Asymmetric Synthesis

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 6,6-dialkoxycyclohexa-2,4-dienones reactive (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 selfdimerized 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 2allyloxyphenol (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]

Our strategy, as illustrated in Scheme 2, entailed a threestep 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

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



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.

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.



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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) Ph₃P, DIAD, THF, 0°C \rightarrow RT, 20 h, **17**: 76%, **18**: 60%, **19**: 19%; b) **2**, TMSOTf, CH₂Cl₂, 0°C \rightarrow RT, 2 d, 63%; c) **2**, BF₃·OEt₂, CH₂Cl₂, 0°C, 18 h, 70%; d) cat. [Pd(PPh₃)₄], AcOH, 80°C, 3 h, 77%; e) 1. NaOMe, MeOH; 2. NaH, BnBr, DMF; 3. cat. [Pd(PPh₃)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 -Dglucopyranosyl pentaacetate did not react with 2 in the presence of acid activators. [Pd(PPh₃)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 2allyloxyphenyl 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-Alderreactions of compounds 17-19 and 24 with allyl alcohol.

1	7, 18, 19	, 24 3 equiv CH <i>T</i> ₁ (6 h) —	$_2$ OH roxidant $_2$ Cl ₂ ► T_2 (16 h	→ RO) 25, 21	7, 29, 31 26, 28, 3	OR 0 30, 32
Entry	$SM^{[a]}$	Oxidant ^[b]	<i>T</i> ₁ [°C]	<i>T</i> 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
1	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
5	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
3	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-benzvlated α -Dmannopyranosyl 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-Obenzylated 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

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



Alcohol	Product (yield [%]) ^[a]	Ratio	
33	37 (72) + 38 (11)	6.5:1	
34	39 (67)	-	
35	40 (74)	-	
36	41 (47)	-	
	Alcohol 33 34 35 36	Alcohol Product (yield [%]) ^[3] 33 37 (72) + 38 (11) 34 39 (67) 35 40 (74) 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 ¹³C 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 H₂SO₄ 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 ¹³C 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.



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 cm³g⁻¹ dm⁻¹ (42: T = 24 °C, c 1.3, CHCl₃; 43: T = 25 °C, c 0.5, CHCl₃; 44: T = 27 °C, c 1.4, CHCl₃; 45: T = 17 °C, c 1.0, CHCl₃; 46: 19 °C, c 3.3, CHCl₃; 47: T = 20 °C, c 1.6, CHCl₃).



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 CH₂Cl₂ (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 NaHCO₃. The whole mixture was extracted three times with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous MgSO₄, 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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- D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* 2004, 104, 1383.
- [2] a) V. Sigh, Acc. Chem. Res. 1999, 32, 324; b) C.-C. Liao, R. K.
 Peddinti, Acc. Chem. Res. 2002, 35, 856; c) C.-C. Liao, Pure Appl. Chem. 2005, 77, 1221.
- [3] H.-Y. Shiao, H.-P. Hsieh, C.-C. Liao, Org. Lett. 2008, 10, 449.
- [4] a) S. P. Cook, A. Polara, S. J. Danishefsky, J. Am. Chem. Soc.
 2006, 128, 16440; b) D.-S. Hsu, C.-C. Liao, Org. Lett. 2007, 9, 4563.
- [5] a) C.-H. Chen, P. D. Rao, C.-C. Liao, J. Am. Chem. Soc. 1998, 120, 13254; b) C.-F. Yen, C.-C. Liao, Angew. Chem. 2002, 114, 4264; Angew. Chem. Int. Ed. 2002, 41, 4090.
- [6] S. K. Chittimalla, H.-Y. Shiao, C.-C. Liao, Org. Biomol. Chem. 2006, 4, 2267.
- [7] Y.-Y. Chou, K. R. Peddinti, C.-C. Liao, Org. Lett. 2003, 5, 1637.
- [8] For an excellent review in this area, see: a) H. Kunz, K. Rück, *Angew. Chem.* **1993**, *105*, 355; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336, and references therein; see also: b) W. R. Roush, M. S. Van Nieuwenhze, *J. Am. Chem. Soc.* **1994**, *116*, 8536; c) P. P. Garner, P. B. Cox, S. J. Klippenstein, *J. Am. Chem. Soc.* **1995**, *117*, 4183; d) A. B. Charette, J.-F. Marcoux, *Synlett* **1995**, 1197; e) C. Chiappe, G. L. Moro, P. Munforte, *Tetrahedron: Asymme*

try 1997, 8, 2311; f) J.-I. Chika, H. Takei, Tetrahedron Lett. 1998, 39, 605; g) T. Yoshida, J.-I. Chika, H. Takei, Tetrahedron Lett.
1998, 39, 4305; h) P. E. Harrington, M. A. Tius, Org. Lett. 2000, 2, 2447; i) N. S. Trotter, D. S. Larsen, R. J. Stoodley, S. Brooker, Tetrahedron Lett. 2000, 41, 8957; j) D. S. Larsen, R. J. Lins, R. J. Stoodley, N. S. Trotter, J. Chem. Soc. Perkin Trans. 1 2001, 2204; k) M. A. Tius, Acc. Chem. Res. 2003, 36, 284; l) R. G. Pritchard, R. J. Stoodley, W.-H. Yuen, Org. Biomol. Chem. 2005, 3, 162; m) D. B. delos Santos, A. R. Banaag, M. A. Tius, Org. Lett. 2006, 8, 2579; n) A. R. Banaag, M. A. Tius, J. Am. Chem. Soc. 2007, 129, 5328.

- [9] Some 2,3,4,6-tetra-O-benzyl-D-hexopyranoses are commercially available. For the preparation of other 2,3,4,6-tetra-O-protected hexopyranosides, see: a) C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang, S.-C. Hung, *Nature* 2007, 446, 896; b) C.-C. Wang, S. S. Kulkarni, J.-C. Lee, S.-Y. Luo, S.-C. Hung, *Nat. Protocols* 2008, *3*, 97.
- [10] a) W. R. Roush, X.-F. Lin, J. Am. Chem. Soc. 1995, 117, 2236;
 b) J.-C. Lee, S.-W. Chang, C.-C. Liao, F.-C. Chi, C.-S. Chen, Y.-S. Wen, C.-C. Wang, S. S. Kulkarni, R. Puranik, Y.-H. Liu, S.-C. Hung, Chem. Eur. J. 2004, 10, 399.
- [11] CCDC 689698 (5) and 689699 (6) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [12] a) M. Y. Chu-Moyer, S. J. Danishefsky, G. K. Schulte, J. Am. Chem. Soc. 1994, 116, 11213; b) S.-C. Hung, C.-C. Liao, J. Chem. Soc. Chem. Commun. 1993, 1457.
- [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.