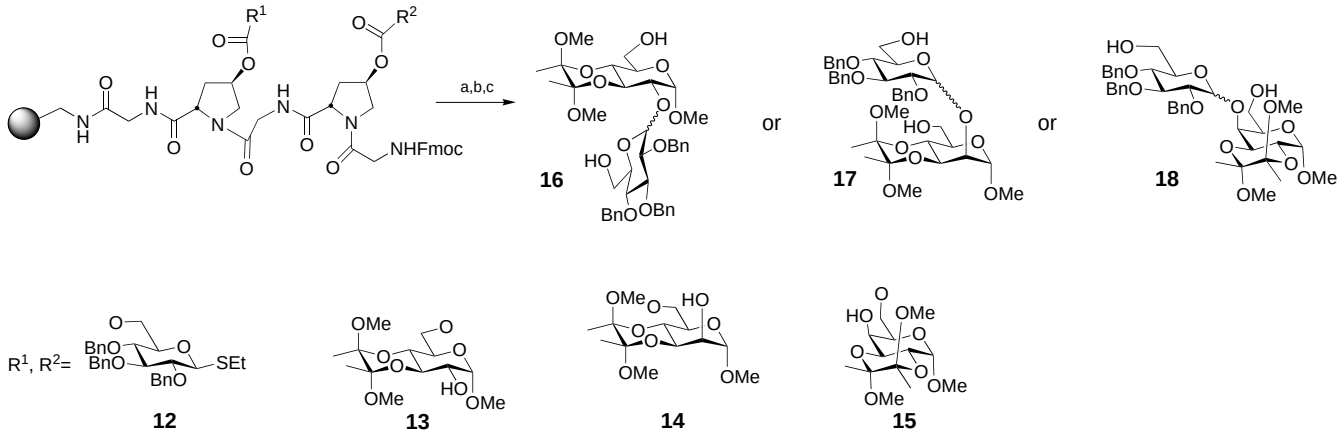
Entry	R^1	R^2	Product	Yield [%][a]	$\alpha:\beta$ selectivity	
					support	solution[b]
1	**12**	**13**	**16**	86	2:1	6:1
2	**13**	**12**	**16**	82	2:1	
3	**12**	**14**	**17**	75	2:1	5:1
4	**14**	**12**	**17**	84	2:1	
5	**12**	**15**	**18**	79	1.8:1	7:1
6	**15**	**12**	**18**	81	9:1	

[a] Based on a pentapeptide loading of 0.39 mmol g^{-1}. [b] Solution selectivities were determined by using the 6*O*-methoxycarbonyl-substituted versions of the donor and acceptor in analogy to the reactions shown in Scheme 5.

was performed on the template and was practically invariant of the order of addition of the building blocks (entries 1–4). When the acceptor hydroxy group was located at the 4-position (to form glucoside **9** and galactoside **18**) the selectivity was crucially dependant on the order of addition of the sugars on the template. In contrast to the case of the synthesis of **9** which displays the highest α selectivity when the donor is towards the C-terminus of the template, formation of galactoside **18** gave a 1.8:1 mixture of isomers with the donor towards the C-terminus but a 9:1 mixture of isomers when the donor was at the N-terminus of the template (entries 5 and 6). In all cases the yields of the isolated disaccharides were excellent. We are currently investigating how the conformation of the peptide controls the glycosidation reaction and studying extension of this methodology to the synthesis of larger saccharides.

Experimental Section

9*α*: Aminomethyl-NovaGel-HL (0.74 mmol g^{-1}, 60 mg, 0.044 mmol) was allowed to swell for 16 h in DMF (1 mL) prior to use. Peptide synthesis was performed on a Milligen 9020 synthesizer by using extended coupling cycles. Fmoc-protected amino acid pentafluorophenyl esters were preactivated with 1-hydroxy-7-azabenzotriazole (HOAt) and added when prompted by the synthesizer. Fmoc-glycine-Pfp (82 mg, 0.176 mmol, 4 equiv) and HOAt (24 mg, 0.176 mmol, 4 equiv) were dissolved in DMF (1 mL), introduced into the synthesizer, and recycled over the resin for 1 h. Following Fmoc removal, **3** (116 mg, 0.11 mmol, 2.5 equiv) and HOAt (15 mg, 0.11 mmol, 2.5 equiv) dissolved in DMF (1 mL) were introduced



Scheme 6. Preparation of several disaccharides on a peptide support. a) 10 equiv NIS, cat. TMSOTf, 4-Å MS THF:CH_2Cl_2 4:1, 16 h; b) 20% piperidine, CH_2Cl_2; c) NaOH, MeOH:THF 4:1, H_2O.

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and recycled for 1.5 h. This process was repeated for the addition of the next three amino acids, Fmoc-glycine-Pfp, **5**, and Fmoc-glycine-Pfp. After completion of the fifth coupling the resin was washed with CH_2Cl_2 for 15 minutes, and the beads were removed from the synthesizer and dried overnight. 4-Å Molecular sieves (5 beads) and CH_2Cl_2 (1 mL) were added to the resin beads, and the suspension was agitated for 1 h. TfOTMS solution (160 μL of a 16% v/v solution in CH_2Cl_2) was added to a solution of NIS (400 mg, 1.78 mmol in THF (4 mL) and CH_2Cl_2 (1 mL). A 1.25-mL aliquot of the resulting mixture was added to the resin beads, and the suspension was agitated for 18 h. The solution was then removed by filtration, and the resin was washed with CH_2Cl_2 (3×2.5 mL). The resin was treated with 20% piperidine in CH_2Cl_2 (2 mL), and the mixture was agitated for 15 min. The solvent was drained and the resin was washed with CH_2Cl_2 (3×2.5 mL). A solution of NaOH (10 mg, 0.25 mmol) in THF (0.5 mL) and methanol (2 mL) was transferred to the resin beads. The mixture was then agitated for 1 h, after which the solution was filtered from the resin and the filtrate concentrated to dryness under reduced pressure. The crude products were dissolved in CH_2Cl_2 (5 mL), washed with water (2×5 mL), and dried ($MgSO_4$), and the major α isomer was purified by preparative HPLC on an Alltech Econosil Silica normal-phase preparative column (10 μm, 250×22 mm) with a flow rate of 10 mL min^{-1} and gradient elution (0 min: hexane 95%, 2-propanol 5%; 20 min: hexane 65%, 2-propanol 35%; then isocratic for 5 min) to give **9*α*** (14 mg). $R_f = 0.77$ (petroleum:EtOAc, 1:1); $[\alpha]_D^{20} = -5.69$ ($c = 0.67$ in $CHCl_3$); IR (thin film): $\tilde{\nu} = 3494$ (OH), 3057, 3030, 2990, 2942, 1461, 1409 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$, 25 °C, TMS); $\delta = 7.33-7.26$ (m, 15H; aromatic protons), 5.70 (d, ^3J(H,H) = 3.8 Hz, 1H; H-1), 4.92 (d, ^2J(H,H) = 10.9 Hz, 1H; 3OCH_aH$_b$Ph), 4.85 (d, ^2J(H,H) = 10.9 Hz, 1H; 3OCH$_a$$H_b$Ph), 4.84 (d, ^2J(H,H) = 11.4 Hz, 1H; 4OCH_aH$_b$Ph), 4.83 (d, ^2J(H,H) = 12.1 Hz, 1H; 2OCH_aH$_b$Ph), 4.80 (d, ^2J(H,H) = 12.1 Hz, 1H; 2OCH$_a$$H_b$Ph), 4.71 (d, ^3J(H,H) = 3.5 Hz, 1H, H-1′), 4.59 (d, ^2J(H,H) = 11.4 Hz, 1H; 4OCH$_a$$H_b$Ph), 4.32 (t, ^3J(H,H) = 9.4 Hz, 1H; H-3′), 4.09 (t, ^3J(H,H) = 9.4 Hz, 1H; H-4′), 3.97 (t, ^3J(H,H) = 9.0 Hz, 1H; H-3), 3.91 (dd, ^2J(H,H) = 12.3 Hz, ^3J(H,H) = 3.0 Hz, 1H; H-6a′), 3.87 (dd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 2.4 Hz, 1H; H-6b), 3.83–3.77 (m, 2H; H-6b′ & 5), 3.74 (dd, ^2J(H,H) = 10.3 Hz, ^3J(H,H) = 3.5 Hz, 1H; H-2′), 3.73–3.69 (m, 1H; H-5), 3.61 (dd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 5.9 Hz, 1H; H-6a), 3.56 (dd, ^2J(H,H) = 9.0 Hz, ^3J(H,H) = 3.8 Hz, 1H; H-2), 3.42 (t, ^3J(H,H) = 9.0 Hz, 1H; H-4), 3.39 (s, 3H; OCH_3), 3.24 (s, 3H; OCH_3), 3.09 (s, 3H; OCH_3), 1.30 (s, 3H; CH_3), 1.22 (s, 3H; CH_3); ^{13}C NMR (125 MHz; $CDCl_3$, 25 °C, TMS): $\delta =$ 138.6 (aromatic C-1), 138.0 (aromatic C-1), 128.5–127.6 (aromatic C-1, 2, 3, 4, 5, 6), 99.7 (C-BDA), 99.3 (C-BDA), 98.0 (C-1′), 97.1 (C-1), 82.0 (C-3), 79.3 (C-2), 78.4 (C-4), 75.6 (3O-*C*H$_2$Ph), 75.2 (4O-*C*H$_2$Ph), 73.9 (2O-*C*H$_2$Ph), 72.2 (C-5), 70.8 (C-5′), 70.3 (C-3′), 69.5 (C-4′), 68.4 (C-2′), 62.2 (C-6), 61.2 (C-6′), 55.0 (C-1-O*C*H$_3$), 48.1 (BDA-O*C*H$_3$), 48.0 (BDA-O*C*H$_3$), 17.8 (BDA-*C*H$_3$), 17.7 (BDA-*C*H$_3$); MS (ES$^+$): *m*/*z* (%): 763 (100%) [*M*+Na$^+$]; HR-MS: calcd for $C_{40}H_{52}O_{13}Na$: 763.3306; found: 763.3302.

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[11] Anomeric ratios were determined by integration of the OMe resonances in the ^{1}H NMR spectrum of the crude product and by HPLC analysis of the mixture.

[12] The methyl carbonates were prepared by treatment of **2** and **4** with methyl chloroformate in analogy to the synthesis of **3** and **5**.

A New Method for the Synthesis of Cycloheptenones by Rh^I-Catalyzed Intramolecular Hydroacylation of 4,6-Dienals

Yoshihiro Sato, Yoshihiro Oonishi, and Miwako Mori*

The development of methodology for the synthesis of cyclic compounds is important in modern synthetic organic chemistry, not least because there are many biologically active compounds with complicated cyclic structures. The construction of a medium-sized ring is relatively difficult due to unfavorable entropy and nonbonding interactions occurring at the transition state during the cyclization. Transition metal catalyzed cyclization is one of the most promising strategies for the construction of such medium-sized ring compounds.[1] Rh^I-mediated cyclization of 4-alkenals to give cyclopentanone derivatives was first reported by Sakai et al. in 1972,[2] and this hydroacylation has subsequently been developed into a catalytic process[3] and asymmetric reaction.[4] On the basis of results of mechanistic studies,[5] it is thought that the reaction proceeds as follows (Scheme 1): a C–H bond of the aldehyde moiety of **1** is oxidatively added to a Rh^I complex followed by insertion of a C=C bond of an olefin to give the rhodacycle intermediate **I**. Reductive elimination from **I** occurs to produce cyclopentanone **2** along with regeneration of the Rh^I complex. We speculated that if a

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