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Short and Efficient Synthesis of Chiral Furyl Carbinols from Carbohydrates

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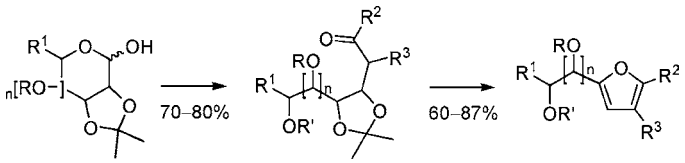
ABSTRACT

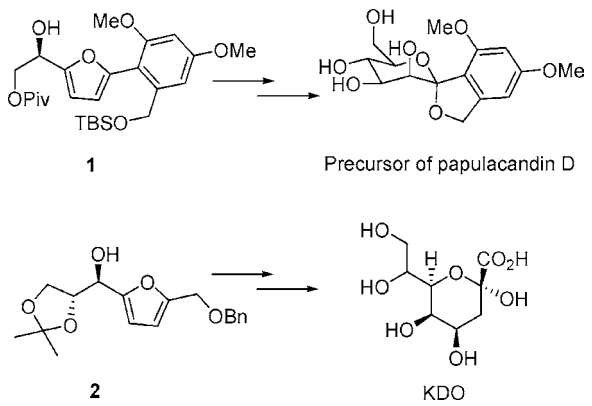


Common sugar derivatives can be transformed in a few steps into chiral-substituted furyl carbinols. The mildness of the reaction conditions and the good yields obtained make this procedure an interesting alternative to the conventional processes.

Furans are versatile building blocks in the synthesis of natural or bioactive products,[1] by reduction or oxidation of the aromatic ring and by Diels−Alder cycloadditions.

Among them, chiral furyl carbinols have proven particularly useful.[2] For instance, the oxidative rearrangement of carbinol **1** (Scheme 1) affords a spirocyclic precursor of the

Scheme 1

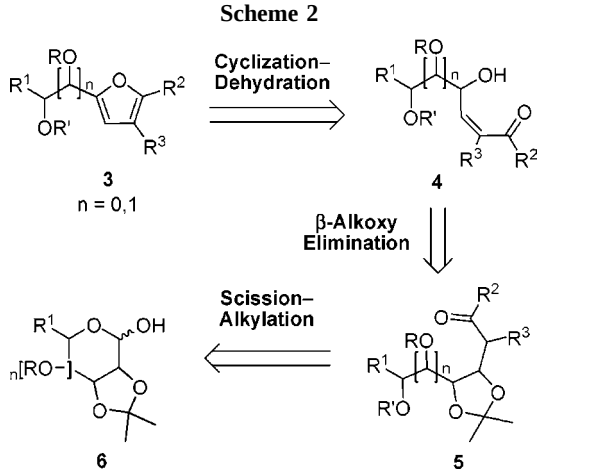


selective antifungal populacandin D.[3a] Furyl carbinols have also been used to obtain higher-carbon sugars,[4] with compound **2** being a key intermediate in the synthesis of KDO, an essential component of the Gram-negative bacteria cell wall.[3b]

To prepare chiral furyl carbinols, several methods have been developed,[5] including asymmetric reduction of furyl ketones,[6] acid- or base-promoted addition of furan to chiral aldehydes,[7] aldol reaction of chiral enolates with furfurals,[8] Sharpless dihydroxylation of vinyl furans,[9] and resolution of racemic mixtures.[10]

We report here a flexible, efficient alternative to the synthesis of chiral furyl carbinols **3** (Scheme 2), which avoids harsh conditions (such as strong bases) and allows introduction of a variety of substituents onto the 2-, 3-, and 5-ring

Scheme 2



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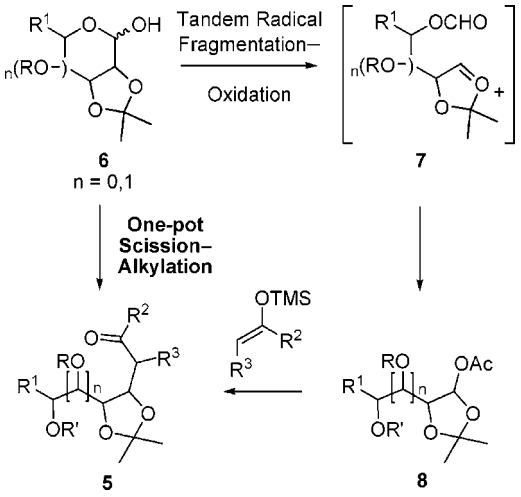
Scheme 3



positions. The furans **3** would be formed by cyclization of unsaturated hydroxyketones **4**, generated in situ from ketones **5** by elimination of the β-alkoxyl group. The substrates **5** would be formed from readily available carbohydrates **6**, using a fragmentation−alkylation reaction developed by our group.[11]

The synthesis of the polyhydroxylated ketones **5** can be performed from readily available sugar derivatives **6** in one or two steps (Scheme 3). Thus, the substrates **6** react with (diacetoxyiodo)benzene (DIB) and iodine, generating anomeric alkoxyl radicals. These intermediates undergo β-scission and oxidation, to give the oxycarbenium ions **7**, which are trapped by acetate ions from the reagent. The resulting acetates **8**, under treatment with a Lewis acid and a silylenol ether, give the corresponding ketones **5**.

The transformation of representative sugar substrates **9**−**11** (derived from ribose, mannose, and rhamnose) into their acetates **12**−**14** is shown in Scheme 4. The reaction proceeded in good yield and good stereoselectivity.

The conversion of acetates **12**−**14** into ketones **15**−**19** (Scheme 4) also proceeded in good yield. In contrast, the one-pot generation of phenyl ketones **15**, **17**, and **19** from sugar substrates **9**−**11** gave low yields. It must be noted that in all cases 1,2-trans stereoselectivity was obtained.

Modification of the polyhydroxylated chains afforded other derivatives. Thus, the formate groups in **18** and **19** were hydrolyzed, and the resulting alcohols were oxidized to diketones **20** and **21**, respectively.

The polyhydroxylated ketones **15**−**18** and **20**−**21** were treated under basic conditions, to obtain the unsaturated

Scheme 4

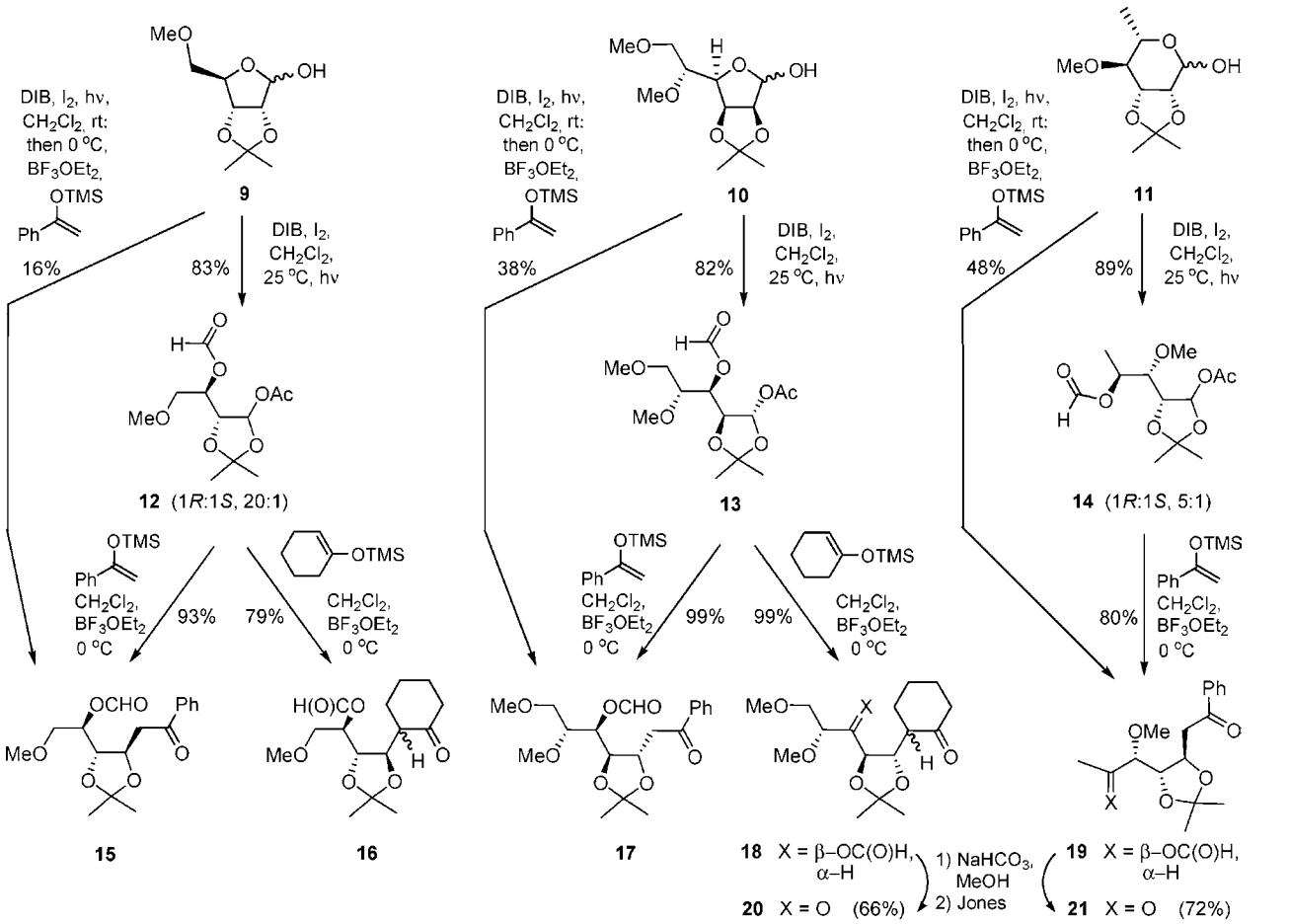
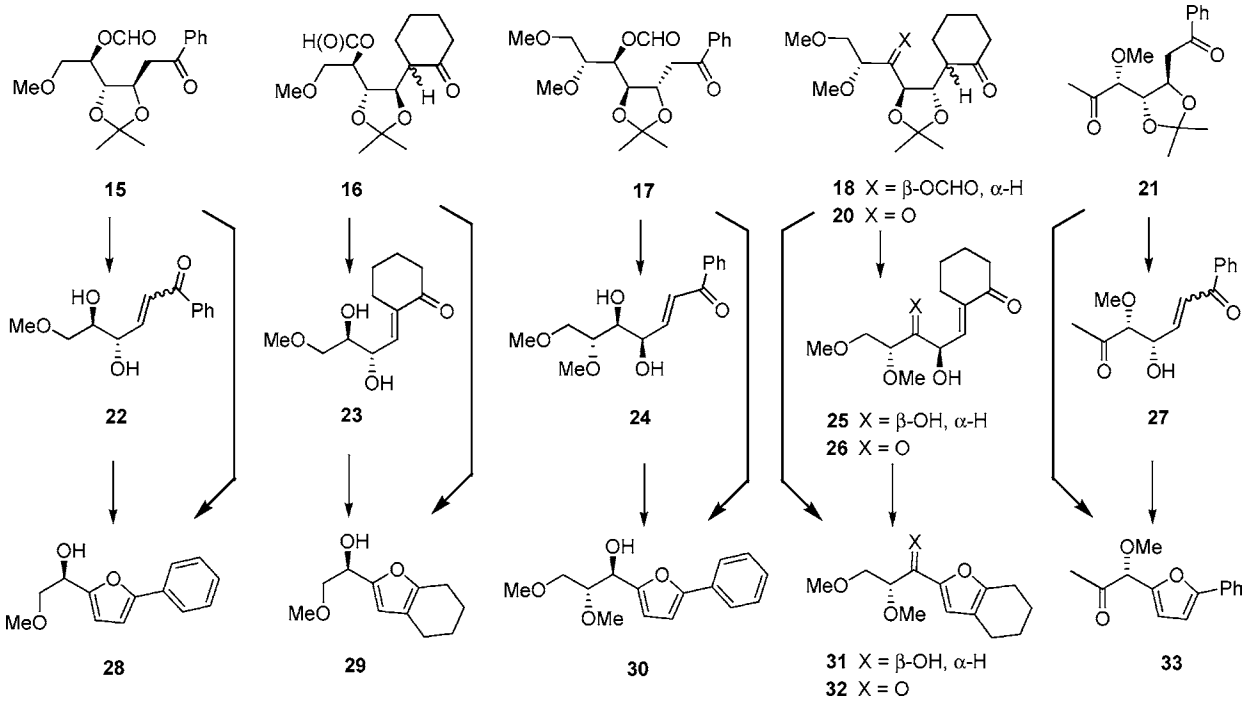


Table 1. Transformation of Polyhydroxylated Ketones into Chiral Furyl Carbinols



entry	ketone	conditions **15**−**21** → **22**−**27**	unsaturated ketone[a]	conditions **22**−**27** → **28**−**33**	furans (%)[a]	one-pot process (**15**−**21** → **28**−**33**) conditions (furan yield, %)[a]
1	**15**	$NaHCO_3$, MeOH, 12 h	**22** (−)[b]	–	**28** (−)	C (74)[e]
2	**16**	$NaHCO_3$, MeOH, 12 h	**23** (90)	A[c]	**29** (65)	C (−)[e]/D (55)[f]/E (32)[g]/F (68)[h]
3	**17**	$NaHCO_3$, MeOH, 12 h	**24** (95)	B[d]	**30** (89)	C (87)[e]
4	**18**	$NaHCO_3$, MeOH, 12 h	**25** (70)	A[c]	**31** (30)	C (−)[e]/D (29)[f]/E (31)[g]/F (67)[h]
5	**20**	$NaHCO_3$ or $BuNH_2$, MeOH, 12 h	**26** (−)[b]	–	**32** (−)	E (60)[g]
6	**21**	$NaHCO_3$ or $BuNH_2$, MeOH, 12 h	**27** (−)[b]	–	**33** (−)	C (74)[e]

[a] The yields are given for products purified by chromatography on silica gel. [b]Not isolated (labile compound). [c]Method A: AcOH, 12 h. [d]Method B: 2% HCl (aq) in MeOH (pH 4), 12 h. [e]Method C: $NaHCO_3$, MeOH, 12 h; then 2% aq HCl to pH = 4, 12 h. [f]Method D: $NaHCO_3$, MeOH, 12 h; then AcOH, 12 h. [g]Method E: $BuNH_2$/MeOH at 60 °C, 6 h; then AcOH, overnight. [h]Method F: Formates **16** or **18** were hydrolyzed with $NaHCO_3$ in MeOH, 0.5 h; the crude alcohols were treated as described in method E.

derivatives **22**−**27** (Table 1). These intermediates would then be transformed into furyl carbinols **28**−**33**.

Although the conjugated ketones **22**, **26**, and **27** (entries 1, 5, and 6) were unstable and could not be isolated, the unsaturated ketones **23**−**25** were formed in good yields (entries 2−4). These three intermediates underwent cyclization to the furans **29**−**31** under acid treatment (method A or B).

To prevent the decomposition of the unsaturated ketones during their isolation, a one-pot β-alkoxy elimination−cyclization procedure was developed (method C or D: $NaHCO_3$ in MeOH, 12 h, then acidification with HCl (aq) or AcOH). The direct transformation of phenyl ketones **15**,

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17, and **21** into the furyl carbinols **28**, **30**, and **33** (entries 1, 3, and 6) proceeded as desired. However, the tetrahydrobenzo furans **29**, **31**, and **32** (entries 2, 4, and 5) were formed in modest or low yields.

A modification of the one-pot procedure (method E) still gave low yields of the tetrahydrobenzofurans **29** and **31** (entries 2 and 4), but in contrast, furan **32** was formed in good yield (entry 5). Finally, good results were achieved with a two-step process (method F: hydrolysis of the formate group in **16** or **18** and cyclization of the crude alcohols).

In summary, we have shown that common sugar derivatives can be easily transformed in few steps into chiral, highly substituted furyl carbinols. These compounds are useful synthetic intermediates, and many have interesting biological properties. The mildness of the reaction conditions and the good yields obtained make this procedure an interesting alternative to the conventional processes.

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Supporting Information Available: Procedures for the synthesis of compounds **12**−**33** and ^{1}H and ^{13}C NMR spectra for compounds **12**−**21**, **23**−**25**, and **28**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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