

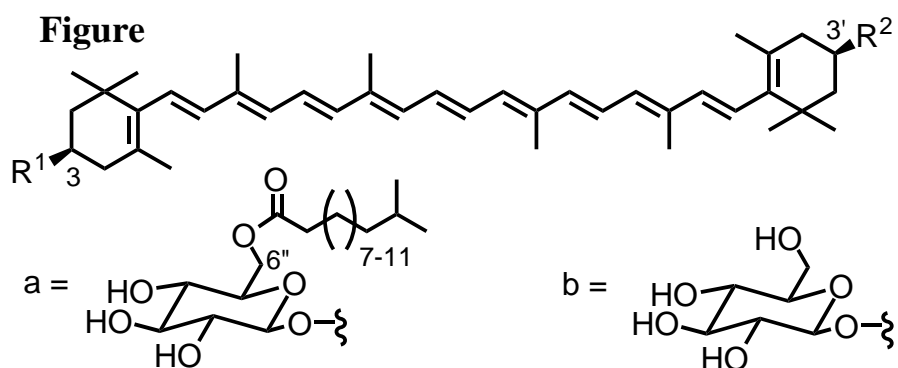
SYNTHESIS OF ZEAXANTHIN- AND CRYPTOXANTHIN- β -D-GLUCOPYRANOSIDES

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Abstract - β -Glucosidation of (3*R*)-3-hydroxy- β -ionone (**6**) was achieved in a reasonable yield by use of tetra-*O*-benzoyl- α -D-glucopyranosyl bromide (**8c**) as a glycosyl donor and silver triflate as an activator. The resulting glucoside (**9**) was transformed into the β -apo-12'-carotenal (**18**), which was condensed with the Wittig salt (**19**) or (**20**) to provide zeaxanthin-mono- β -D-glucopyranoside (**3**) or cryptoxanthin- β -D-glucopyranoside (**4**).

It has been reported^{1,2} that new carotenoid-glucoside-fatty acid esters, thermozeaxanthins (**1**) and thermocryptoxanthins (**2**) (Figure), isolated from the thermophilic eubacterium may contribute to the stabilization of the membrane at high temperature owing to these characteristic "hydrophobic-hydrophilic-hydrophobic" structures. In order to



- 1 $R^1=a$, $R^2=OH$; thermozeaxanthins
- 2 $R^1=a$, $R^2=H$; thermocryptoxanthins
- 3 $R^1=b$, $R^2=OH$; (3*R*,3'*R*)-zeaxanthin-mono- β -D-glucopyranoside
- 4 $R^1=b$, $R^2=H$; (3*R*)-cryptoxanthin- β -D-glucopyranoside

investigate this biological function, we have developed a synthetic method for these carotenoid-glucoside esters. Partial synthesis of zeaxanthin-mono- and diglucosides from zeaxanthin by the Koenigs-Knorr method was reported³ by Pfander's group. However, only a small amount of glucosides was obtained in the method, probably because of the instability of carotenoid molecule. Here we describe the efficient synthesis of zeaxanthin-mono- β -D-glucopyranoside (**3**) and cryptoxanthin- β -D-glucopyranoside (**4**) starting from (3*R*)-3-hydroxy- β -ionone (**6**).

We first examined the glucosidation (Table) of (3*R*)-3-hydroxy- β -ionone (**6**), which was obtained by deprotection of previously synthesized⁴ *tert*-butyldimethylsilyl (TBS) ether (**5**) as shown in Scheme 1. In order to prepare the β -glucoside stereoselectively, glucosides (**8a-c**) carrying participating acyl groups in the C-2 position were chosen as glycosyl donors. According to the mild thioglycoside method,⁵ the compound (**6**) was reacted with methyl tetra-*O*-acetyl- and methyl tetra-*O*-benzoyl-1-thio- β -D-glucopyranosides (**8a**) and (**8b**) using phenylselenenyl triflate as an activator (entries 1,2). However, the former compound (**8a**) provided only the acetylated compound (**7**), and the latter one (**8b**) afforded the desired β -glucoside (**9**) but, unfortunately in low yield.

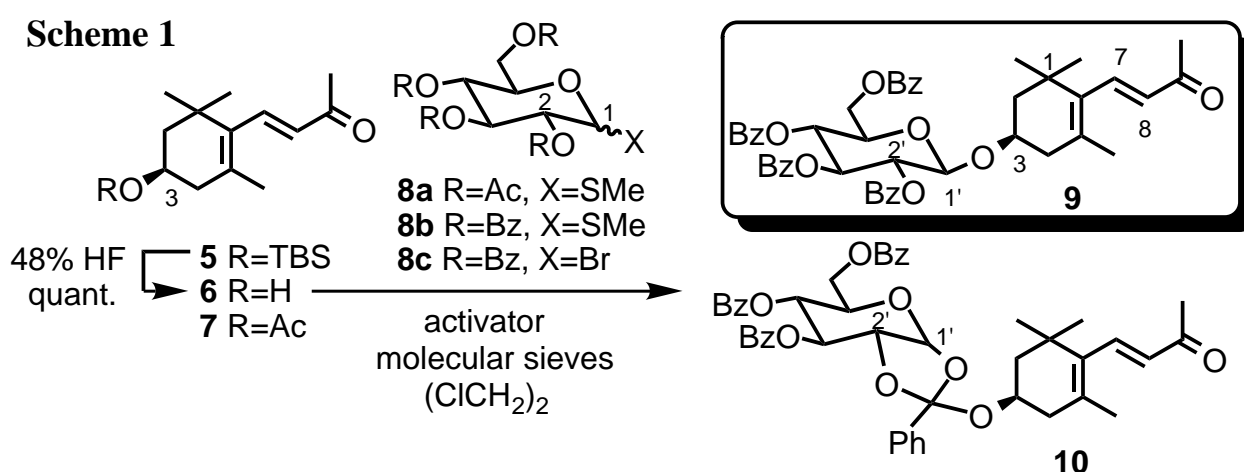
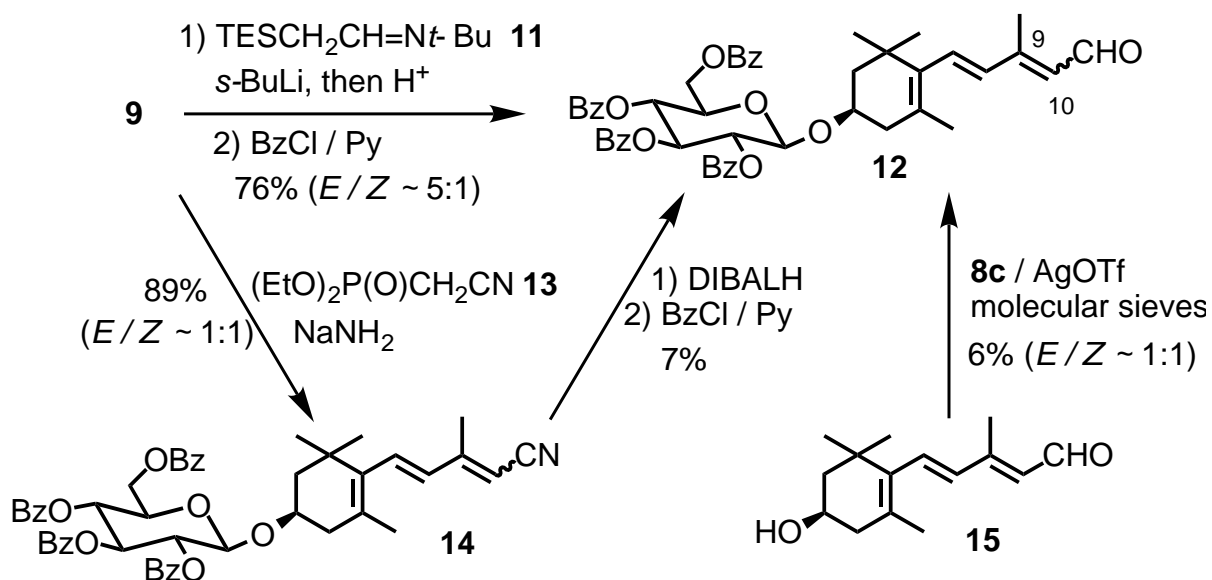


Table Glucosidation of (3*R*)-3-hydroxy- β -ionone (**6**)

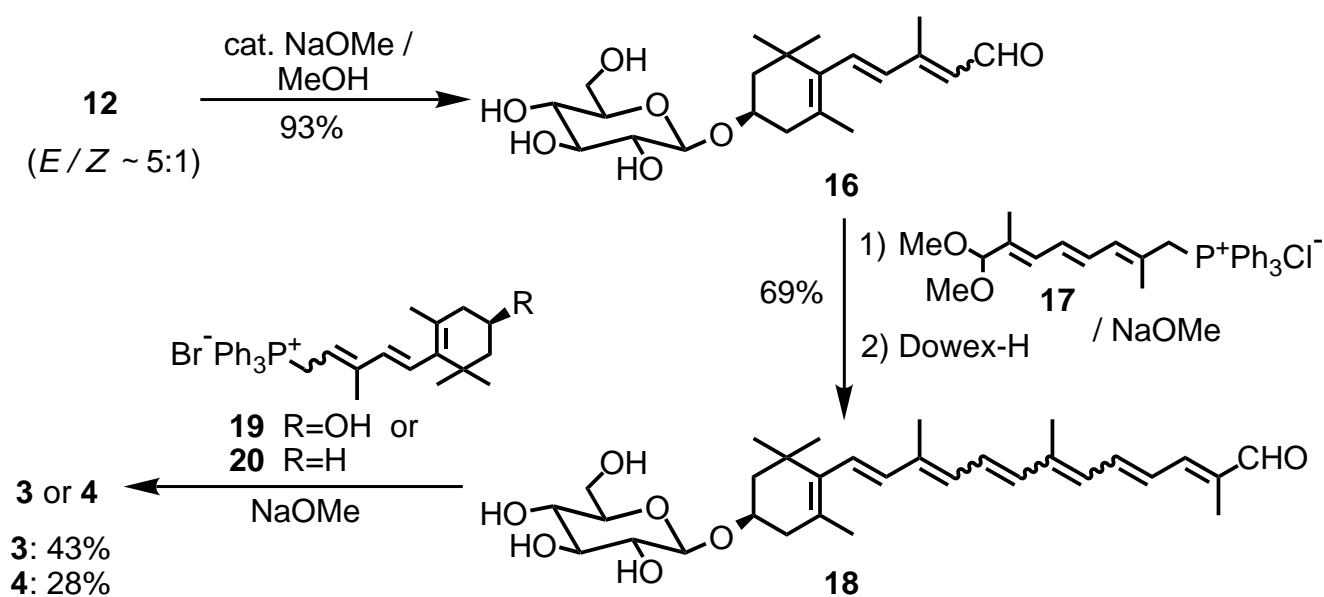
entry	glycosyl donor	activator (eq.)	temp. / time	product	yield (%)
1	8a	PhSeOTf (1.4)	0°C / 50 min	7	46
2	8b	PhSeOTf (1.4)	0°C / 10 h	9	27
3	8c	AgOTf (2.0) Me ₂ NC(O)NMe ₂ (3.0)	0°C / 30 min rt / 1 h	10	76
4	8c	AgOTf (2.0)	rt / 1 h	9	66
5	8c	HgBr ₂ (2.0)	rt / 15 h	9	36

Banoub *et al.* reported⁶ that in the glycosylation reaction between alcohol and acylated glycosyl halide using silver triflate as an activator, 1,2-*trans*-glycosides were formed exclusively when *N,N*-tetramethylurea was used as a proton acceptor, whereas 1,2-ortho esters were the major product if the proton acceptor was 2,4,6-collidine. In our case, combined use of silver triflate and *N,N*-tetramethylurea (entry 3) gave the ortho ester (**10**) as a single product in 76% yield, on the contrary the required β -glucoside (**9**) was obtained (66%) in the absence of *N,N*-tetramethylurea (entry 4). We can not now explain the differences in our results from those of Banoub *et al.*⁶ Although mercury(II) bromide also promoted β -glucosidation, it required longer reaction time (entry 5). The structures of compounds (**9**) and (**10**) were confirmed on the basis of their spectral data.⁷

Glucosidation of (all-*E*)-(3*R*)-3-hydroxy- β -ionylideneacetaldehyde (**15**)⁸ was then carried out (Scheme 2) under optimum conditions as described above. Nevertheless, the desired glucoside (**12**) was obtained only in poor yield. In addition, the isomerization of the 9,10-double bond occurred under the reaction conditions. Thus, the transformation of the ionone-glucoside (**9**) into the ionylideneacetaldehyde-glucoside (**12**) was next examined as shown in Scheme 2. Horner-Emmons reaction of **9** with the cyanophosphonate (**13**) afforded an isomeric mixture (*E* / *Z* ~ 1:1) of the nitrile (**14**) in good yield. However, conversion of **14** into the aldehyde (**12**) by reduction with DIBALH and subsequent benzylation resulted in poor yield, probably due to the formation of organoaluminum complexes with the reducing intermediate. On the other hand, Peterson reaction of **9** with a large excess (8 mol equiv.) of α -triethylsilyl (TES)-imine (**11**)⁹ in the presence of *s*-butyllithium as a base, followed by acid hydrolysis, re-benzylation, and subsequent purification by column chromatography afforded the desired aldehyde (**12**) (*E* / *Z* ~ 5:1) in good yield.



Scheme 2



Scheme 3

The compound (**12**) was then transformed into the β -apo-12'-carotenal (**18**) in 3 steps as shown in Scheme 3. Methanolysis of the tetrabenzoate (**12**) provided the tetraol (**16**) (93%), which was condensed with the Wittig salt (**17**)¹⁰ and then treated with ion-exchange resin, Dowex 50W-X8 (H⁺), to furnish an isomeric mixture of the β -apo-12'-carotenal (**18**) in 69% yield. Finally, **18** was condensed with the Wittig salt (**19**)¹¹ or (**20**)¹² and subsequent purification of the condensed product by preparative HPLC provided (all-*E*)-zeaxanthin- or (all-*E*)-cryptoxanthin- β -D-glucopyranoside (**3**) (43%) or (**4**) (28%) accompanied by some isomers.¹³ The structures of glucosides (**3**) and (**4**) were confirmed by comparison of their spectral data with those of **1**,¹ **2**² and zeaxanthin.¹⁴ The visible absorption spectra of both compounds in ethanol (**3**: 427sh, 450 and 476 nm, **4**: 429sh, 452 and 472 nm) exhibited β,β -carotene type chromophore. In HRMS, **3** showed molecular ion peak at m/z 730.4799 (calcd for C₄₆H₆₆O₇ 730.4804) and **4** at 714.4871 (calcd for C₄₆H₆₆O₆ 714.4856). Their ¹H NMR spectra were quite compatible with those of **1** and **2** respectively, except for the sugar and fatty acid moieties.

This synthesis of the glucosides (**3**) and (**4**) consists of six steps with respective overall yield of 12% and 9% from (3*R*)-3-hydroxy- β -ionone (**6**). Work is in progress on a synthesis of thermozeaxanthins (**1**) and thermocryptoxanthins (**2**).

ACKNOWLEDGMENT

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7. Characteristic data for **9**: $[\alpha]_D^{24}$ -3.99° (*c* 1.00, CHCl₃); IR, 1603 (C=C), 1668 (conj. C=O) and 1732 (OCOPh) cm⁻¹; ¹H NMR (300 MHz), δ 4.03 (1H, m, 3-H), 4.21 (1H, m, 5'-H), 4.53 (1H, dd, *J*=12, 6 Hz, 6'-H), 4.64 (1H, dd, *J*=12, 3 Hz, 6'-H), 4.99 (1H, d, *J*=8 Hz, 1'-H), 5.52 (1H, dd, *J*=10, 8 Hz, 2'-H), 5.64 (1H, t, *J*=10 Hz, 4'-H), 5.93 (1H, t, *J*=10 Hz, 3'-H), 6.00 (1H, d, *J*=16.5 Hz, 8-H) and 7.11 (1H, br d, *J*=16.5 Hz, 7-H); ¹³C NMR (125.7 MHz), δ 164.98, 165.28, 165.82 and 166.07 (OCOPh) and 198.42 (CH₃CO); HRMS calcd for C₄₇H₄₆O₁₁Na (M+Na), 809.295, found *m/z* 809.294; for **10**: $[\alpha]_D^{26}$ -13.74° (*c* 1.02, CHCl₃); IR, 1603 (C=C), 1667 (conj. C=O) and 1725 (OCOPh) cm⁻¹; ¹H NMR (500 MHz), δ 3.71 (1H, m, 3-H), 4.11 (1H, ddd, *J*=8.5, 5, 3, 5'-H), 4.36 (1H, dd, *J*=12, 5 Hz, 6'-H), 4.52 (1H, dd, *J*=12, 3 Hz, 6'-H), 4.79 (1H, ddd, *J*=5.5, 3, 1 Hz, 2'-H), 5.50 (1H, dt, *J*=8.5, 1 Hz, 4'-H), 5.78 (1H, dd, *J*=3, 1 Hz, 3'-H), 6.02 (1H, d, *J*=16 Hz, 8-H), 6.06 (1H, d, *J*=5.5 Hz, 1'-H) and 7.10 (1H, br d, *J*=16 Hz, 7-H); ¹³C NMR (125.7 MHz), δ 121.59 (ortho ester-C), 164.63, 165.17 and 165.97 (OCOPh) and 198.38 (CH₃CO); HRMS calcd for C₄₇H₄₆O₁₁Na (M+Na), 809.294, found *m/z* 809.294.
8. Compound (**15**) was prepared from (3*R*)-3-TBSOxy- β -ionone (**5**)⁴ (Scheme 1) by Peterson reaction with TMS acetonitrile in the presence of LDA, following reduction with DIBALH [(all-*E*)-isomer: 48%; (9*Z*)-isomer: 24%], and subsequent deprotection (quant.) with 48% aqueous HF.
9. α -TES imine (**11**) (bp₅ 75-80°C) was prepared (88%) from *t*-butylimine of acetaldehyde according to the literature; R. H. Schlessinger, M. A. Poss, S. Richardson, and P. Lin, *Tetrahedron Lett.*, 1985, **26**, 2391.
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13. Among minor isomers, one isomer of **4** could be isolated (10%) and be characterized to be (9*Z*)- or (9'*Z*)-isomer by comparison of its ¹H NMR data with those of (9*Z*)- β -carotene.¹⁵ However, other isomers of **3** and **4** could not be separable by HPLC.

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