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CONSTRUCTION OF ALL-CARBON QUATERNARY STEREOCENTERS BY ZINC-MEDIATED BARBIER-TYPE ALLYLATION IN AQUEOUS MEDIA

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Abstract – Stereoselective construction of an all-carbon quaternary stereocenter by Barbier-type allylation in aqueous media is described. Sugar-derived aldehydes, 2,3-*O*-isopropylidene-D-glyceraldehyde and 2,4-*O*-benzylidene-D-threose, were reacted with geranyl chloride in the presence of zinc powder to provide γ-adducts bearing quaternary stereocenters with good stereoselectivity.

Quaternary stereocenters are found in a wide range of complex natural products and pharmaceuticals. For example, (+)-hyperforin (**1**),[1] (+)-perforatumone (**2**),[2] and (+)-vibsanin A (**3**)[3] share a structural motif with a common all-carbon quaternary stereogenic center (Figure 1). In developing a method for the synthesis of these natural products, we were faced with the challenge of developing a practical method to synthesize the quaternary stereocenter. The construction of quaternary stereocenters remains a difficult problem in organic synthesis.[4] One approach to this challenge is the use of 3,3'-disubstituted allylmetal reagents. Although extensive research has been carried out developing stereoselective carbonyl allylation reactions,[5] the synthesis of organic compounds containing quaternary stereocenters through the addition of allylmetals to aldehydes is still a challenge.[6] The majority of nucleophilic addition reactions using organometallic reagents involve lithium and magnesium. These reactions require the strict exclusion of moisture. Some classes of the Barbier-type allylation, however, do not require rigorously anhydrous reaction conditions and can be performed effectively in aqueous media.[7] Zinc is the most popular metal for this type of reaction because it is easy to handle and stable in air. Herein, we describe the construction of an all-carbon quaternary stereocenter using a diastereoselective zinc-mediated Barbier-type allylation of chiral aldehydes in aqueous media.

This paper is dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday.

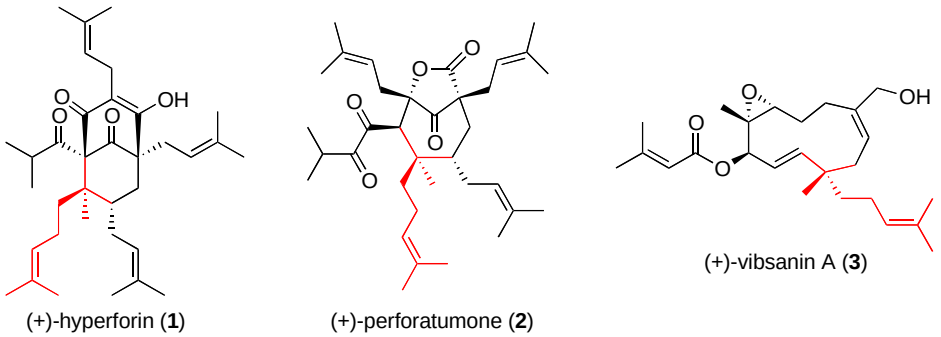
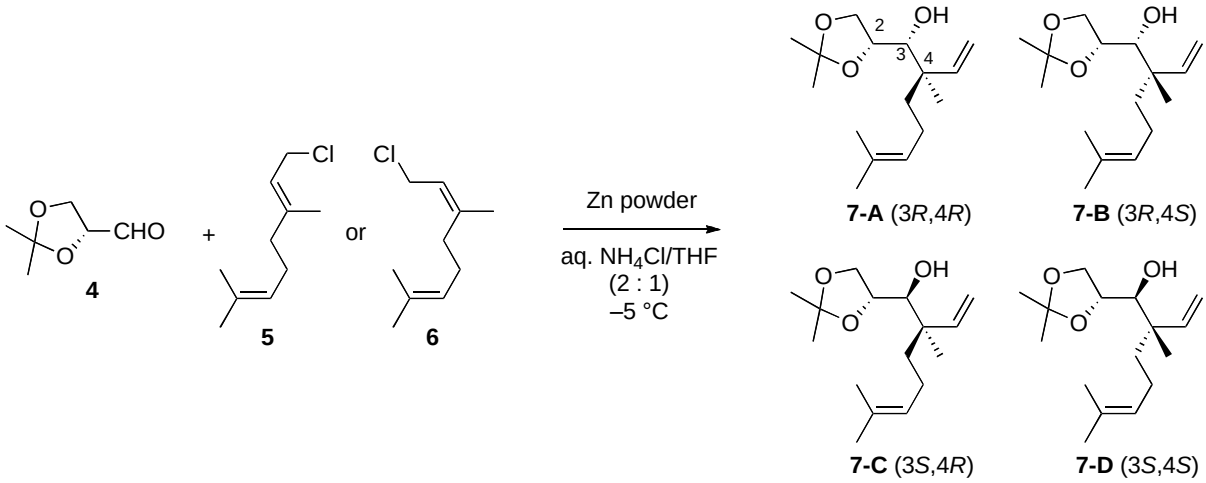


Figure 1. Structures of (+)-hyperforin, (+)-perforatumone, and (+)-vibsanin A

To achieve the desired Barbier-type allylation, the reaction was investigated using easily available sugar derivatives as chiral aldehydes.[8] We observed that 2,3-*O*-isopropylidene-D-glyceraldehyde (**4**)[9] stereoselectively reacted with geranyl chloride (**5**)[10] in the presence of zinc powder in a mixture of aqueous NH_4Cl–THF[11] at –5 °C (Table 1). The reaction produced γ-adducts with complete regioselectivity which were separated into 3*R*-isomers **7-A**/**7-B** (4*R*/4*S* = 1:4) and 3*S*-isomers **7-C**/**7-D** (4*R*/4*S* = 5:1) by column chromatography in yields of 6% and 77%, respectively (entry 1).[12] When using **5**, (3*S*,4*R*)-isomer **7-C** was the major product. By using neryl chloride (**6**)[13] in place of **5** as the allyl halide, (3*S*,4*S*)-isomer **7-D** with the opposite configuration of the quaternary stereocenter (4-position) was preferentially obtained, but a decrease in stereoselectivity was observed (entry 2).

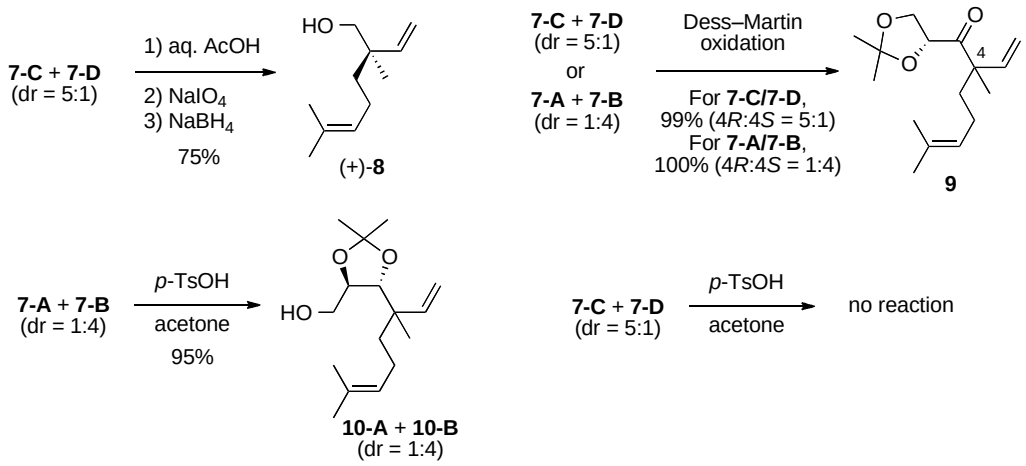
Table 1. Barbier-type allylation of aldehyde **4**



Entry	Allyl Halide	A + B		C + D	
		Yield	**A/B**[a]	Yield	**C/D**[a]
1	**5**	6%	1:4	77%	5:1
2	**6**	4%	2:1	68%	1:2

[a] Ratio was determined by ^{1}H NMR analysis.

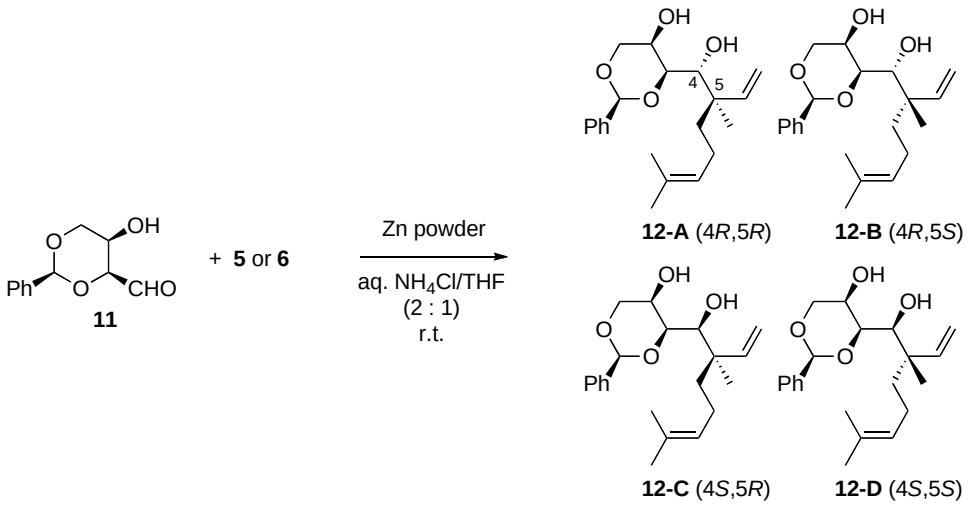
The stereochemistry of the newly formed contiguous stereocenters in adducts **7** was determined by chemical transformation as shown in Scheme 1. The major isomers **7-C**/**7-D** (dr = 5:1) were hydrolyzed to triols, which were subjected to oxidative cleavage followed by reduction of the resultant aldehyde to afford the enantioenriched alcohol (+)-**8**. By comparing the optical rotation of (+)-**8** with that of the known (–)-**8**,[14] whose absolute stereochemistry had been determined {$[\alpha]_D^{23}$ +13.2 (*c* 1.04, $CHCl_3$) for synthetic (+)-**8**; lit.[14] $[\alpha]_D$ –16.9 (*c* 1.23, $CHCl_3$) for authentic (–)-**8**}, the configuration of the quaternary stereocenter in **7-C** was assigned as (*R*). The oxidation of **7-C**/**7-D** provided ketone **9** as a (4*R*):(4*S*) = 5:1 mixture, while **7-A**/**7-B** (dr = 1:4) provided a (4*R*):(4*S*) = 1:4 mixture of **9**. Therefore, all the configurations at the 4-position in adducts **7A-D** were unambiguously assigned. To determine the configurations at the 3-position, **7-A**/**7-B** and **7-C**/**7-D** were treated with acid. The migration of the isopropylidene group occurred in only **7-A**/**7-B**, affording *trans*-dioxolane **10-A**/**10-B**. These results indicate that **7-A**/**7-B** are 2,3-*syn* isomers and **7-C**/**7-D** are 2,3-*anti* isomers.[15]



Scheme 1. Determination of the stereochemistry at C3 and C4 in **7**

To expand the scope of this reaction, we explored the use of other sugar-derived aldehydes. The use of 2,4-*O*-benzylidene-D-threose (**11**), prepared from D-galactose in a two-step reaction,[16] was found to be effective in generating the quaternary stereocenter with (*S*)-configuration (Table 2).[17] Although the reaction temperature was increased from –5 °C to room temperature in order to complete the reaction, the Barbier reaction of **11** with **5** resulted in good stereoselectivity, similar to that observed in the reaction of **4.** (4*R*,5*S*)-Isomer **12-B** was preferentially obtained along with (4*R*,5*R*)-isomer **12-A** (**12-A**/**12-B** = 1:5) in 68% yield (entry 1).[18] When the reaction was conducted using **6**, (4*R*,5*R*)-isomer **12-A** was obtained as the major isomer in slightly lower yield and stereoselectivity (entry 2).

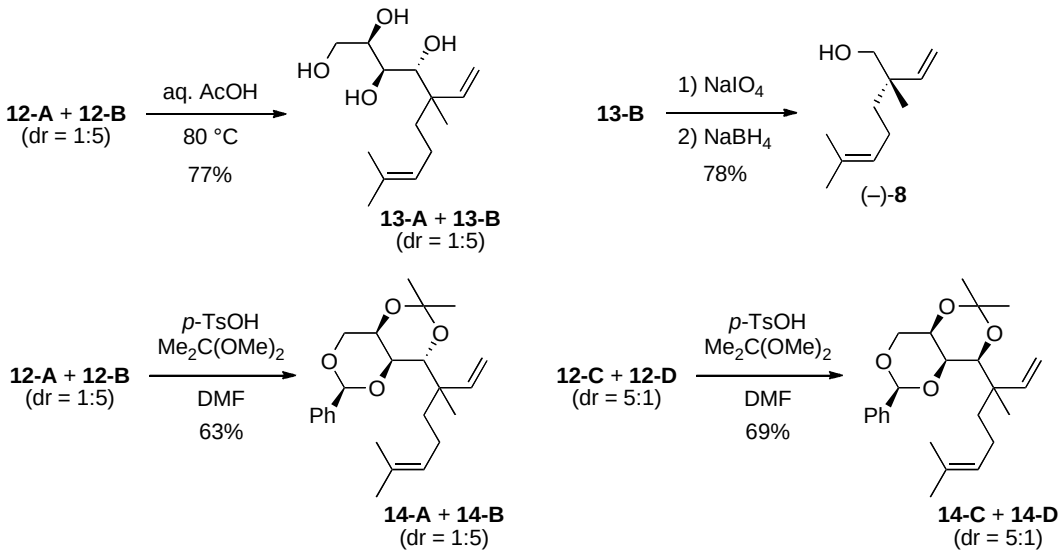
Table 2. Barbier-type allylation of aldehyde **11**



Entry	Allyl Halide	A + B		C + D	
		Yield	**A/B**[a]	Yield	**C/D**[a]
1	**5**	68%	1:5	4%	5:1
2	**6**	51%	4:1	4%	2:1

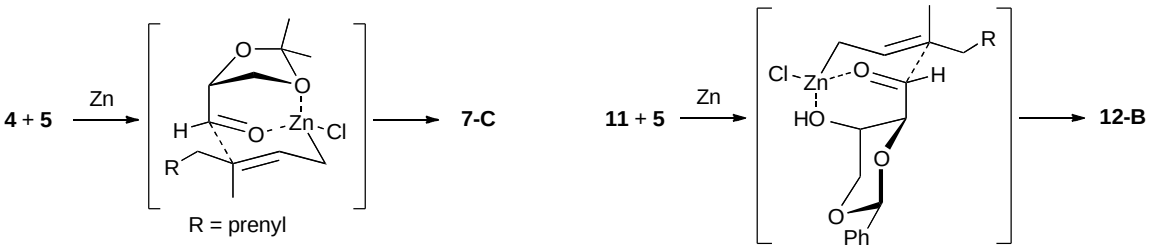
[a] Ratio was determined by ^{1}H NMR analysis.

Repeating a similar transformation to that of Scheme 1, the stereochemistry of the quaternary stereocenters in adducts **12** was assigned (Scheme 2). The hydrolyzed products, **13-A/13-B**, prepared from **12-A/12-B** (dr = 1:5) were recrystallized to provide the almost diastereomerically pure form of **13-B**, which was then converted into highly enantioenriched (–)-**8**.[19] The stereochemistry of the 4-position in **12** was determined by NOE experiments of the isopropylidene derivatives **14-A/14-B** and **14-C/14-D**.



Scheme 2. Determination of the stereochemistry at C4 and C5 in **12**

The stereochemical outcomes obtained in the reaction of **4** or **11** can be explained using the transition states depicted in Scheme 3. Through a combined experimental and theoretical mechanistic investigation, the zinc-mediated Barbier-type allylations in aqueous media were estimated to proceed through a six-membered chair-like transition state.[20] In addition, organozinc reagents have a tendency to form a chelate complex involving the carbonyl and the β-alkoxy group.[21] Therefore, the reaction of **4** or **11** with **5** preferentially produces **7-C** or **12-B** in accordance with the β-chelation/six-membered model. The lower stereoselectivity observed in the case of **6** may be caused by the steric repulsion of the homoprenyl group adopting an axial position in the six-membered transition state.



Scheme 3. Plausible transition states for the Barbier reactions of **4** and **11**

In conclusion, we have developed a stereoselective construction of an all-carbon quaternary stereocenter through a zinc-mediated Barbier-type allylation of sugar-derived aldehydes in aqueous media. This reaction can be performed without the need of rigorously anhydrous conditions, providing a practical and operationally simple method for the construction of quaternary stereocenters. Further studies and applications of this work to natural product synthesis are in progress and will be reported in due course.

ACKNOWLEDGEMENTS

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12. Barbier-type allylation of aldehyde **4** with **5**: To a stirred solution of **4** (10.1 g, 77.7 mmol) in THF (60 mL) and 20wt% aqueous NH_4Cl (160 mL) was added zinc powder (24.0 g, 312 mmol). The mixture was cooled to –5 °C and a solution of **5** (8.99 g, 51.9 mmol) in THF (20 mL) was added dropwise over 1.5 h. After being stirred at –5 °C for 14 h, the mixture was filtered through a pad of Celite and washed with EtOAc (100 mL). The combined filtrate and washings were washed with saturated brine (100 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:70) to provide 0.83 g (6%) of **7-A/7-B** (dr = 1:4) and 10.6 g (77%) of **7-C/7-D** (dr = 5:1). Compound **7-C/7-D** (dr = 5:1) was obtained as a colorless oil: TLC R_f 0.61 (EtOAc/hexane, 1:3); IR 3490, 2985, 2915 cm^{-1}; ^1H NMR (300 MHz) for **7-C** δ 0.99 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.42-1.52 (m, 2H), 1.59 (s, 3H), 1.68 (s, 3H), 1.85-1.97 (m, 2H), 2.02 (br d, 1H, J = 3.2 Hz, OH), 3.75 (br dd, 1H, J = 3.2, 2.8 Hz), 3.85-3.95 (m, 2H), 4.16 (dt, 1H, J = 2.8, 7.1 Hz), 5.03 (dd, 1H, J = 17.5, 1.3 Hz), 5.03-5.15 (m, 1H), 5.14 (dd, 1H, J = 10.9, 1.3 Hz), 5.78 (dd, 1H, J = 17.5, 10.9 Hz); ^{13}C NMR (75 MHz) for **7-C** δ 17.7, 18.1, 22.5, 25.3, 25.6, 26.4, 37.9, 42.9, 64.3, 76.4, 76.7, 107.4, 114.2, 124.6, 131.3, 143.0; HRMS calcd for $C_{16}H_{28}O_3$ (M^+) *m/z* 268.2038,

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17. The reaction of 2,4-*O*-benzylidene-D-erythrose, prepared from D-glucose, with **5** or **6** gave poor stereoselectivity.
18. Barbier-type allylation of aldehyde **11** with **5**: To a stirred solution of **11** (263 mg, 1.38 mmol) in 20wt% aqueous NH_4Cl (6 mL) was added zinc powder (604 mg, 9.23 mmol). The mixture was cooled to 0 °C and a solution of **5** (159 mg, 0.920 mmol) in THF (3 mL) was added dropwise. After being stirred at room temperature for 72 h, the mixture was filtered through a pad of Celite and washed with CH_2Cl_2. The combined filtrate and washings were diluted with H_2O (40 mL) and saturated brine (10 mL) and extracted with CH_2Cl_2 (20 mL × 4). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 216 mg (68%) of **12-A/12-B** (dr = 1:5) and 12.1 mg (4%) of **12-C/12-D** (dr = 5:1). Compound **12-A/12-B** (dr = 1:5) was obtained as a colorless oil: TLC R_f 0.47 (EtOAc/hexane, 1:2); IR 3443, 2969, 2920 cm^{-1}; ^1H NMR (500 MHz) for **12-B** δ 1.12 (s, 3H), 1.46-1.62 (m, 2H), 1.56 (s, 3H), 1.66 (s, 3H), 1.90-1.95 (m, 2H), 2.81 (br, 1H, OH), 3.14 (br, 1H, OH), 3.69 (d, 1H, J = 6.5 Hz), 3.82 (m, 1H), 3.92 (dd, 1H, J = 6.5, 1.2 Hz), 4.07 (dd, 1H, J = 12.1, 1.5 Hz), 4.24 (dd, 1H, J = 12.1, 1.8 Hz), 5.07 (m, 1H), 5.07 (dd, 1H, J = 17.5, 1.5 Hz), 5.15 (dd, 1H, J = 10.9, 1.5 Hz), 5.53 (s, 1H), 5.92 (dd, 1H, J = 17.5, 10.9 Hz), 7.33-7.39 (m, 3H), 7.47-7.49 (m, 2H); ^{13}C NMR (125 MHz) for **12-B** δ 17.6, 18.2, 22.5, 25.6, 37.4, 43.9, 64.8, 72.4, 76.4, 79.4, 100.6, 113.6, 124.8, 125.8 (2C), 128.1 (2C), 128.8, 131.2, 137.7, 143.4; HRMS calcd for $C_{21}H_{30}O_4$ (M^+) *m/z* 346.2144, found 346.2139.
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