Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6867-6868, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01442-6

A Convergent Synthesis of Symmetrical Carotenoids Using the Heck Reaction

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***Key words** : Heck vinylation, Palladium, Carotenoids, β-Carotene.*

***Abstract** : Regioselective Heck-type vinylation of various allylic alcohols with* **2**, *followed by an acidic dehydration, delivers symmetrical carotenoids in good yields.*

Carotenoids display a wide range of uses, from natural dyes and cosmetic additives, to food and feed supplements, owing to their antioxydant properties and pro-vitamin A activity (for β-carotene)[1]. As we believe that catalytic organometallic synthesis is a powerful tool for the preparation of such interesting polyenes[2], we would like to disclose here a short, convenient and general route to various carotenoids.

Our synthetic approach to symmetrical carotenoids features a palladium-catalysed coupling (Heck reaction) between a central bis-vinylic halogenide fragment (**2**, actually a C_{10} di-cation equivalent) and two tertiary allylic alcohols[3], followed by an acidic dehydration (Scheme I). This method makes a highly convergent (C_{15} + C_{10} + C_{15}) synthesis of β-carotene possible, by starting from the inexpensive vinyl-β-ionol.

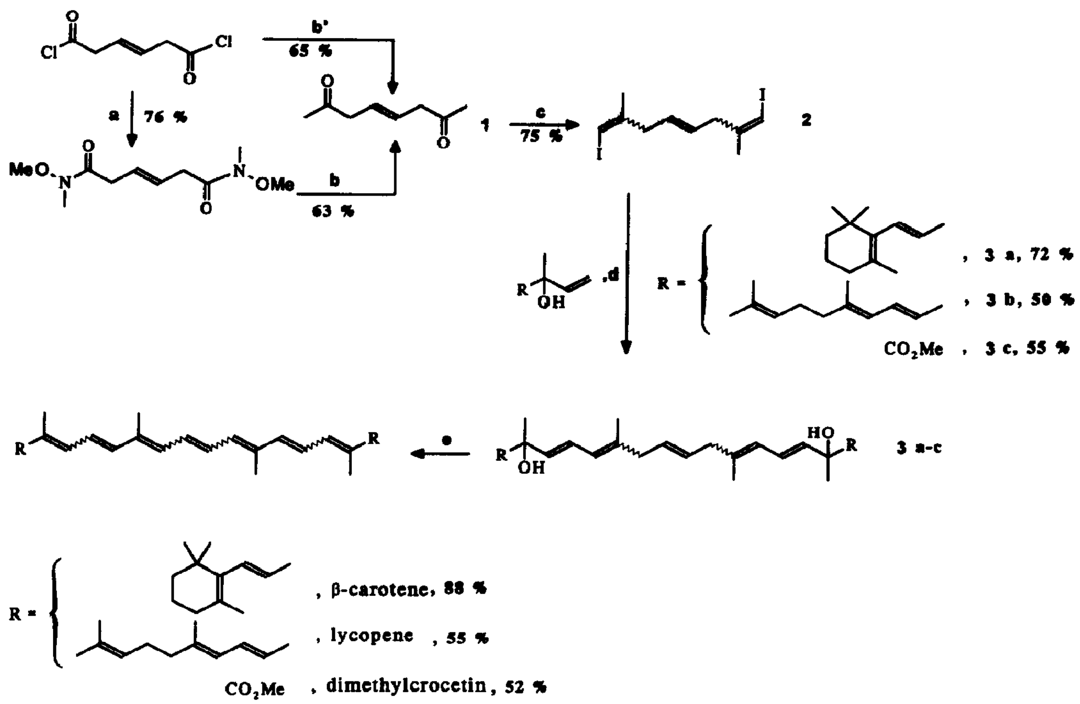
4-Octene-2,7-dione **1** is readily prepared from hexenedioic acid dichloride by methylation with methylzinc iodide[4] or using Weinreb's ketone synthesis[5]. Bis-iodomethylenation of this base sensitive diketone with the iodoform / chromium (II) chloride couple[6], neatly produces the key central component 1,8-diiodo-2,7-dimethyl-1,4,7-octatriene **2** as a mixture of E/Z isomers.

Coupling this bis-vinylic iodide with vinyl-β-ionol is best accomplished with the silver assisted version of the Heck reaction[7], to give diol **3a** regioselectively in good yield[8].

Finally, this very sensitive diol is smoothly dehydrated in the presence of a catalytic amount of hydrobromic acid[9]. β-carotene thus obtained, is a mixture of stereoisomers (approximately E/Z = 70/30 for each trisubstituted double bond) which can easily be isomerized into the valuable all-trans isomer[1a, 10].

A similar reaction sequence starting from vinyl-ψ-ionol or 2-hydroxy-2-methyl-3-butenoic acid methyl ester delivers the natural carotenoids lycopene and dimethylcrocetin respectively, both in reasonable yields.

Scheme I



a) MeONHMe : HCl, Pyr, Et_2O. b) MeMgBr (4 eq.), THF, 0°C. b') see ref. 3. c) CHI_3 (3 eq.), $CrCl_2$ (14 eq.), THF, 25°C. d) $Pd(OAc)_2$ (0,05 eq.), Ag_2CO_3 (1 eq.), allylic alcohol (6 eq.), DMF, 50°C. e) HBr (0,3 eq.), acetone, 0°C.

Acknowledgments

We would like to thank the analytical service at CRIT-C, and Rhône-Poulenc for permission to publish these results

References

1. a) Isler, O. *"Carotenoids"*, Birkhäuser Verlag. Basel, 1971. b) Straub, O. *"Key to carotenoids"*, Birkhäuser Verlag, Basel, 1987. c) Ullmann *"Encycl. Techn. Chem."* **1983**, *23*, 621-638.
2. Bienayme, H.; Yezeguelian, C. *Tetrahedron*, **1994**, *50*, 3389-96.
3. See : Duhamel, L.; Duhamel, P.;Ancel, J.E. *Tetrahedron Lett.* **1994**, *35*, 1209-10.
4. Kabbe, H.-J.; Truscheit, E.; Eiter, K. *Liebigs Ann. Chem.* **1965**, *684*, 14-24.
5. Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, *22*, 3815-18.
6. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-10.
7. Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133-36 Jeffery, T. *J. Chem. Soc. Chem. Commun.* **1991**, 324-325.
8. Correct analysis, including ^1H and ^{13}C NMR, IR, MS and HRMS were obtained for all new compounds.
9. Surmatis, J.D.; Gibas, J.; Thommen, R. *J. Org. Chem.* **1969**, *34*, 3039-41. Milas, N.A.; Davis, P.; Belic, I.; Fles, D.A. *J. Am. Chem. Soc.* **1950**, *72*, 4844.
10. Isler, O.; Lindlar, H.; Montavon, M.; Rüegg, R.; Zeller, P. *Helv. Chim. Acta*, **1956**, *39*, 249-259. Inhoffen, M.H.; Bohlmann, F.; Bartram, K.; Rummert, G.; Pommer, H. *Ann.* **1950**, *570*, 54-69.

(*Received in France* 16 *May* 1994; *accepted* 22 *July* 1994)