Novel Platinum-Catalyzed Ring-Opening of 1,2-Cyclopropanated Sugars with Alcohols. Stereoselective Synthesis of 2-C-Branched Glycosides

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Many C-branched sugars have been found in nature particularly as glycan portions of antibiotics.[1,2] C-Branched sugars have also been identified as important subunits in many natural products,[3,4] and especially in macrolides the macrocyclic ring structure is often comprised of a long-chain C-branched sugar.[2] Accordingly, many total syntheses of natural products have started from a suitable protected C-branched sugar.[3−5] However, synthesis of C-branched sugars is not trivial and problems are frequently encountered with controlling stereochemistry at the C-branching point and the anomeric center.[1,6] Herein, we report a new glycosylation reaction for preparation of 2-C-branched glycosides[7] by employing a platinum-catalyzed ring-opening of 1,2-cyclopropanated sugars.[8] Additionally, this represents to the best of our knowledge the first example of a platinum-catalyzed ring-opening of a cyclopropane with an alcohol.

Recently, several efficient methods have been developed for stereocontrolled synthesis of 1,2-cyclopropanated sugars from glycals.[9] Ring-opening of these cyclopropanes has previously been achieved by mercury,[9b] strong acid,[9c,10] or halonium ion[9a,11] mediated solvolysis. We were, however, attracted to a different strategy and decided to explore a transition metal-catalyzed ring-opening. In this context, substantial work has described the insertion of platinum into cyclopropanes to give platinacyclobutanes[12] which are usually fairly stable and can be isolated. However, for alkoxy and siloxy cyclopropanes platinum-catalyzed ring-opening of the cyclopropane with rearrangement to olefins has been described.[13−15] We anticipated[16] that 1,2-cyclopropanated sugars would undergo a similar transformation and treated cyclopropane **1** with Zeise's dimer $[Pt(C_2H_4)Cl_2]_2$ (**2**) (Scheme 1). Unexpectedly, the major product observed was the benzyl glycoside **4** isolated in 21% yield as a 12/1 α/β mixture. Presumably, during the reaction some benzyl alcohol is released, which reacts with platinacyclobutane **3**. In fact, when the reaction was carried out with added benzyl alcohol, the glycoside **4** was obtained in 95% yield, again as a 12/1 α/β mixture.[17] On scale-up the amount of Zeise's dimer could be lowered to 1 mol % without affecting the yield of **4**. Use of deuterated benzyl alcohol gave the monodeuterated glycoside **5**. To further probe the scope of this transformation, we investigated other cyclopropanes and nucleophiles (Chart 1) as shown in Table 1.

Scheme 1

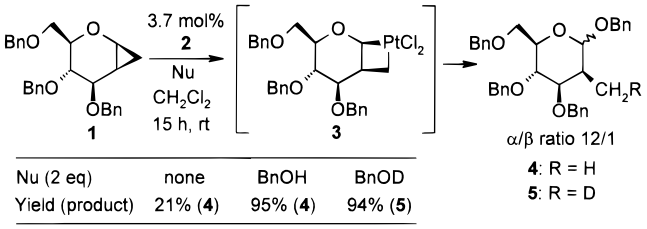
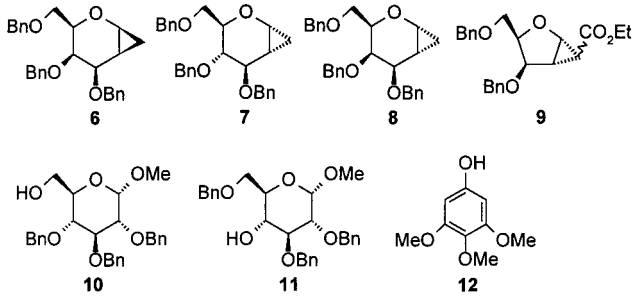


Chart 1



A wide variety of alcohols can participate in the ring-opening reaction, giving C-branched glycosides ranging from simple methyl glycosides to more complex disaccharides.[18] Yields range from 50 to 97% and very high diastereoselectivity is obtained at

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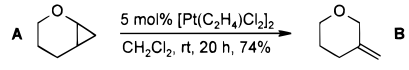
(15) Pt(II)-catalyzed isomerization of ethoxy cyclopropanes gives alkylated ketones, see: Hoberg, J. O.; Jennings, P. W. *Organometallics* **1996**, *15*, 3902.
(16) When we treated cyclopropane **A** with Zeise's dimer we obtained olefinic product **B**:



(17) No reaction occurred in the absence of Zeise's dimer. $PtCl_2(PhCN)_2$ was less reactive while acids (TsOH, $BF_3{\cdot}OEt_2$, TMSOTf) and other platinum catalysts ($Pt(PPh_3)_4$, $(PPh_3)_2Pt(C_2H_4)$, $(PPh_3)_2PtCl_2$) failed to catalyze the ring-opening.
(18) No ring-opening occurred with water as nucleophile under the conditions in Table 1.

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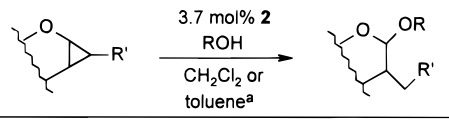
Table 1. Pt(II)-Catalyzed Ring-Opening of Cyclopropanes

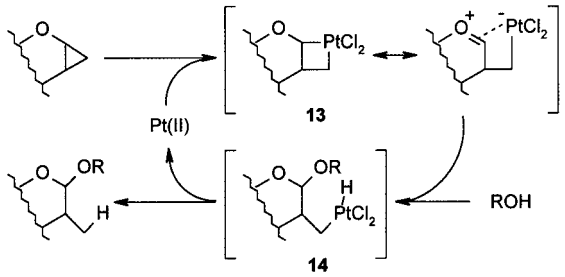


Entry	Cyclopropane	Product	ROH	Yield[b] (α/β ratio)
1			MeOH	82% (21/1)
2			CH_2=$CHCH_2OH$	92% (only α)
3			t-BuOH	53% (9/1)
4	**1**		PhOH	64% (21/1)
5			**10**	65% (only α)
6			**11**	50% (only α)
7			MeOH	67% (only α)
8	**6**		CH_2=$CHCH_2OH$	84% (24/1)
9			BnOH	74% (only α)
10	**7**		BnOH	97% (5/1)
11			**10**	77% (7/1)
12	**8**		CH_2=$CHCH_2OH$	80% (7/1)
13			BnOH	87% (7/1)
14	**9**		MeOH	59%[c] (9/1)
15			BnOH	75% (4/1)
16	**1**		**12**	51% (1/1)

[a] Reactions were conducted with 0.8 mmol of cyclopropane and 1.6 mmol of alcohol in 4 mL of solvent. CH_2Cl_2 at room temperature for 15 h was used for cyclopropanes **1**, **6**, **7**, and **8** while toluene at 50−70 °C for 1.5−4 h was used for **9**. [b] Isolated yield after column chromatography. [c] The product contained 17% of the corresponding methyl ester.

the newly formed C-1 stereocenter. The α-glycoside, favored by the anomeric effect, is the major product in all O-glycosylations regardless of the stereochemistry of the starting cyclopropane (entries 1−15). Also less reactive cyclopropanes containing electron-withdrawing ester substituents undergo the ring-opening reaction (entries 14 and 15) although some transesterification can occur. Glycosyl arenes can also be obtained when electron-rich phenols are used as O-nucleophiles (entry 16). The reaction probably goes through an intermediate O-aryl glycoside that subsequently undergoes a Fries-type rearrangement[19] to the corresponding glycosyl arene.

Scheme 2



A plausible reaction sequence for the ring-opening is depicted in Scheme 2. Oxidative addition of the cyclopropane to platinum(II) would give platinacyclobutane **13**. In **13** the polarization of the platinum(IV)-carbon σ bond[20] is further enhanced by electron donation from the sugar ring oxygen. Accordingly, **13** is believed to have substantial oxocarbonium ion character.[21] Nucleophilic attack of the alcohol would give glycoside **14** in which platinum can be coordinated to either one of the two oxygens at C-1. Reductive elimination from **14** would then give the C-branched glycoside and platinum(II).[22]

In summary, we have developed a novel platinum-catalyzed ring-opening of carbohydrate-derived cyclopropanes with alcohol nucleophiles. Further studies on the applications of this new transformation are currently in progress.

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Supporting Information Available: Experimental procedures and characterization data for all ring-opening products as well as details of stereochemical proofs (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(22) For ester-substituted cyclopropanes the involvement of a six-membered oxaplatinacycle also has to be considered in the catalytic cycle (see ref 13).