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

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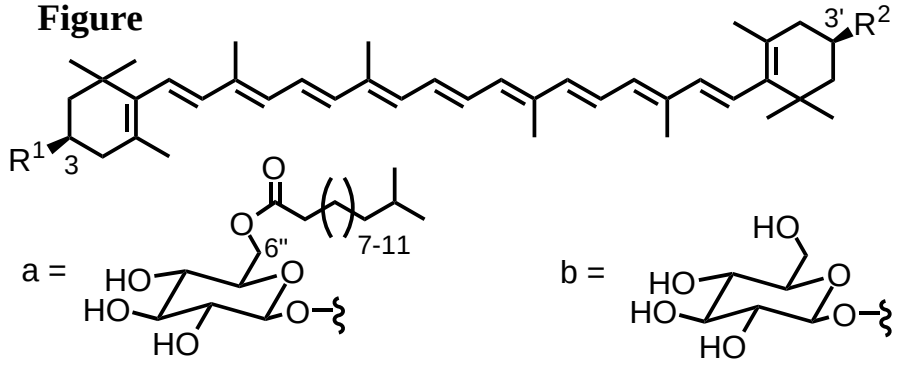
Abstract - β-Glucosidation of (3*R*)-3-hydroxy-β-ionone (**6**) was achieved in a reasonable yield by use of tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**8c**) as a glycosyl donor and silver triflate as an activator. The resulting glucoside (**9**) was transformed into the β-apo-12'-carotenal (**18**), 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

Figure



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

This paper is dedicated to Professor Teruaki Mukaiyama of his 73rd birthday.

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 reported[3] 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 synthesized[4] *tert*-butyldimethylsily (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 phenylselenyl 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.

Scheme 1

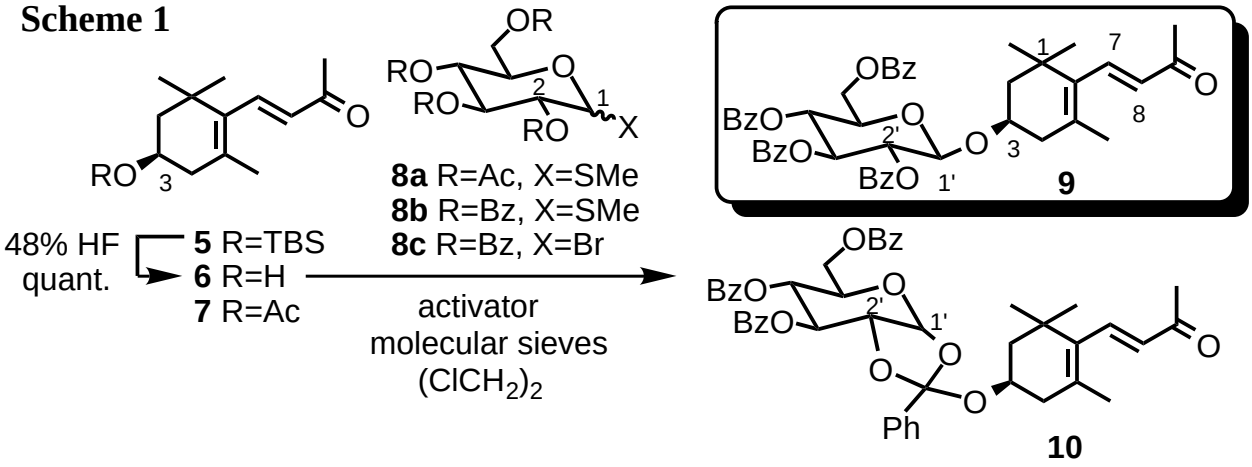
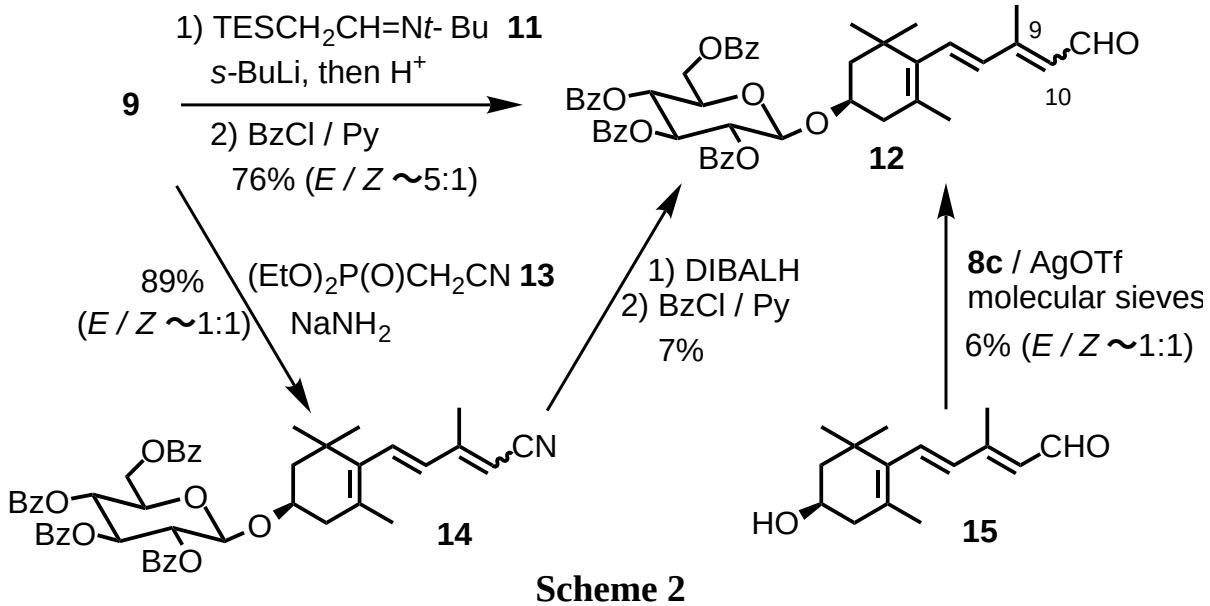


Table Glucosidation of (3*R*)-3-hydroxy-β-ionone (**6**)

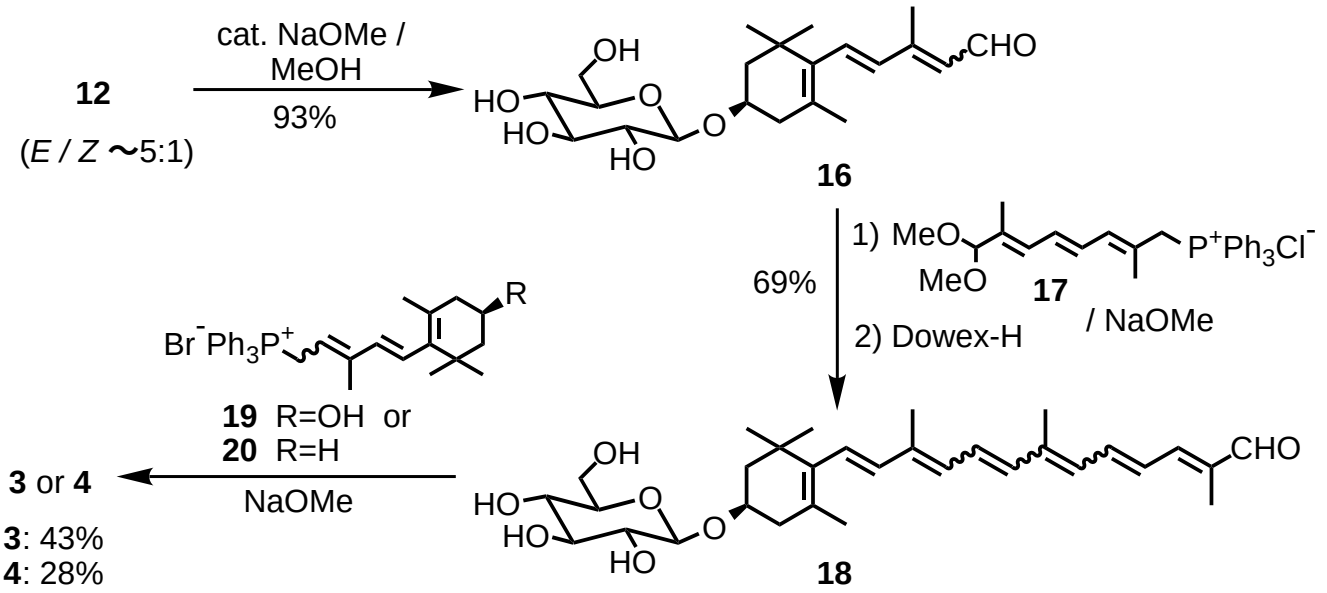
entry	glycosyl donor	activator (eq.)	temp. / time	product	yield (%)
1	**8a**	PhSeOTf (1.4)	0°C / 50 min	**7**	46
2	**8b**	PhSeOTf (1.4)	0°C / 10 h	**9**	27
3	**8c**	AgOTf (2.0) $Me_2NC(O)NMe_2$ (3.0)	0°C / 30 min → rt / 1 h	**10**	76
4	**8c**	AgOTf (2.0)	rt / 1 h	**9**	66
5	**8c**	$HgBr_2$ (2.0)	rt / 15 h	**9**	36

Banoub *et al*. reported[6] 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 thier 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 bound 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 benzoylation 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-benzoylation, 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 $C_{46}H_{66}O_7$ 730.4804) and **4** at 714.4871 (calcd for $C_{46}H_{66}O_6$ 714.4856). Their ^{1}H 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**).

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REFERENCES AND NOTES

1. A. Yokoyama, G. Sandmann, T. Hoshino, K. Adachi, M. Sakai, and Y. Shizuri, *Tetraheron Lett.*, 1995, **36**, 4901.
2. A. Yokoyama, Y. Shizuri, T. Hoshino, and G. Sandmann, *Arch. Microbiol.*, 1996, **165**, 342.
3. H. Pfander and M. Hodler, *Helv. Chim. Acta,* 1974, **57**, 1641.
4. Y. Yamano, C. Tode, and M. Ito, *J. Chem. Soc., Perkin Trans. 1,* 1998, 2569.
5. Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1988, **29**, 1061.
6. J. Banoub and D. R. Bundle, *Can. J. Chem.*, 1979, **57**, 2091.
7. Characteristic data for **9**: $[\alpha]_D^{24}$ -3.99° (*c* 1.00, $CHCl_3$); 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); ^{13}C NMR (125.7 MHz), δ 164.98, 165.28, 165.82 and 166.07 (O*C*OPh) and 198.42 (CH_3*C*O); HRMS calcd for $C_{47}H_{46}O_{11}Na$ (M+Na), 809.295, found m/z 809.294; for **10**: $[\alpha]_D^{26}$ -13.74° (*c* 1.02, $CHCl_3$); 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); ^{13}C NMR (125.7 MHz), δ 121.59 (ortho ester-*C*), 164.63, 165.17 and 165.97 (O*C*OPh) and 198.38 (CH_3*C*O); HRMS calcd for $C_{47}H_{46}O_{11}Na$ (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**) (bp_5 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.
10. K. Bernhard, F. Kienzle, H. Mayer, and R. K. Müller, *Helv. Chim. Acta*, 1980, **63**, 1473.
11. H. Pfander, A. Lachenmeier, and M. Hadorn, *Helv. Chim. Acta*, 1980, **63**, 1377.
12. H. Pommer, *Angew. Chem.*, 1960, **72**, 811.
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.

14. G. Englert, K. Noack, E. A. Broger, E. Glinz, M. Vecchi, and R. Zell, *Helv. Chim. Acta*, 1991, **74**, 969.
15. Y. Yamano, M. Yoshizawa, and M. Ito, *J. Nutr. Sci. Vitaminol.*, 1999, **45**, 49.