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Reversal of the regioselectivity in a cycloaddition of *o*-quinones by varying the position of alkoxy substituents

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Abstract

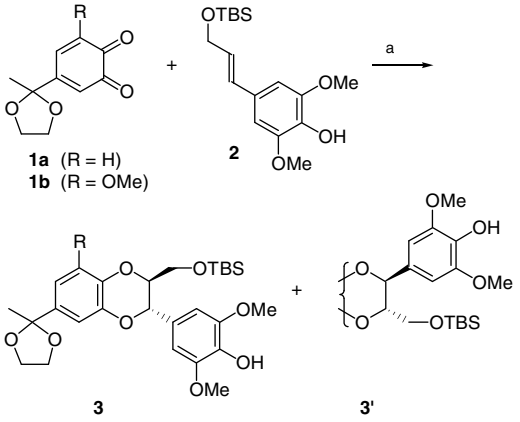
We have investigated the regioselective cycloaddition of *o*-quinones **1b–e** with the protected sinapyl alcohol **2**. It was found that the position of the alkoxy substituent on the *o*-quinone ring controlled the regioselectivity of the cycloaddition. In addition, our reported procedure for determining the location of the side chains on 1,4-benzodioxanes has been improved.

Keywords: *o*-Quinone; 1,4-Benzodioxane; Cycloaddition; Regioselectivity

Considerable interest has been shown in neolignans having 1,4-benzodioxane moiety in the structure due to their potent biological activities. We first synthesized 1,4-benzodioxane **3a** and its regioisomer **3′a** as a 2:1 mixture by a cycloaddition of *o*-quinone **1a** with the protected sinapyl alcohol **2**.[1] Subsequently, it was found that the reaction of **1b**, bearing a methoxy substituent at C-3, with **2** afforded **3b** as the sole product in a much better yield than that of **3a**[1] (Scheme 1).

We have now investigated the effect of alkoxy substituents attached to the *o*-quinone component upon the regioselectivity of the cycloaddition, using *o*-quinones **1b–e** as shown in Figure 1. In addition, a plausible mechanism for the cycloaddition is proposed to explain the results.

Preparation of *o*-quinone **1c** is shown in Scheme 2. Conversion of one acetyl group in the *para*-position of triacetate **4** into a PMB group afforded **5** in 77% yield. The remaining two acetyl groups of **5** were exchanged for benzyl groups to give **6** in 86% yield, which was transformed into **8** almost quantitatively via the Weinreb amide **7**. Simultaneous protection of the carbonyl moiety of **8** as a cyclic acetal and deprotection of the PMB group provided phenol **9** in 81% yield. Subsequent oxidation of **9** with IBX[2,3] gave **1c** in 56% yield.



Scheme 1. Reagents and conditions: (a) THF, rt [R = H: 3 h, 69% (**3a**/**3a′** 2:1), R = OMe: 83% (**3b** only)].

Synthesis of *o*-quinone **1d** commenced with TBS protection of commercially available 4-hydroxy-2-methoxybenzaldehyde (**10**) (Scheme 3). The protected **10** was treated with methyllithium and then subjected to TPAP-catalyzed

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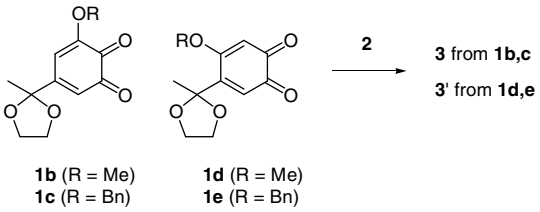
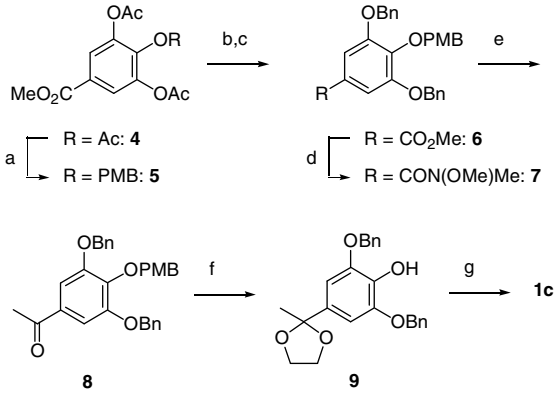
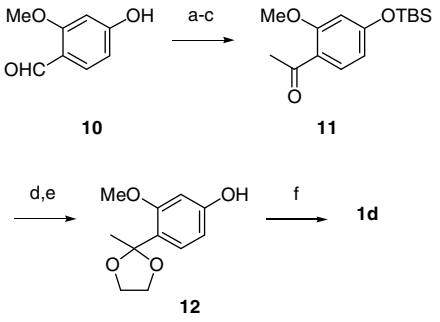


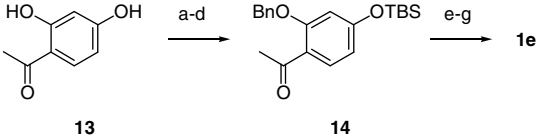
Fig. 1. Investigation of regioselectivity into the cycloaddition of **1b–e** with **2**.



Scheme 2. Reagents and conditions: (a) PMBCl, KI, K_2CO_3, acetone, 50 °C, 19 h (77%); (b) K_2CO_3, H_2O, MeOH, 50 °C, 0.5 h (quant.); (c) BnBr, K_2CO_3, TBAI, DMF, 50 °C, 0.5 h (86%); (d) MeHN(OMe)HCl, MeMgBr, THF, rt, 0.5 h (**7**: 50%, **8**: 49%); (e) MeMgBr, THF, 0 °C to rt, 0.5 h (99% from **7**); (f) ethylene glycol, PPTS, benzene, reflux, 1 h (81%); (g) IBX, DMSO, rt, 0.5 h (56%).



Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 0.5 h (94%); (b) MeLi, THF, −78 °C to rt, 1 h (85%); (c) TPAP, NMO, MS4A, CH_2Cl_2, rt, 0.5 h (88%); (d) ethylene glycol, *p*-TsOH, benzene, reflux, 3 h (90%); (e) TBAF, THF, rt, 0.5 h (79%); (f) IBX, DMSO, rt, 0.5 h (82%).

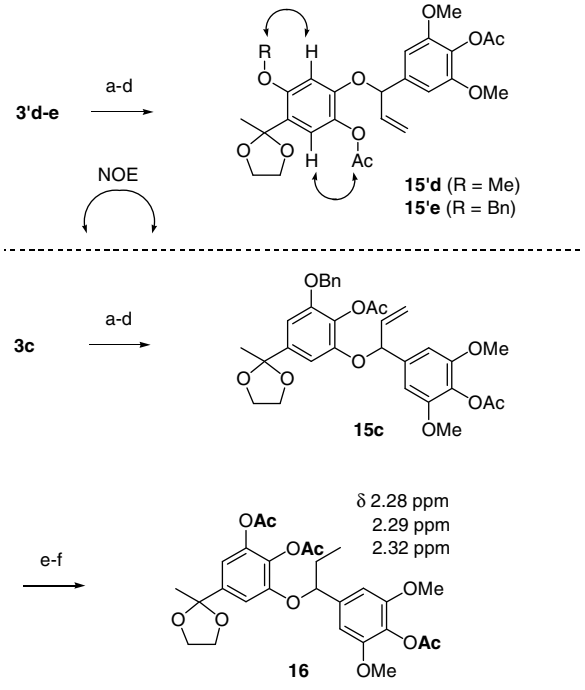


Scheme 4. Reagents and conditions: (a) MOMCl, K_2CO_3, acetone, 0 °C to rt, 0.5 h (94%); (b) BnBr, NaH, TBAI, DMF, 0 °C to rt, 1 h (95%); (c) AcCl, MeOH, 0 °C to rt, 0.5 h (95%); (d) TBSCl, imidazole, DMF, 0 °C to rt, 0.5 h (95%); (e) ethylene glycol, *p*-TsOH, benzene, reflux, 0.5 h (89%); (f) TBAF, THF, 0 °C to rt, 0.5 h (95%); (g) IBX, DMSO, rt, 0.5 h (95%).

oxidation to provide acetophenone **11** in 75% yield. Protection of the ketone moiety of **11** as a cyclic acetal and subsequent removal of the TBS ether group gave phenol **12** in 71% yield. Oxidation of **12** with IBX[2] afforded *o*-quinone **1d** in 82% yield.

o-Quinone **1e** was prepared from the commercially available 2′,4′-dihydroxyacetophenone (**13**) by a similar route as used for the synthesis of **1d** (Scheme 4). Regioselective protection of **13** with MOM and benzyl groups,[4] followed by the replacement of the MOM group by a TBS group, afforded **14** in 81% yield over four steps. A sequence involving the protection of the carbonyl moiety of **14** as a cyclic acetal, removal of the TBS group, and oxidation with IBX[3,4] provided **1e** in 80% yield over three steps.

The reactions of **1b–e** with **2** selectively afforded **3b**,[1] **3c**,[5] **3′d**,[6] and **3′e**,[7] respectively, the structures of which were determined through a modification of our previous procedure[1] (Scheme 5). Iodides derived from the cycloadducts were briefly treated with excess *n*-butyllithium. In situ acetylation of the two phenoxy groups that were liberated by ring cleavage and elimination of the methanesulfonyl group gave the corresponding diacetates **15c**, **15′d**,[8] and **15′e**[9] with good reproducibility. The substitution patterns of the benzene rings of **15′d**,**e** were determined by NOE experiments. However, the structure of **15c** could not be assigned on the basis of NOE experiments at this point. Therefore, it was transformed into triacetate **16**[10] through



Scheme 5. Reagents and conditions: (a) TBAF, THF, rt, 2 h; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min (**c**: 96%, **d**: 83%, **e**: 91% in 2 steps); (c) NaI, *i*-Pr_2NEt, DMF, 80 °C, 1 h (**c**: 66%, **d**: 75%, **e**: 64%); (d) *n*-BuLi, THF, −78 °C, 1 min, then Ac_2O, −78 °C, 15 min (**c**: 65%, **d**: 19%, **e**: 35%); (e) H_2, Pd/C, EtOAc, rt, overnight; (f) Ac_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 1.5 h (61% in 2 steps).

debenzylation and acetylation. The unsymmetrical structure of **16** proved the structure of **15c**.

The yields and ratios of **3** and **3′** obtained from the cycloaddition of *o*-quinones (**1b–e**) with **2** are summarized in Table 1. *o*-Quinones **1b** and **1c** predominantly gave **3b** and **3c**, respectively. In contrast, **1d** and **1e** provided **3′d** and **3′e**. The regioselectivity was thus reversed by changing the position of the alkoxy group on the *o*-quinone ring. The reactivity, yield, and regioselectivity were somewhat lower with the benzyl ethers (**1c**,**e**) than with the methyl ethers (**1b**,**d**). With **1c**,**e**, the addition of base (K_2CO_3) proved to be crucial for the progress of the reaction.

To explain these results, we propose a stepwise reaction mechanism for the cycloaddition, which includes a single-electron transfer (SET), as outlined below (Fig. 2). Deprotonation[11] of **2** and subsequent SET to **1** gives radical **C** as well as anion radicals **A** or **B**, each of which may be characterized by three major resonance forms (**A1–3**, **B1–3**). When R^1 is an alkoxy group and R^2 is hydrogen (**1b**,**c**), anion radical **A** is more stable than **B** due to the contribution of form **A3**, in which the alkoxy group stabilizes the adjacent carbon radical. Similarly, anion radical **B** is more stable than **A** when R^2 is an alkoxy group and R^1 is hydrogen (**1d**,**e**) due to the contribution of form **B2**. Radical coupling of **C** with either **A** or **B** gives an anionic intermediate **D** or **D′**, which undergoes conjugate addition to afford product **3** or **3′**, respectively. The intermediates, which include *para*-quinomethide structure, may lose an information of the geometry to give thermodynamically stable trans adducts preferentially. In the case of **1c** and **1e**, elimination of a benzyl radical from **A3** or **B2** may lead to the decomposition of the anion radical intermediates, which may lower the yield.

In summary, we have demonstrated regioselective cycloadditions of **1b–e** with the protected sinapyl alcohol **2**. The selectivity is controlled by the position of the alkoxy group on the *o*-quinone ring. Moreover, a plausible mechanism has been proposed, and the procedure for determining the structures of the resulting cycloadducts has been improved in the course of this work. Our current efforts are directed toward the regiocontrolled synthesis of natural products that have the 1,4-benzodioxane structures.

Table 1
Cycloadditions of *o*-quinones (**1b–e**) with **2**

o-quinone (**1**) + **2** —(additive, THF; r.t., time)→ **3**[a] + **3′**[a]

Entry	Quinone	Additive	Time (h)	Yield (%)	Ratio (**3**:**3′**)
1	**1b**[b]	None	3	83	1:0
2	**1c**[c]	K_2CO_3	10	57	5:1
3	**1d**	None	14	82	1:15
4	**1e**	K_2CO_3	14	59	1:8

[a] A trace amount of cis isomers was observed.
[b] See Ref. 1.
[c] The reaction was carried out at 50 °C.

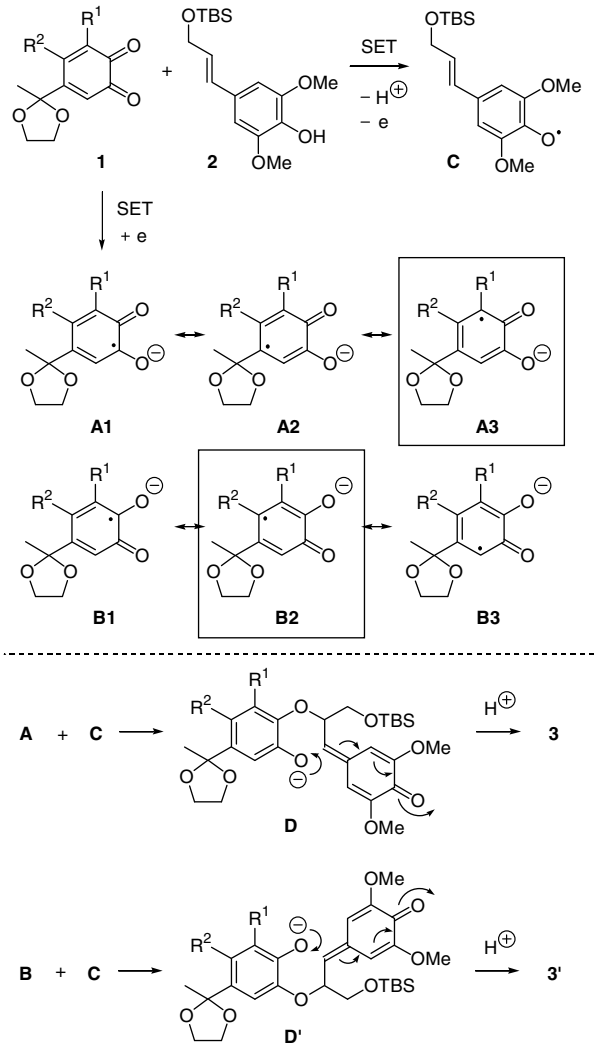


Fig. 2. A plausible mechanism for the cycloaddition of **1** with **2**.

Acknowledgment

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References and notes

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2. Magdziak, D.; Rodriguez, A. A.; Water, R. W. V. D.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285.
3. Ozanne, A.; Pouysegu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903.
4. Methylation instead of benzylation at this stage led to the C-alkylated product as the major product. Thus, we prepared **1c** from **10**, not **13**.
5. *Spectral data for* **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.63 (s, 3H), 3.58 (dd, $J = 2.4$, 11.7 Hz, 1H), 3.74–3.78 (m, 2H), 3.90 (s, 6H), 3.90–3.95 (m, 2H), 3.97–4.00 (m, 2H), 5.00 (d, $J = 7.8$ Hz, 1H), 5.11 (d, $J = 11.7$ Hz, 1H), 5.17 (d, $J = 11.7$ Hz, 1H), 5.61 (s, 1H), 6.71 (s, 2H), 6.72 (d, $J = 2.0$ Hz, 1H), 6.80 (d, $J = 2.0$ Hz, 1H), 7.30–7.40 (m, 3H), 7.46–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4, −5.0, 18.3, 25.7, 25.9, 27.5, 56.3, 62.2, 64.41, 64.43, 71.1, 76.2, 78.5, 104.1, 104.2, 107.3, 108.5, 127.6, 127.7, 128.3, 133.6, 134.8, 135.1, 136.9, 143.9, 146.9, 147.5.

6. *Spectral data for* **3′d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.77 (s, 3H), 3.55 (dd, $J = 2.4$, 11.2 Hz, 1H), 3.81 (s, 3H), 3.82–3.88 (m, 4H), 3.91 (s, 6H), 4.02–4.06 (m, 2H), 4.97 (d, $J = 7.8$ Hz, 1H), 5.58 (br s, 1H), 6.60 (s, 1H), 6.68 (s, 2H), 7.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4, −5.0, 18.3, 25.5, 25.9, 56.27, 56.31, 62.4, 64.58, 64.63, 76.1, 78.2, 101.6, 104.1, 108.1, 115.2, 123.8, 127.6, 134.9, 136.3, 143.4, 147.0, 151.2.
7. *Spectral data for* **3′e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.83 (s, 3H), 3.54 (dd, $J = 2.4$, 12.2 Hz, 1H), 3.70–3.91 (m, 4H), 3.88 (s, 6H), 4.04–4.09 (m, 2H), 4.95 (d, $J = 7.8$ Hz, 1H), 5.08 (s, 2H), 5.60 (s, 1H), 6.62 (s, 1H), 6.66 (s, 2H), 7.14 (s, 1H), 7.26–7.33 (m, 1H), 7.35–7.39 (m, 2H), 7.47–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3, −5.0, 18.4, 25.7, 25.9, 56.3, 62.4, 64.5, 64.6, 71.0, 76.8, 78.2, 103.4, 104.2, 108.2, 115.4, 124.6, 126.9, 127.4, 127.6, 128.4, 135.0, 136.7, 137.4, 143.3, 147.0, 150.1.
8. *Spectral data for* **15′d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.23 (s, 3H), 2.33 (s, 3H), 3.72 (s, 3H), 3.82 (s, 6H), 3.87–3.92 (m, 2H), 4.00–4.04 (m, 2H), 5.30 (d, $J = 10.4$ Hz, 1H), 5.30 (d, $J = 17.1$ Hz, 1H), 5.39 (d, $J = 6.0$ Hz, 1H), 6.05 (ddd, $J = 6.0$, 10.4, 17.1 Hz, 1H), 6.50 (s, 1H), 6.66 (s, 2H), 7.17 (s, 1H).
9. *Spectral data for* **15′e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (s, 3H), 2.23 (s, 3H), 2.31 (s, 3H), 3.80 (s, 6H), 3.83–3.86 (m, 2H), 4.01–4.05 (m, 2H), 5.01 (s, 2H), 5.22 (d, $J = 10.8$ Hz, 1H), 5.28 (d, $J = 16.8$ Hz, 1H), 5.33 (d, $J = 6.0$ Hz, 1H), 5.97 (ddd, $J = 6.0$, 10.8, 16.8 Hz, 1H), 6.49 (s, 1H), 6.60 (s, 2H), 7.19 (s, 1H), 7.28–7.38 (m, 5H).
10. *Spectral data for* **16**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, $J = 7.3$ Hz, 3H), 1.51 (s, 3H), 2.01–1.87 (m, 2H), 2.28 (s, 3H), 2.29 (s, 3H), 2.32 (s, 3H), 3.29–3.33 (m, 1H), 3.47–3.52 (m, 1H), 3.79 (s, 6H), 5.04 (dd, $J = 5.4$, 7.3 Hz, 1H), 6.57 (s, 2H), 6.74 (d, $J = 2.0$ Hz, 1H), 6.75 (d, $J = 2.0$ Hz, 1H).
11. We assume that the initial deprotonation plays an important role in the cycloaddition, because it was accelerated by addition of base in case of **1b** and **1d** and could not proceed under acidic conditions in all cases.