Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3524–3526
Tetrahedron Letters

Dicarotenoid esters of bivalent acids

Magdolna Háda, Veronika Nagy, Anikó Takátsy, József Deli, Attila Agócs *

Department of Biochemistry and Medical Chemistry, University of Pécs, Medical School, Szigeti út 12, H-7624 Pécs, Hungary

Received 11 February 2008; revised 6 March 2008; accepted 27 March 2008
Available online 29 March 2008

Abstract

For the evaluation of the synthesis of dendritic esters from carotenoids the C_{20} apocarotenoid retinol was chosen for model studies, being a commercially available hydroxy carotenoid. Dimers were synthesized from retinol with dicarboxyl cores and from retinol succinate with other hydroxy carotenoids.

Keywords: Carotenoid; Retinol; Diester; Dimer

Carotenoids, being naturally occurring antioxidants and having various biological effects including anti-cancer and cardioprotective, have been the focus of food biochemists recently.[1] Dimers and dendrimers of these compounds have not been synthesized until now, although they can have interesting properties especially when combined with the advantages of carotenoids. These compounds may have enchanced antioxidant activity and could be used for aggregation studies.[2] Carotenoid diesters are not unknown in the literature, and there are examples including enzymatic reactions with carotenoid acids[3] and reactions between carotenoid acids and carotenols.[4] However, the chemistry described there cannot be directly applied for the synthesis of the esters described in this Letter.

In our present Letter we describe the synthesis of some retinol dimers and their precursors which can serve as a starting point for further studies with other hydroxy carotenoids and later form a basis for the synthesis of carotenoid dendrimers.

Retinol was chosen as a model compound for other carotenoids being not too expensive and easily accessible (Fig. 1). Other carotenoids were isolated from natural sources or purchased except for 4′-hydroxy-echinenone, which was produced by the partial reduction of canthaxanthin with sodium borohydride.

Our aim was to make dicarotenoid diesters of bivalent acids in which secondary interactions are possible between the two polyene chains. To achieve this, retinol and various other carotenoids were esterified with several cyclic acid anhydrides. The results of these experiments are summarized in Table 1. These anhydrides were chosen after several unsuccessful trials with the corresponding acyl dichlorides. In general, the reactions of carotenoids with acyl chlorides in pyridine or in dichloromethane/pyridine gave several by-products, whereas anhydrides gave cleaner reactions.[5,6]

All of the hydroxyl groups of the carotenoids were esterified with succinic anhydride forming the corresponding mono- and disuccinates bearing free carboxyl groups. Unfortunately, maleic anhydride appeared to be too reactive, whereas phthalic anhydride did not give even the corresponding monoesters.

The retinol succinate monoester formed (**1**) can be coupled with other carotenoid alcohols via the Steglich-method using dicyclohexyl carbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in dichloromethane (Fig. 2).[7] The reaction gave homo- and heterodimers (**2a**–**c**) in good yields, and the conversion of the alcohols was about 70–80%. The dimers could be crystallized from

---

* Corresponding author. Tel.: +36 72 536001x1864; fax: +36 72 536225.
E-mail address: attila.agocs@aok.pte.hu (A. Agócs).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.03.137

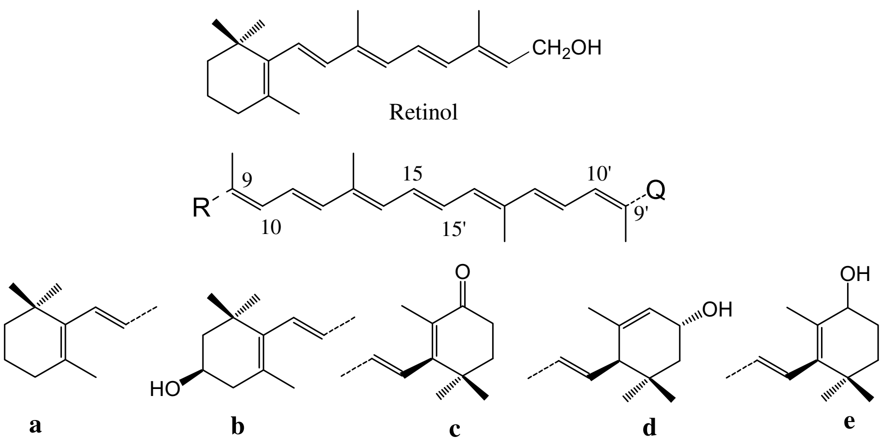

Fig. 1. Structures of the carotenoid starting materials: R = **a**, Q = **b**: β-cryptoxanthin; R = **b**, Q = **d**: lutein; R = Q = **e**: isozeaxanthin; R = **c**, Q = **e**: 4′-hydroxy-echinenone.

Table 1
Esterification of mono- and dihydroxy carotenoids

$$\text{Carotenoid-OH} + 2.5\ \text{eq. anhydride} \xrightarrow[3\ \text{eq. DMAP}]{CH_2Cl_2\text{, r.t.}} \text{Carotenoid mono- or diester}$$

	Retinol	Lutein	Isozeaxanthin	β-Cryptoxanthin	4-Hydroxy-echinenone
Maleic anhydride	Decomp. even at −70 °C	—	Decomp. even at −70 °C	Decomp. even at −70 °C	—
Succinic anhydride	85%	74%	Unstable product	81%	65%
Phthalic anhydride	No reaction	No reaction	No reaction	—	—

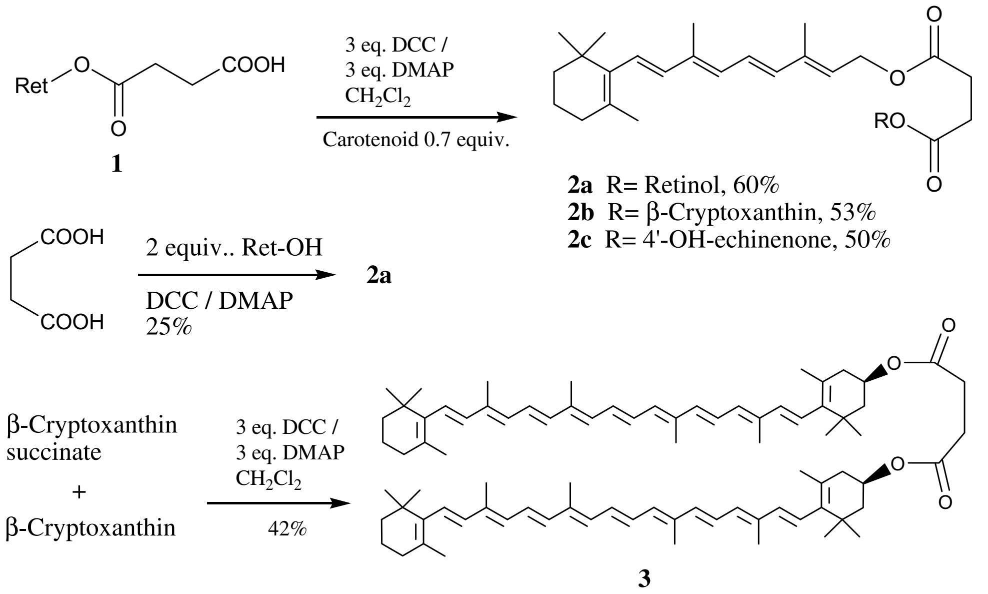

Fig. 2. Synthesis of carotenoid dimers.

methanol in reasonable yields. After the successful trials with retinol, a homodimer of β-cryptoxanthin (**3**) was also synthesized from its succinate. The yield in this case was modest, and the conversion was only 70–80% even if 30% excess succinate was used. The structures of dimers were proven on the basis of NMR, MALDI-TOF, and UV data. The purity of the compounds (>90%) was determined by HPLC.[8]

This method was also tested for the direct synthesis of a retinol homodimer (**2a**, Fig. 2). In this case the diacid (phthalic, maleic, or succinic) was esterified with an excess of retinol in the presence of DCC and DMAP. Maleic and phthalic acids proved to be non-reactive again presumably for steric reasons which suggests that diacids with a larger distance between the two carboxylic acids can serve as appropriate starting materials.

Our results confirm that even a simple reaction such as esterification can have a different outcome among carotenoids, and carotenoids with strong structural resemblance can react rather differently under the same conditions.

The new compounds are to be tested for their in vitro and in vivo antioxidant activity.

Acknowledgments

We thank Mrs. Andrea Bognár, Mrs. Judit Kriszt, and Mr. Norbert Götz for their assistance. This study was supported by *OTKA K 60121* (*Hungarian National Research Foundation*). We also thank *Carotenature* for providing us with a sample of isozeaxanthin.

References and notes

1. Krinsky, N. I.; Johnson, E. J. *Mol. Asp. Med.* **2005**, *26*, 459–516.
2. Simonyi, M.; Bikádi, Z. S.; Zsila, F.; Deli, J. *Chirality* **2003**, *15*, 680–698.
3. Vassilia Partali, V.; Kvittingen, L.; Sliwka, H. R.; Anthonsen, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 329–330.
4. Levy, L. W.; Binnington, R. H.; Tabatznik, A. S., Patent WO/2002/068385, 2002.
5. Frey, D. A.; Kataisto, E. W.; Ekmanis, J. L.; O'Malley, S.; Lockwood, S. F. *Org. Process Res. Dev.* **2004**, *8*, 796–801.
6. Nadolski, G.; Cardonuel, A. J.; Zweier, J. L.; Lockwood, S. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 775–781.
7. Neises, B.; Steglich, W. *Angew. Chem.* **1978**, *90*, 556–557.
8. *Spectroscopic data for dimer* **2b**: UV (hexane): 327 (421), 448 (475); MS (MALDI-TOF) $m/z = 920.6$ (calcd for $C_{64}H_{88}O_4$ 920.67). ^{1}H NMR (400 MHz) δ (ppm) = 0.85–2.1 (m, 62H), 2.63 (m, 4H, CH_2s succ.), 4.77 (d, 2H, H-16 Ret., $J_{16,17} = 7.2$ Hz), 5.08 (m, 1H, H-3′ β-Crypt.), 5.60 (m, 1H, H-17 Ret.), 6.1–6.7 (m, 18H, olefinic protons). ^{13}C NMR (125 MHz) δ (ppm) = 12.8, 19.2, 21.4, 21.7, 25.6, 28.4, 28.9, 29.2, 29.5, 30.0, 30.3, 33.1, 33.7, 34.3, 36.7, 38.3, 39.6, 43.9, 61.5, 68.8, 124.3, 125.8, 127.0, 129.3, 129.6–130.2 (m), 130.7, 131.4, 132.3, 133.1, 135.7, 136.6, 137.5–138 (m), 138.6, 139.2, 171.9, 172.2. Anal. Calcd for $C_{64}H_{88}O_4$: C, 83.43; H, 9.63; O, 6.95%. Found: C, 83.48; H, 9.60; O, 6.94%.