# Diastereoselective Construction of New 5a-Substituted Carbaallose by *exo*-β-Selective Conjugate Addition to *endo-exo* Cross-Conjugated Cyclohexadienone as Key Reaction

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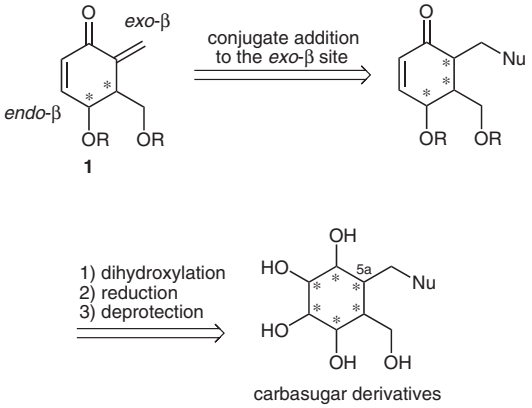
**Abstract:** Practical synthesis of a new chiral *endo-exo* cross-conjugated cyclohexadienone was achieved, and its synthetic utility was illustrated by highly *exo*-β-selective conjugate addition with various nucleophiles. Further diastereoselective transformation of the adduct to an unprecedented 5a-substituted carbaallose is also described.

**Key words:** rearrangement of endoperoxide, cross-conjugated dienone, regioselective conjugate addition, stereoselective synthesis, carbasugar

There are a number of fascinating synthetic targets with a six-membered carbocyclic skeleton with various functional groups on the stereogenic ring-carbon atoms.[1] Among them are 5a-carbapyranoses,[2] which named after their structural similarity to the parent monosaccharides: the original pyranose ring-oxygen atom is replaced by carbon atom. So far, a large range of 5a-carbapyranoses, which are typically 5a-methylene variants, have been either isolated from natural sources or synthesized to unveil their unique biological functions.[2] It is interesting to note that human cannot distinguish between a pyranose and its 5a-methylene analogue as exemplified by the fact that 5a-carba-α-D-glucopyranose is felt sweet like α-D-glucopyranose.[3] These structural and biologic aspects have motivated us for further modification of the carbapyranoses. In particular, we envisioned that the carbasugars could enjoy any extra property by the introduction of a substituent to the 5a-carbon center, keeping the biological roles of their parent saccharides intact. To the best of our knowledge, however, such chiral carbapyranoses with an asymmetric 5a-carbon center have been scarcely scrutinized.[4] Thus, the development of a versatile stereoselective method for the synthesis of 5a-substituted carbapyranoses should be significant to accelerate the research on the functional sugar mimics. We assigned the *endo-exo* cross-conjugated cyclohexadienone[5] **1** to be a potential synthetic building block, because the regioselective conjugate addition to the *exo*-β carbon atom provides a cyclohex-2-enone framework for further stereoselective functionalizations to access carbapyranoses with a variety of substituents at 5a-position (Scheme 1). In this paper, we disclose the diastereoselective construction of **1** (R = Bz) and its transformation into an unprecedented 5a-substituted carbaallose.[6]




**Scheme 1** Chiral *endo-exo* cross-conjugated cyclohexadienone **1** as a useful synthetic building block for 5a-substituted carbapyranoses (*: stereogenic center)

The requisite **1** was synthesized as shown in Scheme 2. The photooxygenation of **2**[7] in the presence of tetraphenylporphyrin (TPP) as a sensitizer afforded endoperoxide **3** in 45% yield. The relative stereochemistry of **3** was undoubtedly determined by X-ray crystallographic analysis (Figure 1).[8] Upon treatment with an excess amount of triethylamine, the endoperoxide **3** underwent Kornblum–DeLaMare rearrangement[9] to the 4-hydroxycyclohex-2-enone derivative **4**, which was found to be susceptible to a β-elimination of the benzoyl group under the applied basic conditions to give the *endo-exo* cross-conjugated cyclohexadienone **5** in excellent yield. The subsequent one-pot treatment of **5** with benzoyl chloride, triethylamine, and DMAP gave **1** in 94% yield for the three steps from **3**.

We next examined the conjugate addition to **1**. With a higher-order cuprate[10] prepared from phenyllithium and cuprous cyanide, the conjugate addition proceeded in excellent chemo- and regioselective manners to give the desired *exo*-β adduct **6a** as a single diastereomer in high chemical yield (Table 1, entry 1). The relative configuration of **6a** was determined to be 1*R**,2*S**,6*S** by X-ray crystallography of a derivative (vide infra, Figure 3). The diastereoselectivity in the protonation to a dienolate intermediate primarily generated upon the conjugate addition could be explained by the transition-state model either **A**

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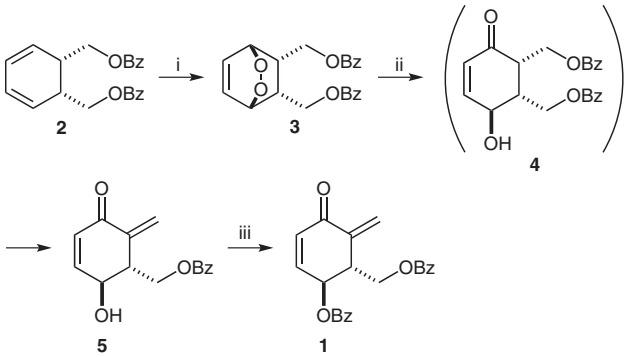
or **B** depicted in Figure 2. In the model **A**, the dienolate locates the substituents on the two stereogenic ring-carbon centers in an *anti*-periplanar conformation so that the protonation should occur at a quasi-equatorial site to avoid a 1,3-repulsive interaction with the benzoyl group. Alternatively, the model **B** with a gauche conformation for the two relevant substituents should account for the protonation at a quasi-axial site from a stereoelectronic effect.[11] The conformation of the dienolate is thermodynamically more stable in **A** than in **B**, whereas the axial attack by a proton source as in **B** is kinetically preferable to the equatorial attack as in **A**. Other higher-order cuprates were also examined and those with aromatic ligands such as 2-methoxyphenyl, 1-naphthyl, and 2-naphthyl exhibited similarly excellent regio- and diastereoselectivities (entries 2–4). Butyl group was also transferred to the *exo*-methylene in good yield, though a very small amount of unidentified byproduct[12] accompanied in this case (entry 5). It should be noted that the undesired *endo*-β adduct was not detected in each reaction. That would be partly because the oncoming nucleophile feels higher steric hindrance at the *endo*-β than at the *exo*-β site. Not only higher-order cuprates but also a stabilized carbanion derived from dimethyl malonate underwent highly regioselective Michael addition at the *exo*-β position of **1** followed by the diastereoselective protonation event to afford **7** (Scheme 3, left). Corey–Chaykovsky cyclopropanation[13] was also effected with an *exo*-β-selective manner to provide **8** (Scheme 3, right).




**Scheme 2** Synthesis of the *endo-exo* cross-conjugated cyclohexadienone **1**. *Reagents and conditions*: i) $O_2$ (air), TPP, hν (110 V, 150 W, halogen lamp), $CH_2Cl_2$, r.t., 5.5 h; 45%, ii) $Et_3N$, $CH_2Cl_2$, r.t., 19 h; iii) BzCl, $Et_3N$, DMAP, $CH_2Cl_2$, r.t., 1.5 h, 94% (2 steps).

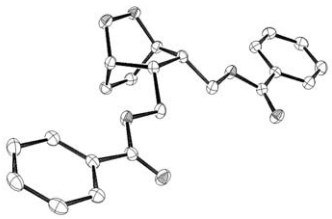
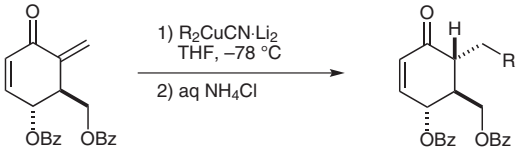


**Figure 1** An ORTEP diagram for the X-ray structure of **3**. Hydrogen atoms are omitted for clarity.

**Table 1** *exo*-β-Selective Conjugate Addition to **1** with Higher-Order Cuprates[a]




| Entry | Cuprate (*R*) | Time (min) | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph | 15 | **6a**[c] | 91 |
| 2 | 2-$MeOC_6H_4$ | 20 | **6b**[c] | 74 |
| 3 | 1-$C_{10}H_7$ | 20 | **6c**[c] | 62 |
| 4 | 2-$C_{10}H_7$ | 20 | **6d**[c] | 80 |
| 5 | *n*-Bu | 15 | **6e**[d] | 77 |

[a] Reaction was carried out with a 1:1 molar ratio of **1** and $R_2CuCN{\cdot}Li_2$.
[b] Isolated yield.
[c] Diastereomeric byproduct was not detected by $^1H$ NMR analysis.
[d] Accompanied by a small amount (<5%) of unidentified byproduct with a similar pattern of $^1H$ NMR spectrum to that of **6e**.

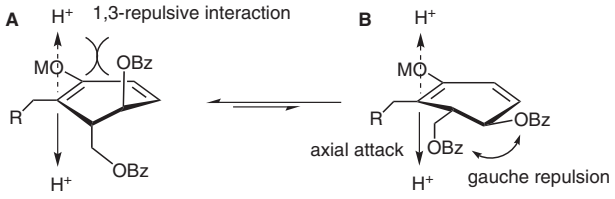
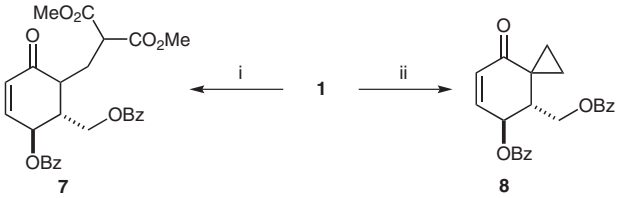


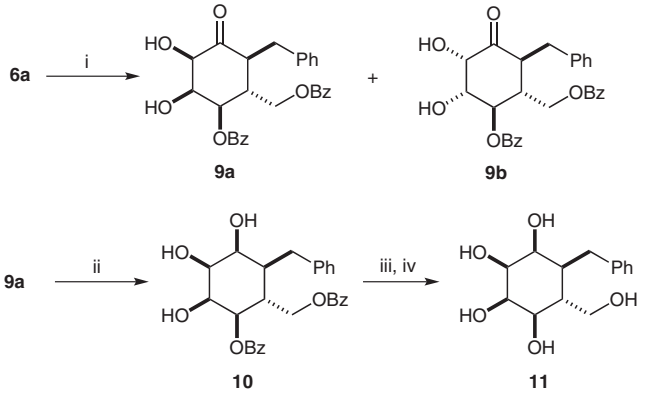

**Figure 2** Transition-state models **A** and **B** accounting for the observed diastereoselectivity in the protonation of a dienolate intermediate generated upon the conjugate addition to **1**.




**Scheme 3** Michael addition and Corey–Chaykovsky cyclopropanation. *Reagents and conditions*: i) dimethyl malonate, NaH, THF, –78 °C, 3 h, 67%; ii) trimethylsulfonium iodide, NaH, THF–DMSO, r.t., 4.5 h, 48%.

Eventually, the synthesis of a new 5a-substituted carbaallose was achieved from **6a** (Scheme 4). Thus, osmium-catalyzed dihydroxylation of **6a** afforded a 3.5:1 diastereomeric mixture of **9a** and **9b**. After separation of these diastereomers by column chromatography on silica gel, the major isomer **9a** was subjected to the carbonyl reduction with $NaBH_4$ to give the triol **10** quantitatively as a sole diastereomer. A single crystal of **10** was subjected to X-ray crystallography[14] and its relative stereochemistry was unambiguously determined to be 1*R**,2*R**,3*S**,4*S**,5*S**,6*S** (Figure 3). This also established the stereochemical out-

come in the conjugate addition–protonation sequence on the cross-conjugated dienone **1** (Figure 2). Methanolysis of the benzoyl groups of **10** with sodium methoxide in methanol followed by neutralization with an acidic resin afforded a 5a-carba-α-allopyranose **11** in quantitative yield.




**Scheme 4** Synthesis of a 5a-carba-α-allopyranose **11** from **6a**. *Reagents and conditions*: i) $K_2OsO_4{\cdot}2H_2O$, NMO, DABCO, acetone–$H_2O$, r.t., 3 h, 96%, **9a/9b** (3.5:1); ii) $NaBH_4$, MeOH, –78 °C, 1 h, 81%; iii) NaOMe, MeOH, r.t., 2 h; iv) Dowex HCR W-2, 99% (2 steps).

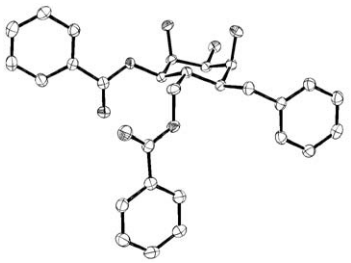


**Figure 3** An ORTEP diagram for the X-ray structure of **10**. Hydrogen atoms and solvate molecule are omitted for clarity.

In summary, we were able to construct a novel *endo-exo* cross-conjugated cyclohexadienone **1**, which was demonstrated to undergo regioselective conjugate addition at the *exo*-β position with various nucleophiles followed by highly diastereoselective protonation of a dienolate intermediate. Furthermore, one of the adducts, **6a**, was successfully converted to the unprecedented carbaallose derivative **11** with a chiral 5a-carbon center, which will be subjected to screenings for the assessment of its biological activities. Asymmetric synthesis of the optically active *endo-exo* cross-conjugated cyclohexadienones[15] and their further synthetic applications are also currently under way in our laboratory.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) In a preliminary experiment, the enantioenriched dienone **5** (90% ee) was obtained by asymmetric Kornblum DeLaMare rearrangement of **3** under Toste's conditions.[16] For details, see the Supporting Information.
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