Asymmetric Synthesis

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Carbohydrate-Templated Asymmetric Diels–Alder Reactions of Masked *ortho*-Benzoquinones for the Synthesis of Chiral Bicyclo-[2.2.2]oct-5-en-2-ones**

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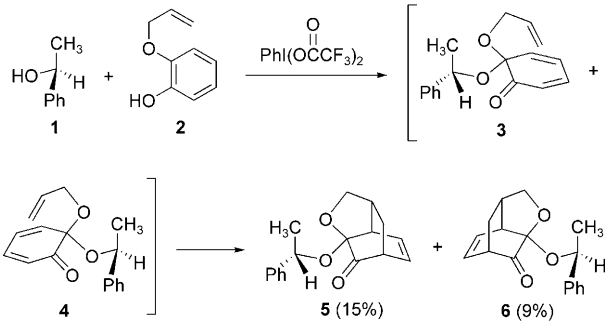
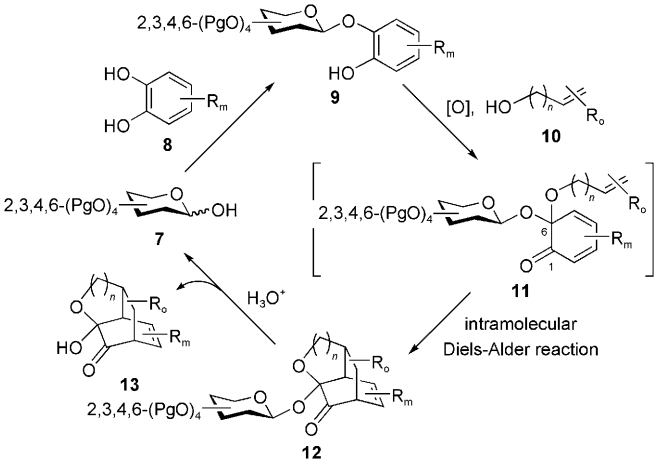
Dedicated to Professor Chi-Huey Wong on the occasion of his 60th birthday

Bicyclo[2.2.2]oct-5-en-2-ones have been widely applied in natural product synthesis for several decades.[1] Highly reactive 6,6-dialkoxycyclohexa-2,4-dienones (namely, masked *o*-benzoquinones or MOBs)[2] and their orthoquinol variants,[3] which can be conveniently generated by oxidation of the corresponding 2-alkoxy- and 2-alkylphenols in an alcoholic solvent, are often used for synthesizing the bicyclo-[2.2.2]oct-5-en-2-ones in racemic form through in situ intra-[4] or intermolecular[5] Diels–Alder reactions with various dienophiles. However, two major hurdles are frequently encountered in these studies: avoiding the self-dimerization of the MOBs[6] and preparing optically pure enantiomers.[7] For example, oxidative addition of 2-methoxyphenol with methanol led to a MOB intermediate, which immediately self-dimerized to give the [4+2] cycloadducts. When an allyl or homoallyl alcohol was used in the reaction, a racemic mixture of the intramolecular cyclic products was obtained in very low yield. For the synthesis of the chiral forms, (*S*)-1-phenylethanol (**1**) was initially studied. However, the reaction of 2-allyloxyphenol (**2**) with **1** in the presence of $PhI(OCOCF_3)_2$, via the MOB intermediates **3** and **4**, furnished diastereomers **5** and **6** in only 15% and 9% yields, respectively (Scheme 1). We report herein a new and straightforward asymmetric methodology that involves carbohydrates as chiral auxiliaries and that tackles these problems.[8]



Scheme 1. Low-yielding reaction of (*S*)-1-phenylethanol (**1**) and 2-allyloxyphenol **2**.

Our strategy, as illustrated in Scheme 2, entailed a three-step protocol. Coupling of the 2,3,4,6-tetra-O-protected hexopyranose **7**[9] with a catechol **8** by Mitsunobu-type glycosylation[10] could give the phenolic derivative **9**. Oxidative assembly of **9** with an alkenyl alcohol **10** would yield the MOB intermediate **11**, which could undergo intramolecular [4+2] cycloaddition to furnish the adduct **12** in a one-pot manner. The glycone part is expected to control the diastereoselective induction at the C6 position of cyclohexadienone **11** and increase the steric hindrance to avoid intermolecular Diels–Alder dimerization of **11**. Once the configuration of the C6 position in **11** is fixed, the remaining new asymmetric carbon atoms in compound **12** can be created and controlled through intramolecular cyclization. Hydrolysis of **12** under acidic conditions should provide the desired chiral bicyclo-[2.2.2]oct-5-en-2-one **13** and recover the initial sugar **7** for recycling and reuse.



Scheme 2. Three-step sugar-templated asymmetric synthesis of chiral bicyclo[2.2.2]oct-5-en-2-ones from catechols. Pg: protecting group; R_m, R_o: H or alkyl.

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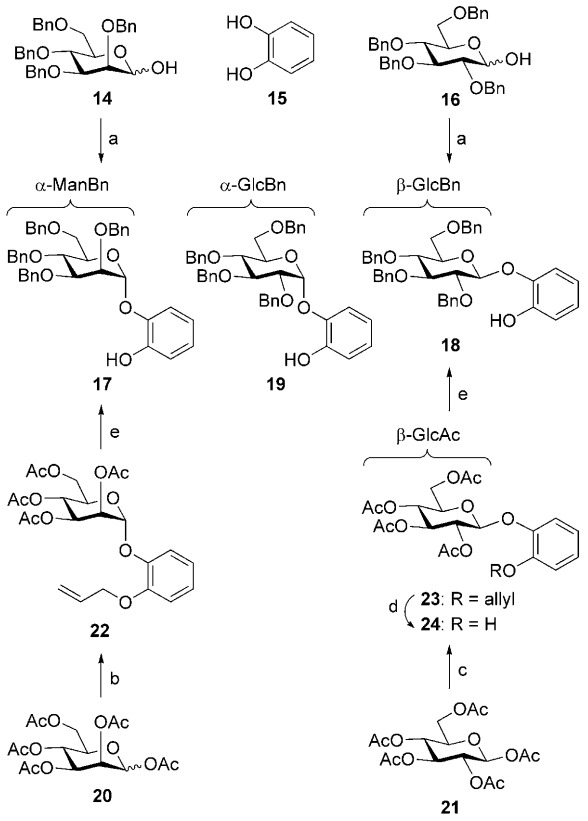
The preparation of the sugar-derived phenols is depicted in Scheme 3. Coupling of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**14**) with catechol (**15**) by using a combination of triphenylphosphine and diisopropylazadicarboxylate

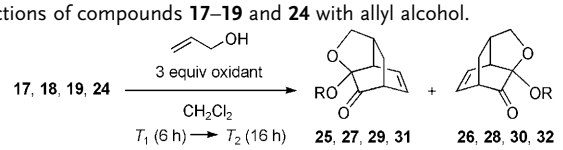


Scheme 3. Reagents and conditions: a) Ph_3P, DIAD, THF, 0 °C→RT, 20 h, **17**: 76%, **18**: 60%, **19**: 19%; b) **2**, TMSOTf, CH_2Cl_2, 0 °C→RT, 2 d, 63%; c) **2**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 18 h, 70%; d) cat. $[Pd(PPh_3)_4]$, AcOH, 80 °C, 3 h, 77%; e) 1. NaOMe, MeOH; 2. NaH, BnBr, DMF; 3. cat. $[Pd(PPh_3)_4]$, AcOH, 80 °C, 3 h, **17**: 70%, **18**: 77%. Bn: benzyl; TMSOTf: trimethylsilyl trifluoromethanesulfonate; DMF: *N*,*N*-dimethylformamide.

(DIAD) in THF afforded the single α-form phenol **17** in 76% yield. Treatment of the D-glucopyranose **16** under similar conditions furnished the β-glycosylated phenol **18** and its α-anomeric isomer **19** in 60% and 19% yields, respectively. An alternative approach with the per-O-acetylated sugars as starting materials was also investigated. TMSOTf-activated coupling of compound **20** with 2-allyloxyphenol (**2**) led to α derivative **22** (63%; recovered **20**: 30%). Similar conditions could not be applied to β-D-glucopyranosyl pentaacetate (**21**). In this case, $BF_3{\cdot}OEt_2$ was found to be a better promoter than TMSOTf, and the desired product, **23**, was obtained in 70% yield. It should be noted that α-D-glucopyranosyl pentaacetate did not react with **2** in the presence of acid activators. $[Pd(PPh_3)_4]$-catalyzed cleavage of the allyl group in **23** gave the corresponding phenol **24** in 77% yield. Deacetylation of compound **23** (NaOMe, MeOH) followed by per-O-benzylation (NaH, BnBr) provided the 2-allyloxyphenyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside, which underwent deallylation to yield the expected phenolic product **18** (77% in 3 steps). Application of this three-step transformation to compound **22** afforded the α-D-mannosyl phenol **17** in 70% overall yield.

Table 1 outlines the conditions and results of the oxidative coupling of compounds **17**–**19** and **24** with allyl alcohol followed by an intramolecular Diels–Alder reaction in a one-pot manner. In general, the reactions were carried out in two stages, being initiated at low temperature and continued at

Table 1: One-pot oxidative coupling and intramolecular Diels–Alder reactions of compounds **17**–**19** and **24** with allyl alcohol.



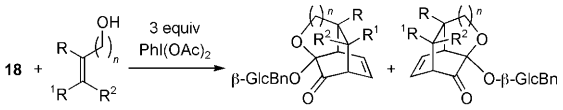
Entry	SM[a]	Oxidant[b]	T_1 [°C]	T_2 [°C]	Products (ratio)	Yield [%]
1	**17**	$PhI(OAc)_2$	−30	RT	**25**/**26** (3.5:1)[c]	56
2	**17**	$PhI(OTFA)_2$	−30	RT	**25**/**26** (3.6:1)[c]	45
3	**19**	$PhI(OAc)_2$	−30	RT	**29**/**30** (4.3:1)[c]	53
4	**19**	$PhI(OTFA)_2$	−30	RT	**29**/**30** (3.1:1)[c]	50
5	**24**	$PhI(OAc)_2$	−30	0	**31**/**32** (2.7:1)[c]	37
6	**18**	$PhI(OAc)_2$	−20	0	**27**/**28** (2.8:1)[d]	61
7	**18**	$PhI(OAc)_2$	−30	0	**27**/**28** (5.1:1)[d]	61
8	**18**	$PhI(OAc)_2$	−30	reflux	**27**/**28** (7.6:1)[d]	69

[a] SM: starting material. [b] TFA: trifluoroacetyl. [c] The ratio was determined by HPLC. [d] The ratio was determined by the yields of isolated **27** and **28**.

higher temperature. The former is expected to induce high diastereoselectivity during the MOB formation, whereas the latter is for the completion of the [4+2] cycloaddition. The initial studies at room temperature or 0 °C did not give satisfactory results and the oxidants were insoluble in solvents below −40 °C, so the reaction was first conducted at −30 °C for 6 h and then the temperature was raised to 0 °C or room temperature or the mixture was heated to reflux for 16 h. $PhI(OAc)_2$-oxidized assembly of the per-O-benzylated α-D-mannopyranosyl phenol **17** with allyl alcohol gave a mixture of cycloadducts **25** and **26** in 56% yield (Table 1, entry 1). When $PhI(OTFA)_2$ was used (Table 1, entry 2), a similar ratio of **25** and **26** was obtained in lower yield (45%). In the cases with the per-O-benzylated α-D-glucopyranosyl phenol **19** (Table 1, entries 3 and 4), a mixture of the products **29** and **30** was generated in 53% and 50% yields, respectively. The reaction of the per-O-acetylated β-D-glucopyranosyl phenol **24** with $PhI(OAc)_2$ (Table 1, entry 5) furnished an isomeric mixture of **31** and **32** in low yield (37%). When the per-O-benzylated β-D-glucopyranosyl phenol **18** was oxidized at −20 °C and then stirred at 0 °C (Table 1, entry 6), compounds **27** and **28** were isolated, after column chromatography on silica gel, in a 2.8:1 ratio. By lowering of the temperature to −30 °C (Table 1, entry 7), the ratio of **27** and **28** could be improved to 5.1:1. When the latter part of the reaction was carried out at reflux temperature (Table 1, entry 8), **27** and **28** were obtained in a 7.6:1 ratio and a slightly increased yield.

With this set of optimized conditions in hand, a variety of alkenyl alcohols were investigated. With (*E*)-2-buten-1-ol (**33**; Table 2, entry 1) the cycloadducts **37** and **38** were isolated

Table 2: $PhI(OAc)_2$-oxidized intramolecular [4+2] cycloadditions of compound **18** with various allyl and homoallyl alcohols under optimized conditions.



33: n = 1, R, R^2 = H, R^1 = Me
34: n = 1, R = Me, R^1, R^2 = H
35: n = 1, R = H, R^1, R^2 = Me
36: n = 2, R = Me, R^1, R^2 = H

37 **38**
39
40
41

Entry	Alcohol	Product (yield [%])[a]	Ratio
1	**33**	**37** (72) + **38** (11)	6.5:1
2	**34**	**39** (67)	–
3	**35**	**40** (74)	–
4	**36**	**41** (47)	–

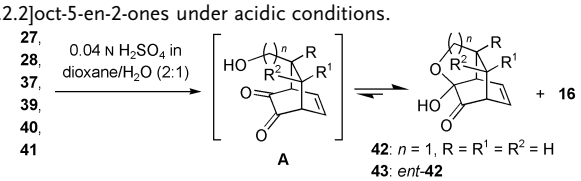
[a] The yields were obtained after purification by column chromatography on silica gel.

in 72% and 11% yields, respectively. 2-Methyl-2-propen-1-ol (**34**) led to compound **39** (67%) as a single product, and no other diastereomers were found after purification (Table 2, entry 2). Similar results were observed in the cases of 3-methyl-2-buten-1-ol (**35**; Table 2, entry 3) and 3-methyl-3-buten-1-ol (**36**; Table 2, entry 4), which furnished the products **40** and **41** in 74% and 47% yields, respectively.

The structures of compounds **27** and **28** were determined through the chemical correlation method. First, the configurations of compounds **5** and **6** were individually confirmed by X-ray single-crystal diffraction analyses.[11] Hydrolysis of **5** and **6** in a mixture of 3% aqueous HCl and acetic acid at 100 °C gave the corresponding enantiomeric ketones **42** ($[\alpha]_D^{24} = -287$) and **43** ($[\alpha]_D^{25} = +257$), respectively (see Table 3). The preferred configuration of compound **42**, as indicated by the peaks of its ^{13}C NMR spectrum (see the Supporting Information) at $\delta = 203.4$ (ketone) and 96.8 ppm (hemiketal), is the hemiketalic ketone (not the hydroxy diketone intermediate **A**). Similar phenomena have been reported for other hemiketals.[12] Cleavage of compounds **27** and **28** under similar conditions did not work well. Finally, a solution of 0.04 N H_2SO_4 in dioxane/water (2:1) was found to hydrolyze **27** and **28**, and the corresponding products **42** and **43** (Table 3, entries 1 and 2) were obtained in 94% and 93% yields, respectively. Under these conditions, the initial sugar **16** was also recovered in excellent yield. The cleavages of compounds **37** and **39–41** were individually carried out (Table 3, entries 3–6), and the specific rotations of the obtained products **44–47** exhibit high negative values, which indicate that their skeletons are similar to that of **27**.[13] The ^{13}C NMR spectra of compounds **44–47** also show that their configurations favor the hemiketal forms (see the Supporting Information).

A mechanism for the induction of high diastereoselectivity is proposed from examination of the possible reactive conformations of the oxocarbenium intermediate (**48** and **49**) that is presumably formed during the formation of the ketal with the allylic or homoallylic alcohols. Through the π–π interaction between the phenyl ring and the cationized cyclohexadienone, the carbonyl group in **49** not only has a higher steric hindrance with the anomeric proton but also

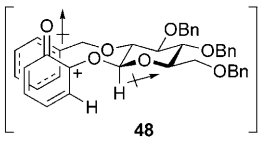
Table 3: Hydrolysis of the per-O-benzylated β-D-glycopyranosyl bicyclo-[2.2.2]oct-5-en-2-ones under acidic conditions.

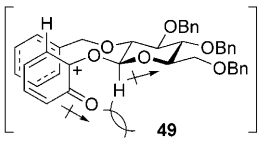


42: n = 1, R = R^1 = R^2 = H
43: *ent*-**42**
44: n = 1, R, R^2 = H, R^1 = Me
45: n = 1, R = Me, R^1, R^2 = H
46: n = 1, R = H, R^1, R^2 = Me
47: n = 2, R = Me, R^1, R^2 = H

Entry	SM	Product	Yield [%]	$[\alpha]_D^{T}$[a]	**16** [%]
1	**27**	**42**	94	−287.5	84
2	**28**	**43**	93	+257.2	81
3	**37**	**44**	87	−300.4	98
4	**39**	**45**	93	−288.5	97
5	**40**	**46**	90	−311.1	86
6	**41**	**47**	86	−345.6	95

[a] In 10^{-1} deg cm^3 g^{-1} dm^{-1} (**42**: T = 24 °C, c 1.3, $CHCl_3$; **43**: T = 25 °C, c 0.5, $CHCl_3$; **44**: T = 27 °C, c 1.4, $CHCl_3$; **45**: T = 17 °C, c 1.0, $CHCl_3$; **46**: 19 °C, c 3.3, $CHCl_3$; **47**: T = 20 °C, c 1.6, $CHCl_3$).





possesses a stronger dipole–dipole interaction with the C1′–O bond in the pyranosyl ring. These effects presumably result in a preference for conformer **48**, which can be attacked by an alkenyl alcohol from the β face.

In summary, we have developed a three-step synthesis of optically pure bicyclo[2.2.2]oct-5-en-2-ones in good yields through carbohydrate-templated asymmetric intramolecular Diels–Alder reactions of MOBs. The per-O-benzylated sugar moiety can inhibit self-dimerization of MOBs and induce high diastereoselectivity. The strategy described herein should provide access to substituted catechols for the preparation of highly functionalized chiral bicyclo[2.2.2]oct-5-en-2-ones. A variety of commercially available D and L sugars could be applied for the synthesis of either enantiomer.

Experimental Section

General procedure for $PhI(OAc)_2$-oxidized one-pot coupling and Diels–Alder reaction of compound **18** with various alkenols: $PhI(OAc)_2$ (3.0 equiv) was added to a solution of compound **18** (1.0 equiv) in anhydrous alkenyl alcohol (100 mL per 1 g of **18**) and CH_2Cl_2 (20 mL per 1 g of **18**) at −30 °C under nitrogen. After the mixture had been stirred for 6 h, the reaction flask was gradually warmed up and the mixture was heated to reflux for 16 h. The solution was cooled to room temperature, and the reaction was quenched by saturated aqueous $NaHCO_3$. The whole mixture was extracted three times with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and

concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to afford the desired cycloadduct.

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[13] Our previous CD studies of some optically pure bicyclo-[2.2.2.]octa-5-en-2-ones (see the Supporting Information in reference [7]) have revealed that chiral compounds with the same skeletons and different substituent groups result in similar curve patterns.

