A PRACTICAL SYNTHETIC METHOD FOR α- AND β-GLYCOSYLOXYACETIC ACIDS

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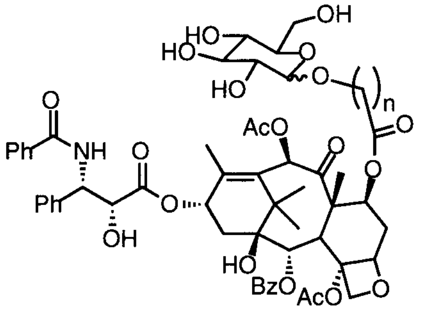
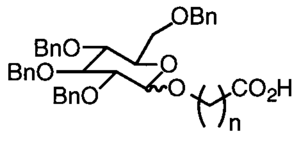
Abstract - Dihydroxylation of allyl 2,3,4-tri-*O*-benzyl-6-*O*-tritylglycosides provides diols, the anomers of which can easily be separated by column chromatography in a practical scale. These anomers can be cleanly transformed into α- and β-glycosyloxyacetic acids, respectively, *via* oxidative cleavage of the diol followed by oxidation.

In our project directed toward the synthesis of new paclitaxel derivatives which exhibit much higher water solubility as well as the higher level of cytotoxicity than that of paclitaxel, we recently synthesized new paclitaxel derivatives (**1**) *via* the condensation of 2'-*O*-TES-paclitaxel with ω-2,3,4,6-tetra-*O*-benzyl-glucosyloxycarboxylic acids (**2**).

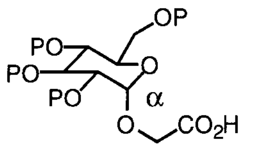


1 (n=1~5, 7, 9)

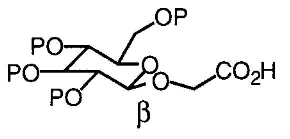


2 (n=1~5, 7, 9)

Through the research, we were compelled to develop a practical synthetic method for stereo-defined **2** indispensable for both precise evaluation of water solubility and structure-activity relationship studies of paclitaxel.[1] In this context, we envisaged an efficient synthetic method for protected α- and β-glucosyloxy-acetic acids (**A** and **B**) (n=1), which would lead to stereo-defined **2** (n≥2).



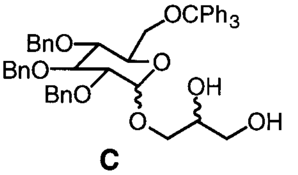
A



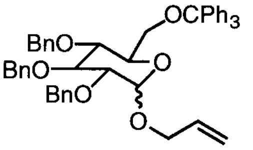
B

P: protecting group

We consequently found that anomers of diols (**C**) derived from allyl 2,3,4-tri-*O*-benzyl-6-*O*-tritylglucosides (**D**) can easily be separated by column chromatography (SiO_2) and that each anomer separated can be transformed into the carboxylic acids (**A**) and (**B**) quantitatively in two steps. Of particular interest is that the 6-*O*-trityl group was found to be much superior to 6-*O*-benzyl group as to the column chromatographic separation. These observations prompted us to search a practical method for the preparation of **D**.



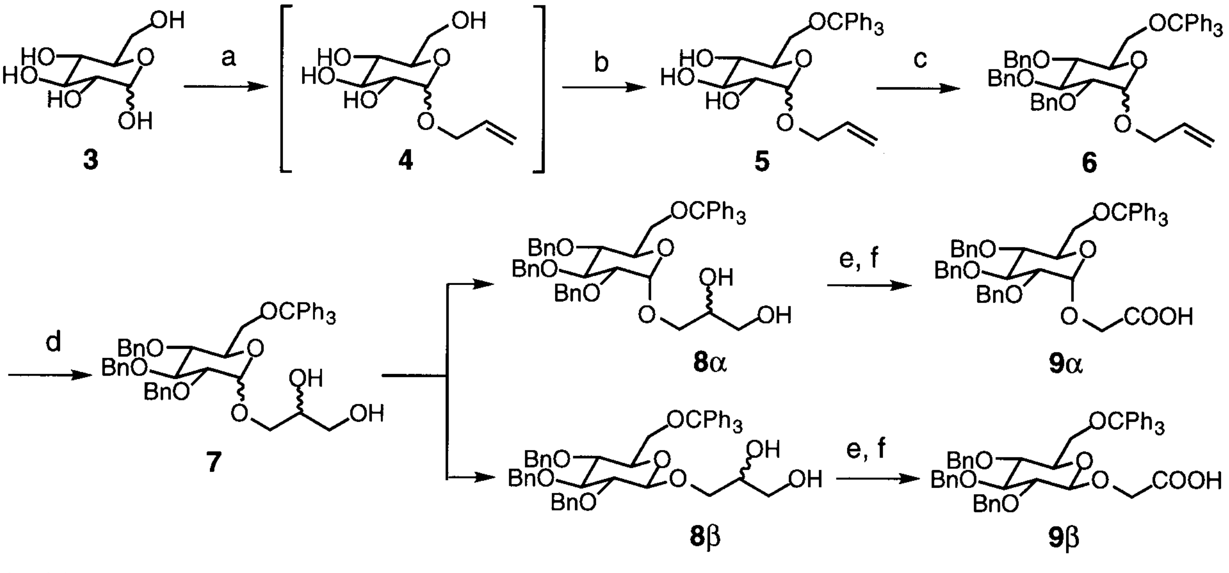
C



D

Since the conventional synthetic methods for allyl glucoside[2] seemed far from practical as to expensive sugars, we explored various reaction conditions of the glycosidation with allyl alcohol. Eventually we found that glycosidation proceeds very smoothly with a combination of triallyl orthoformate, allyl alcohol, and acetyl chloride as a source of dry HCl to provide allyl glucosides in an α-selective manner. This protocol is also applicable to both galactose and mannose. With ample allyl glucosides in hand, we established a practical route to α- and β-glucosyloxyacetic acids as shown in Scheme 1.

Scheme 1

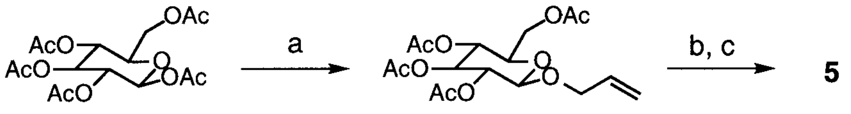


a)$HC(OCH_2CH{=}CH_2)_3$/allyl alcohol/AcCl, 50 °C, 24 h b) Ph_3CCl/Py/cat. DMAP, rt, 24 h, 45% in two steps c) BnBr/NaH/cat. dibenzo-18-crown-6, DMF/THF, rt, 12 h d) OsO_4/50%NMO/dioxane, rt, 24 h, 86% in two steps e) $NaIO_4$/dioxane, rt, 12 h f) $NaClO_2$/*tert*-BuOH/dioxane, rt, 3 h, 85-90% in two steps

Glucose (**3**) was heated at 50 °C with a mixture of triallyl orthoformate[3,4] (1.2 eq) and acetyl chloride (1.2 eq) in allyl alcohol (10 eq) as a solvent for 24 h. Neutralization by the addition of pyridine followed by evaporation of allyl alcohol provided the crude **4**, which without purification was treated with trityl chloride (1.1 eq based on glucose) in pyridine in the presence of cat. DMAP (0.05 eq) at room temperature for 24 h. The solvent was removed *in vacuo* and the crude triol (**5**) was distributed between toluene and 1*N* HCl. Toluene extract was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated to give a viscous oil which was purified by column chromatography (SiO_2) using toluene/EtOAc (1/1.5-1/3) as an eluent. The triol (**5**), an inseparable mixture of anomers, was benzylated to give allyl 2,3,4-tri-*O*-benzyl-6-*O*-tritylglucoside (**6**), which provided diol (**7**) as a mixture of four diastereomers by the dihydroxylation with OsO_4. At this stage, these anomers were found to be separable in a practical scale (up to *ca.* 30 g) by a medium-pressure silica gel column chromatography (Ultra Pack®, 40 μm, 60 Å, D 50 x 300 mm) using toluene/EtOAc (1/1-1/3) as an eluent. Diols (**8**α) and (**8**β) (**8**α/**8**β=70/30) thus separated were uneventfully converted to carboxylic acids (**9**α) and (**9**β), respectively, by oxidative cleavage with $NaIO_4$ and ensuing oxidation of the crude aldehydes with $NaClO_2$.

On the other hand, we examined the glycosidation giving rise to β-allyl glucoside predominantly, the outline being depicted in Scheme 2. Allyl 2,3,4,6-tetra-*O*-acetyl-β-glucoside (**11**) was furnished preferentially by the treatment of β-glucose pentaacetate (**10**) with allyl alcohol (1.2 eq) and BF_3 etherate (1.1 eq) in methylene chloride at room temperature for 10 h. The stereoselectivity of **11** proved to be more than 87% by the NMR analysis of **5** derived through transesterification with MeOH/cat. MeOLi followed by tritylation.

Scheme 2



10 **11**

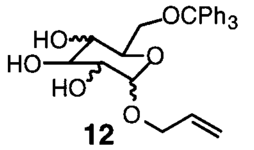
a) allyl alcohol, $BF_3 \cdot Et_2O$, rt, 10 h b) MeOLi/MeOH, rt, 3 h
c) Ph_3CCl/pyridine/cat. DMAP, rt, 24 h, 40 % in three steps

This protocol is also applicable to β-galactose pentaacetate. As expected, no β-anomer was formed in case of mannose. The anomeric ratios and the yields of allyl 6-*O*-tritylglycosides (**12**) obtained by two methods were summarized in Table 1.

Table 1

The starting sugars	α/β	Yield (%)[a] **12**
D-Glucose	70/30	45
β-D-Glucose pentaacetate	13/87	40
D-Galactose	75/25	38
β-D-Galactose pentaacetate	5/95	50
D-Mannose	α>95	58
D-Mannose pentaacetate	α>95	30

a) Total isolated yields by column chromatographic purification.



12

In summary, we have established a practical synthetic method for α-glucosyloxyacetic acid (**9**α),[5] α-galactosyloxyacetic acid, α-mannosyloxyacetic acid, β-glucosyloxyacetic acid (**9**β),[5] and β-galactosyloxyacetic acid. These building blocks are of great synthetic use for the preparation of stereo-defined ω-2,3,4-tri-*O*-benzyl-6-*O*-tritylglycosyloxycarboxylic acids required for both precise evaluation of water solubility and structure-activity relationship studies of paclitaxel.

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1. For review: *Taxol® Science and Applications,* ed. by M. Suffness, CRC:Boca Raton, FL, 1995.
2. E. A. Talley, M. D. Vale, and E. Yanovsky, *J. Am. Chem. Soc.*, **1945**, *67*, 2037 and references cited therein.
3. (a) M. A. Calter and P. M. Sugathapala, *Tetrahedron Lett.*, **1998**, *39*, 8813. (b) For review: R. H. DeWolfe, *Synthesis*, **1974**, 153. cf: The author in the literature (a) prepared triallyl orthoformate and cited literature (b). However, none of the yield and synthetic procedure was described anywhere.
4. Triallyl orthoformate was prepared by the acid-catalyzed transesterification: A mixture of trimethyl orthoformate (53 g, 0.5 mol), allyl alcohol (116 g, 2.0 mol), and CSA (1.16 g, 5 mmol) was heated at 90-100 ℃ for 3-5 h with continuous removal of released methanol. The mixture was cooled to room temperature and basified by the addition of NaHCO$_3$ powder. After the volatile components having been distilled under an atmospheric pressure, the residue was distilled *invacuo* (90-100 ℃/*ca.* 20 mmHg) to give 38-45% of triallyl orthoformate with the satisfactory purity for usual synthetic use.
5. ^{1}H-nmr (CDCl$_3$, 500 MHz) spectra of the corresponding methyl esters are as follows.
   Methyl ester of **9**α: δ 3.20 (1H, dd, J = 4.8, 10.0, H-6), 3.47 (1H, dd, J = 1.8, 10.0, H-6'), 3.64 (1H, dd, J = 9.2, 10.0, H-4), 3.72 (1H, dd, J = 3.3, 9.4, H-2), 3.77 (3H, s, COOCH_3), 3.86 (1H, m, H-5), 4.01 (1H, dd, J = 9.2, 9.4, H-3), 4.23 (1H, d, J = 16.5, OCH_2CO), 4.28 (1H, d, J = 10.4, OCH_2), 4.38 (1H, d, J = 16.5, OCH_2CO), 4.70 (1H, d, J = 10.4, OCH_2), 4.79 (1H, d, J = 10.5, O-CH_2), 4.82 (1H, d, J = 12.0, OCH_2), 4.92 (1H, d, J = 12.0, OCH_2), 4.98 (1H, d, J = 10.5, OCH_2), 5.20 (1H, d, J = 3.3, H-1), 6.86 (2H, aromatic), 7.16-7.47 (28H, aromatic).
   Methyl ester of **9**β: δ 3.25 (1H, dd, J = 4.0, 10.0, H-6), 3.40 (1H, ddd, J = 1.6, 4.0, 10.0, H-5), 3.57 (1H, dd, J = 1.6, 10.0, H-6'), 3.59-3.65 (2H, H-2, H-4), 3.78 (3H, s, COOCH_3), 3.82 (1H, t, J = 9.1, H-3), 4.35 (1H, d, J = 10.4, OCH$_2$), 4.40 (1H, d, J = 16.0, OCH_2CO), 4.53 (1H, d, J = 16.0, OCH_2CO), 4.56 (1H, d, J = 7.3, H-1), 4.69 (1H, d, J = 10.4, OCH_2), 4.78 (1H, d, J = 11.0, OCH_2), 4.79 (1H, d, J = 11.0, OCH_2), 4.92 (1H, d, J = 11.0, OCH_2), 5.14 (1H, d, J = 11.0, O-CH_2), 6.86 (2H, aromatic), 7.16-7.40 (28H, aromatic).

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