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Preparation of the C1~C10 Fragment of Carbonolide B. A Relay Approach to Carbomycin B

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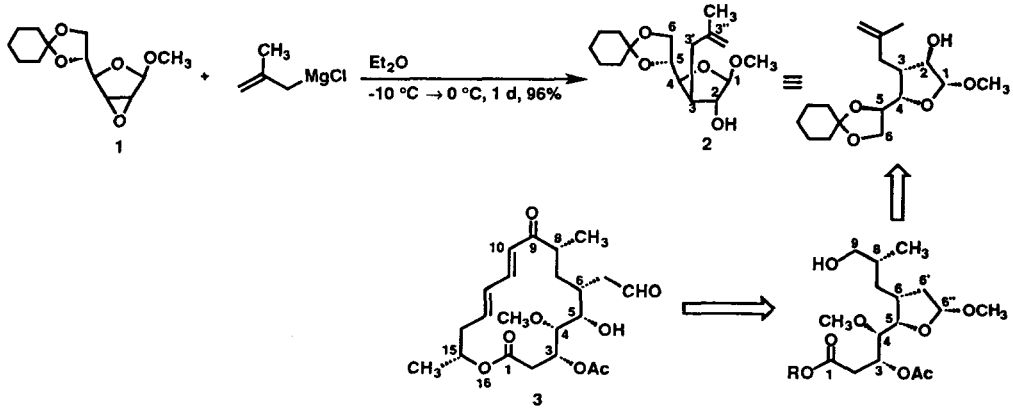
Abstract: Reaction of methyl 2,3-anhydro-5,6-O-cyclohexylidene-β-D-allofuranoside with 2-methyl-2-propenylmagnesium chloride selectively gave methyl 5,6-O-cyclohexylidene-3-deoxy-3-C-(2-methyl-2-propenyl)-β-D-glucofuranoside, which was converted into the C1~C10 fragment of carbonolide B by a sequence of reactions involving hydroboration of the prochiral double bond, oxidative cleavage between C5-C6, and subsequent stereoselective three-carbon elongation at the C5 position.

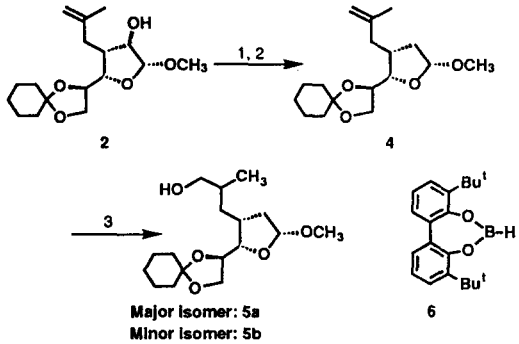
Carbohydrates have been used as a versatile chiral source in the synthesis of natural products with multiple centers of chirality and, therefore, a number of useful methodologies have been reported so far. However, there still exists an ongoing need to develop efficient procedures for introducing functionalized carbon chains into the carbohydrate matrices and their conversion into the desired framework. A previous paper described regioselective introduction of allylic groups into the C2 or C3 position of furanoside rings.[1] Thus, the reaction of methyl 2,3-anhydro-5,6-O-cyclohexylidene-β-D-allofuranoside (**1**) with 2-methyl-2-propenylmagnesium chloride exclusively gave methyl 5,6-O-cyclohexylidene-3-deoxy-3-C-(2-methyl-2-propenyl)-β-D-glucofuranoside (**2**) (Scheme 1). Inspection of the substitution pattern, **2** could be correlated to the C5-C6-C6'-C6" fragment of some 16-membered macrolide antibiotics which include carbonolide B (**3**), carbonolide A, leuconolide A_3, and maridonolide II. In this paper, we wish to report a relay synthesis of **3** based on this correlation by taking the C3 of **2** as the C6 of the target molecule **3** (Scheme 1).[2]



Scheme 1

Compound **2** was deoxygenated by the Barton procedure to give 2-deoxyfuranoside **4** which reacted with various kinds of borane reagents. Thus, the reaction of **4** with $BH_3 \cdot SMe_2$ in THF gave two diastereomers

5a (major product; 54%) and **5b** (minor product; 25%) which could be separated by silica gel column chromatography (Scheme 2). Hydroboration-oxidation of **4** with disiamylborane resulted in 33% de, while diisopinocampheylboranes prepared from (–)- and (+)-α-pinenes gave **5** in 45% and 39% de's, respectively (Scheme 2 and the Table inserted). In all the reactions examined, the major diastereomer was invariably the same (Scheme 2). In the hope of attaining higher stereoselectivity in hydroboration, 4,8-di-*tert*-butyldibenzodioxaborepine (**6**) was prepared by the reaction of (*R*, *S*)-3,3'-Di-*tert*-butyl-2,2'-biphenol with $BH_3{\cdot}SMe_2$. Hydroboration-oxidation of **4** with **6** afforded **5** in 62% de (37% yield with 59% recovery of **2**). Considering the hydroboration with enantiometrically pure diisopinocampheylborane, higher selectivity would be expected in the reaction using (*R*)- or (*S*)-**6** instead of (*R,S*)-**6**. However, no attempt has yet been made to prepare enantiometrically pure **6**.



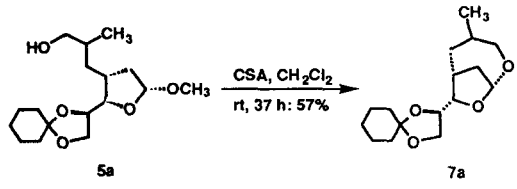
4 ⟶ 5 Borane reagent (solvent)	Isolated Yield/% 5a	5b	% de
$BH_3{\cdot}SMe_2$ (THF)	54	25	35
$(Sia)_2BH$ (Et_2O)	40	20	33
$(Ipc)_2BH$[a] (THF)	45	17	45
$(Ipc)_2BH$[b] (THF)	39	17	39
6 (Et_2O)	30	7	62

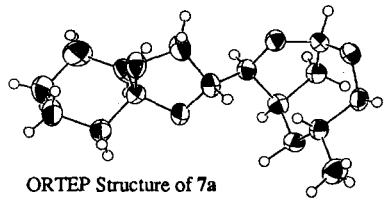
a) Prepared from (-)-α-pinene.
b) Prepared from (+)-α-pinene.

1) NaH, CS_2, MeI, THF, rt, 3 h, 84%. 2) n-Bu_3SnH, Et_3B, benzene, rt, 3.5 h, 71%.
3) Borane reagent (see Table), then H_2O_2, OH^-

Scheme 2

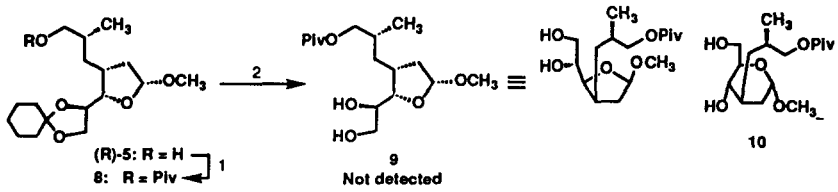
The following experiments were carried out to determine the stereochemistry of the hydroboration product. Intramolecular cyclization of major isomer **5a** under acidic conditions afforded the crystalline bicyclo compound **7a**, mp 94.5-96.5 °C,[3] whose structure was determined by single crystal X-ray analysis confirming the newly created asymmetric center to be *R* [Scheme 3; **5a** = (*R*)-**5**].




ORTEP Structure of **7a**

Scheme 3

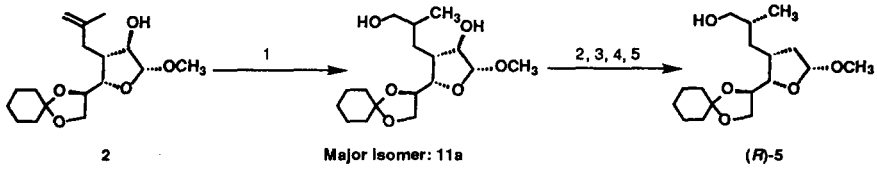
The next stage of the synthesis required manipulation at the C5 and C6 positions (furanoside numbering). Thus, (*R*)-**5** reacted with pivaloyl chloride to give **8**. Hydrolysis of **8** in HBF_4aq (42%)-MeOH at room temperature for 14 h gave 2-deoxypyranoside **10** in quantitative yield rather than the expected 2-deoxyfuranoside **9** (Scheme 4). The result could be explained by the instability of 2-deoxycarbohydrates. Therefore, the reconstruction of the sugar ring could be prevented if the removal of the cyclohexylidene group was carried out before deoxygenation at the position 2.



1) PivCl, Et_3N, THF, rt, 100 h, 80%. 2) HBF_4aq (42%) : MeOH = 1 : 40, rt, 14 h, quant.

Scheme 4

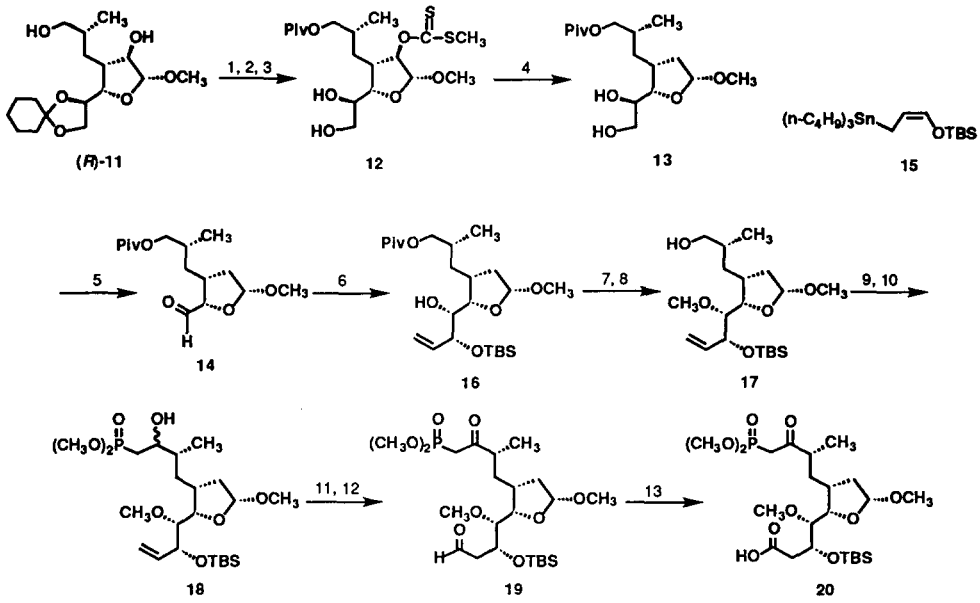
The hydroboration-oxidation of **2** with BH_3·SMe_2 in ether gave a mixture of diastereomers **11a** (major isomer) and **11b** (minor isomer) in 86% yield with 44% de (Scheme 5). The newly created asymmetric center in the major isomer **11a** was determined to be *R* by correlating to (*R*)-**5** [**11a** = (*R*)-**11**] (Scheme 5). Contrary to the case of **4**, higher stereoselectivity could not be obtained by the use of bulky borane reagents such as diisopinocampheylborane generated from (–)-α-pinene (64% yield; 13% de), diisopinocampheylborane generated from (+)-α-pinene (99% yield; 44% de) or **6** (92% yield; 26% de). However, the major diastereomer formed was (*R*)-**11** irrespective of the borane reagents examined.



1) BH_3·SMe_2, rt, 12 h, THF, then H_2O_2, OH^-, 86% (44% de). 2) *t*-BuPh$_2$SiCl (TBDPSCl), imidazole, DMF, rt, 8 h, 84%. 3) NaH, CS_2, MeI, THF, rt, 3 h, 78%. 4) n-Bu_3SnH, Et_3B, benzene, rt, 3 h, 71%. 5) n-Bu_4NF, THF, rt, 7 h, 72%.

Scheme 5

The primary hydroxyl group of (*R*)-**11** was selectively protected by the pivaloyl group. The pivarate was converted into xanthate, followed by treatment with HBF_4aq (42%)-MeOH to afford diol **12** in 73% overall yield without any detectable formation of pyranoside derivative (Scheme 6). Treatment of **12** with n-Bu_3SnH in the presence of 2,2'-azobis(isobutyronitrile) (AIBN) gave **13** in 78% yield. Oxidative cleavage of the diol moiety of **13** gave aldehyde **14**, which reacted with (*Z*)-1-*tert*-butyldimethylsiloxy-3-tributylstanyl-1-propene (**15**) in the presence of $MgBr_2$ in dichloromethane at –5 °C for 10 h to give *syn-syn*-adduct **16** in 70% yield with high diastereoselectivity (>99% de).[4,5] The stereochemistry at the positions 3 and 4 (macrolide numbering) was determined to be *R* and *R* by the Mosher method. After the hydroxyl group at the position 4 was methylated, the pivaloyl group was removed by treatment with MeLi in ether to give **17** (81% over 2 steps). The **17** was oxidized with Dess-Martin periodinane, followed by the reaction with dimethyl lithiomethylphosphonate to afford hydroxyphosphonate **18** (quantitative yield), which was converted into **19** (crude) by hydroboration-oxidation and subsequent Dess-Martin oxidation. The final stage of the synthesis was carried out by Keck's procedure. Thus, aldehyde **19** in *tert*-butanol was treated with $KMnO_4$-KH_2PO_4 to give **20**, which was characterized after conversion into the corresponding methyl ester. Since the transformation of **20** to the aglycone of carbomycin B has already been reported by Keck and coworkers,[2g] the preparation of **20** indicates the completion of a relay synthesis of carbonolide B.



1) PivCl, Et_3N, THF, rt, 17 h, 88%. 2) NaH (0.5 h), CS_2 (1 h), MeI (1 h), THF, rt, 93%. 3) HBF_4aq (42%) : MeOH =1 : 50, rt, 14 h, 89%. 4) n-Bu_3SnH, AIBN, benzene, reflux, 1 h, 78%. 5) $NaIO_4$, 10% THFaq, rt, 15 min, 95%. 6) **15** (TBS = t-$BuMe_2Si$-), $MgBr_2$, CH_2Cl_2, -5 °C, 10 h, 70% (>99% de). 7) NaH, MeI, THF, rt, 1 h, 91%. 8) MeLi, Et_2O, 0 °C, 10 min, 89%. 9) Dess-Martin reagent, CH_2Cl_2, rt, 1.5 h, quant. 10) $(MeO)_2P(O)$-CH_2Li, THF, -78 °C, 2 h, quant. 11) BH_3·SMe_2, THF, rt, 6 h, then H_2O_2, OH^-, 71%. 12) Dess-Martin reagent, CH_2Cl_2, rt, 1.5 h (crude). 13) $KMnO_4$, KH_2PO_4, t-BuOH, rt, 3 h, 80%.

Scheme 6

The work described in this paper and that previously reported suggest that furanosides having allylic substituents could be utilized as a versatile intermediate for the construction of natural products and related compounds with multiple centers of chirality.[1,3,6]

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