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Synthetic Study on Carthamin. 2. Stereoselective Approach to *C*-Glycosyl Quinochalcone via Desymmetrization

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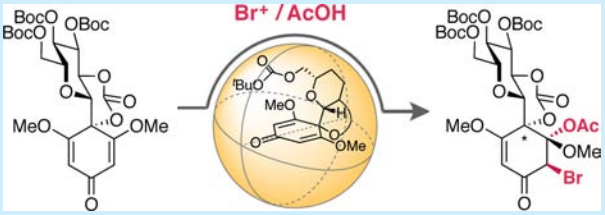
Supporting Information

ABSTRACT: Toward the total synthesis of carthamin, a stereoselective approach to the *C*-glycosyl quinochalcone intermediate is reported via the desymmetrization of a pseudo-C_s-symmetric *C*-glycosyl cyclohexadienone.



In our continued synthetic study on carthamin (**1**),[1] a red pigment of safflower petals, we recently reported an approach to *C*-glycosyl quinochalcone intermediate **B**[2] via oxidative dearomatization of aryl *C*-glycoside **A** (Figure 1).

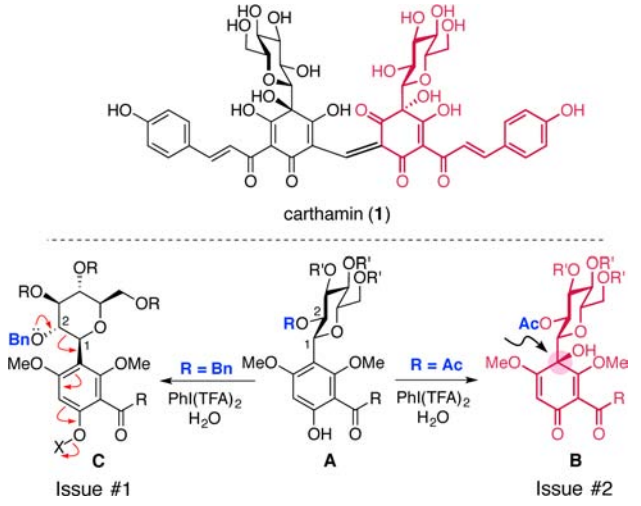


Figure 1. Oxidative dearomatization with poor stereocontrol.

Early attempts were hampered by a serious side reaction that cleaved the C_1−C_2 bond of the sugar moiety as shown in **C** (issue no. 1),[2] which was solved by using a 2-*O*-acyl group, enabling the projected transformation of **A** → **B**. However, another issue was the poor stereochemical control at the *tert*-alcohol center (issue no. 2).

At this juncture, we became interested in executing two missions (dearomatization and stereocontrol) in separate steps that inspired us to pursue the "symmetrization−desymmetrization" concept (Figure 2).[3] Retrosynthetic removal of the side-chain moiety in **D** suggests the precursor **E** has a pseudo-C_s symmetry, which would be available by the dearomatization of phloroglucinol derivative **F**. Conversely, in the synthetic direction, the first step **F** → **E** is a nonstereogenic process,

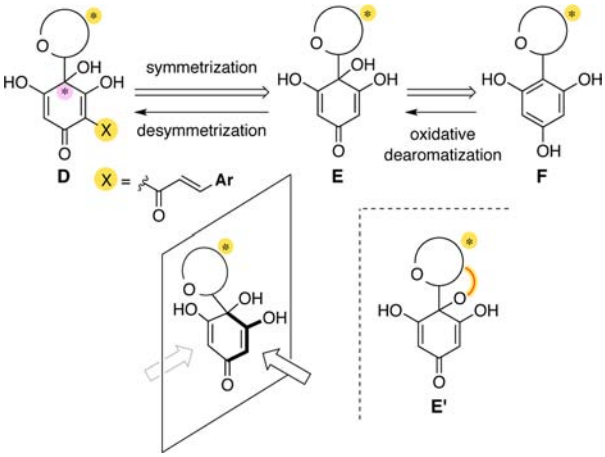


Figure 2. Symmetrization−desymmetrization approach.

while the second step **E** → **D** corresponds to a group-selective installation of the side chain or its surrogate X by discriminating two diastereotopic C═C bonds. Hoping for maximum reflection of chiral information on the sugar moiety onto the process, we planned to employ a tethered substrate **E′** in order to restrict the conformational freedom.

With this outline in mind, we chose *tert*-butoxycarbonyl (Boc) for protecting the sugar moiety because of the following expectations (Figure 3): (1) The 2-*O*-Boc group would suppress the undesired degradative reaction, allowing the oxidative dearomatization (vide supra);[4] (2) neighboring-group participation from the 2-*O*-Boc group would allow access to the required cyclic intermediate with pseudo-*Cs*-symmetry, amenable for the key group-selective functionalization (cf. **E′**); and (3) the Boc groups at other positions would allow the final global deprotection to be achieved under acidic conditions.[5]

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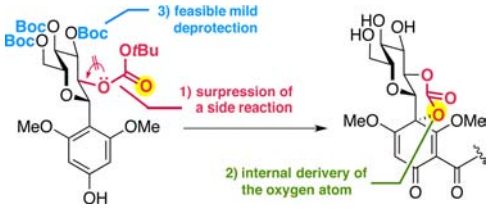
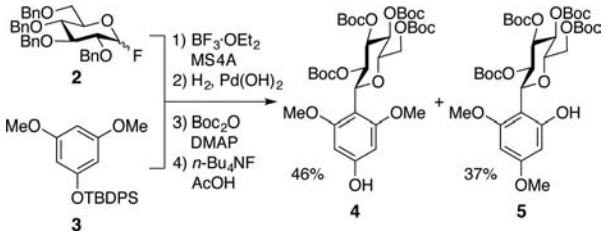


Figure 3. Three roles of Boc protecting groups.

In this paper, we report the realization of this scenario, achieving a stereoselective access to the *C*-glycosyl quinochalcone as an advanced synthetic intermediate in our projected total synthesis of **1**.

Scheme 1 shows the preparation of phenol **4** as a model substrate to test this possibility. The Friedel–Crafts reaction of

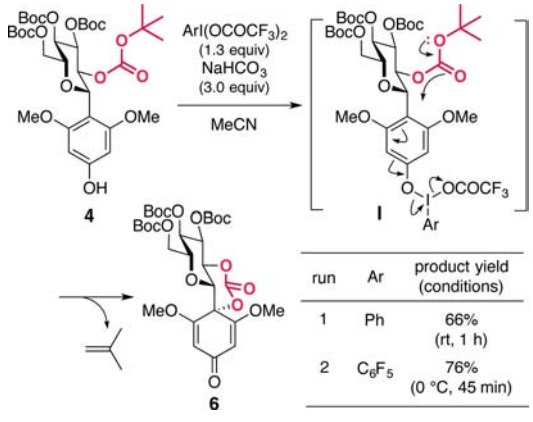
Scheme 1. Preparation of *C*-Glycosides 4 and 5



glycosyl fluoride **2**[6] and silyl ether **3**[2] ($BF_3{\cdot}OEt_2$, MS4A, CH_2Cl_2, −78 → 0 °C) gave the *β*-*C*-glycoside as a mixture of regioisomers.[7] The benzyl protecting groups were replaced by Boc groups (H_2, 5% $Pd(OH)_2$/C on carbon;[8] rt, 24 h; Boc_2O, DMAP, rt, overnight) and the silyl protection was removed (*n*-Bu_4NF, AcOH, 0 °C, 15 min), affording the desired *p*-*C*-glycoside **4** in 46% yield and its *ortho* counterpart **5** in 37% yield.[9]

Oxidative dearomatization of *C*-glycosyl phenol **4** was examined using hypervalent iodine reagents (Scheme 2). The

Scheme 2. Oxidative Dearomatization of 4

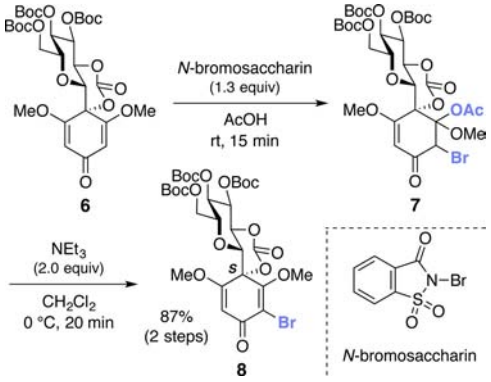


initial attempt was made by treating phenol **4** with $PhI(OCOCF_3)_2$ in the presence of powdered $NaHCO_3$, giving cyclic carbonate **6** in 66% yield. As shown by **I**, the outcome could be rationalized by the neighboring-group participation and concomitant loss of 1 mol of isobutene.

By employing a stronger oxidant, $C_6F_5I(OCOCF_3)_2$,[10] the conversion was even more facile in a shorter reaction time at 0 °C, giving an improved yield of **6** ready for testing the key desymmetrization. Initial attempts at the monohalogenation of **6** with various reagents (I_2, NIS, $IOCOCF_3$,[11] *N*-iodosaccharin and NBS)[12] all resulted in failure due to the poor reactivity of **6**.

After considerable experimentation, a breakthrough was eventually achieved by bromoacetoxylation (Scheme 3). By

Scheme 3. Stereocontrol by Desymmetrization of Cyclic Carbonate 6



treating **6** with *N*-bromosaccharin,[13] bromoacetate **7** was obtained as a single diastereomer (vide infra). Since adduct **7** was fairly unstable to silica gel chromatography, it was immediately treated with Et_3N to induce elimination, leading to bromide **8** as a single diastereomer in 87% yield over two steps.[14]

The ^1H and ^{13}C NMR of bromide **8** showed only a single set of peaks, suggesting it to be a single, diastereomerically pure product, which later proved to be the case. At this stage, however, we suspected the possibility of accidental overlap of the NMR peaks with the other diastereomer that would result from the opposite group selection. To gain conclusive evidence for the structural and stereochemical identity, we sought a comparison sample, which fortunately became available by simply reversing the two processes, i.e., bromination followed by oxidative dearomatization (Figure 4).

Treatment of *C*-glycosyl phenol **4** with NBS gave monobromide **9** in 86% yield, which was treated with $PhI(OCOCF_3)_2$, giving a readily separable mixture of *C*-glycosides **8** and **10** (R_f = 0.61 and 0.38, hexane/EtOAc = 6/4).

The respective stereochemistry of **8** and **10** was assigned by observing the diagnostic NOE correlations,[9] which allowed (*S*)-

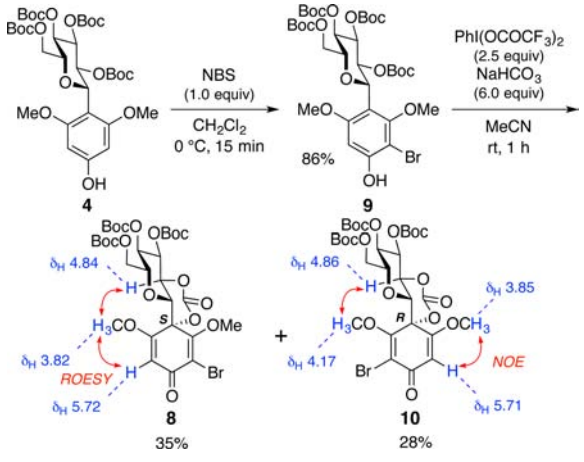


Figure 4. Nonselective oxidative dearomatization of **9**.

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stereochemistry to be determined for the quaternary center in **8** and (*R*)-stereochemistry for the counterpart **10**.[14] Pleasingly, the product **8** proved to be the desired stereoisomer, which could be employed for further synthetic scheme for introducing the side-chain moiety.

Concerning the mechanism of the successful group-selective reaction (**6** → **7**), a further hint was obtained from the single crystal X-ray diffraction analysis of the colorless needles that were obtained after recrystallization of acetoxy bromide **7** from Et_2O/pentane (Figure 5).[15] Importantly, it was proven that the

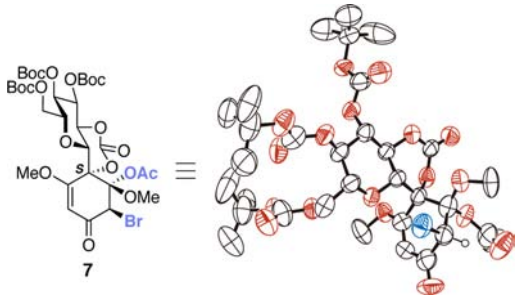


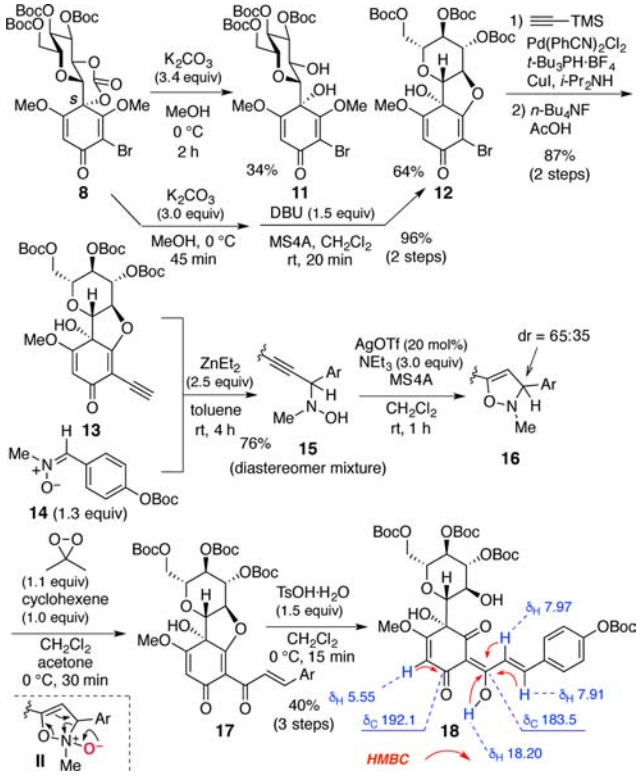
Figure 5. X-ray structure of acetoxy bromide **7**.

bromoacetoxylation reaction proceeded in a *trans*-manner and that the acetoxy group was positioned *cis* to the cyclic carbonate, suggesting the origin of the regio- and stereoselectivity of the reaction.

Figure 6 shows a schematic representation to explain the mechanism of the group selection. This "quadrant model" places the dienone substrate on a plane, and **A** is used to define the steric environment of each quadrant. Inspection of a molecular model suggested that the second quadrant is sterically hindered by the overhanging sugar moiety and that hindrance is much less serious at the first quadrant. Likewise, the third and fourth quadrants beneath the plane are easily accessible. If one compares the relative accessibility to the Br^+ ion, the second quadrant is highly inaccessible as in **C** due to the steric hindrance described above. Given the reversible formation of the bromonium species, the reaction course would be decided by the ease of the subsequent nucleophilic attack. If so, bromonium ion **D**, although easily formed, is not productive because the nucleophilic attack is sterically blocked. As for the seemingly unimpeded access to Br^+ by the fourth quadrant to generate bromonium ion **E**, the subsequent attack is also disfavored, as the trajectory is blocked by the sugar moiety. Note that the acetate attack occurs from the position near the sugar moiety (see, **7**). Finally, bromonium **B**, although less populated, has no problem undergoing the second attack, explaining the exclusive formation of acetoxy bromide **7**.

This was a highly favorable result, as the *tert*-alcohol center in **8** was *S*; if the bromine atom could be replaced by the side-chain moiety, a viable way would be opened to the stereodefined *C*-glycosyl quinochalcone with the natural stereochemistry. Along these lines, we focused attention on installation of the side-chain moiety by exploiting the bromo group. Methanolysis of the cyclic carbonate in **8** gave diol **11** in 34% yield (Scheme 4), and in addition, ether **12** (64% yield)

Scheme 4. Side-Chain Elongation



resulted from an internal conjugate addition−elimination process. Although unexpected, we surmised that ether **12** might be a favorable substrate for the following elaborations in view of the diminished steric demand around the bromine atom. Pleasingly, ether **12** became selectively available in 96% yield by treating the mixture of **11**/**12** with DBU and 4A

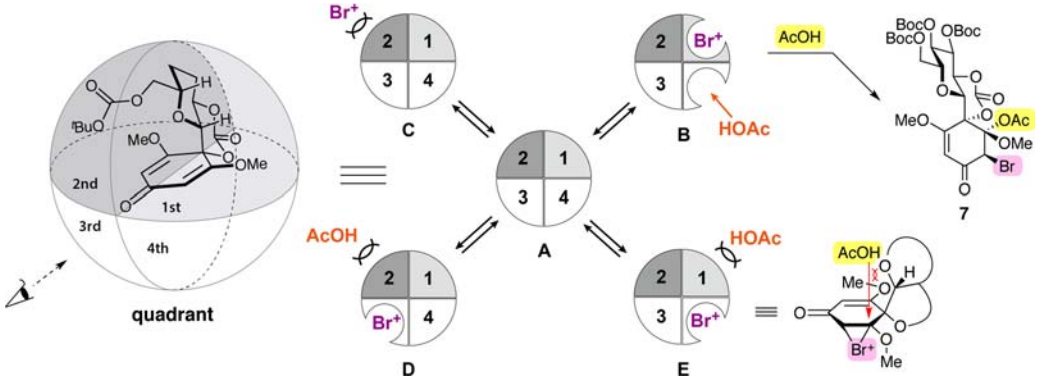


Figure 6. Quadrant model to rationalize group-selective bromoacetoxylation.

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molecular sieves. Several trials for the transformation of the bromo substituent in **12** caused the rearomatization of the quinol core. However, Sonogashira coupling of bromide **12** and TMS-acetylene [$Pd(PhCN)_2Cl_2$ (10 mol %), *t*-$Bu_3PH{\cdot}BF_4$ (23 mol %), CuI (15 mol %), *i*-Pr_2NH, MeCN, rt, 24 h][16] followed by desilylation gave terminal alkyne **13** in 87% yield. Treatment of alkyne **13** and nitrone **14** with $ZnEt_2$ gave hydroxyamine **15** in 76% yield.[17] Construction of the chalcone moiety was carried out by a three-step procedure starting with the cyclization of hydroxyamine **15** into isoxazoline **16**.[18] In order to trigger a cheletropic reaction as shown in **II**, the *N*-oxide was formed from the isoxazoline **16**.[19] However, our initial attempt using *m*-CPBA[19a,b] gave only a low yield of **17** and many side products. A survey of various oxidants showed that dimethyldioxirane (DMDO)[20] was effective: Dropwise addition of DMDO in acetone to a CH_2Cl_2 solution of isoxazoline **16** in the presence of cyclohexene over 20 min at 0 °C led to chalcone **17** in high yield.

Treatment of **17** with TsOH opened the tetrahydrofuran ring to give the desired triketone **18** in 40% yield over three steps. The structure of **18** was assigned by NMR, IR, and HRMS analyses. The COSY, HSQC, and HMBC data supported its framework. Careful analysis of the HMBC data ($CDCl_3$) allowed us to identify the major keto−enol tautomer **18**.[9]

In conclusion, we have developed a stereoselective approach to stereodefined quinochalcone **18**, which is a promising intermediate for the total synthesis of **1**. Further studies are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03899.

Full experimental procedure, characterization data, and NMR spectra for all new compounds (PDF)

X-ray crystallographic data for **7** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Teruaki Mukaiyama on occasion of his 90th birthday.

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(12) Details for reaction conditions: I_2 (1.3 equiv), CCl_4−pyridine (1/1), 80 °C, 1 h; NIS (6.6 equiv), MeCN, reflux, 2.5 h; I_2 (0.7 equiv), $PhI(OCOCF_3)_2$, (0.7 equiv), pyridine (1.3 equiv), BHT (0.1 equiv), CH_2Cl_2, reflux, 3 h; *N*-iodosaccharin (1.2 equiv), CH_2Cl_2, reflux, 2 h; NBS (1.3 equiv), CH_2Cl_2, reflux, 1.5 h.

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(14) With diastereomer **10** as a comparison sample in hand, essentially perfect selectivity (>100:1) at the bromoacetoxylation was reconfirmed.

(15) Crystallographic data for **7** have been deposited with the accession number CCDC 1519481 and can be obtained free of charge via www.ccdc.cam.ac.uk/structures.

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