87. Technical Procedures for the Syntheses of Carotenoids and Related Compounds from 6-Oxo-isophorone: Syntheses of (3*R*,3'*R*)-Zeaxanthin

Part I

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Dedicated to Dr. *Otto Isler* on the occasion of his 80th birthday

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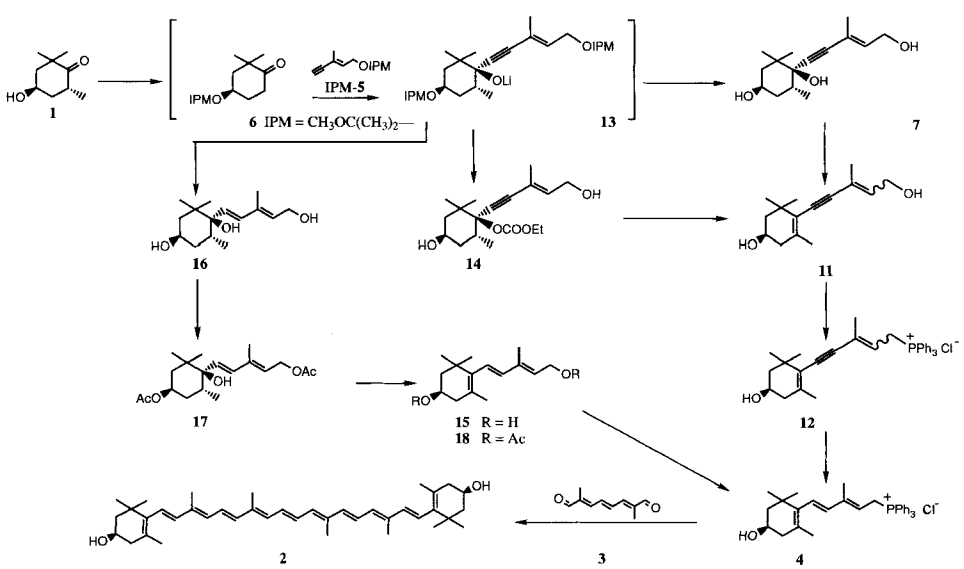
Starting from the readily available, optically active (4*R*)-4-hydroxy-2,2,6-trimethylcyclohexanone (**1**), a new technical synthesis of (3*R*,3'*R*)-zeaxanthin is described. According to a $2(C_9 + C_6) + C_{10} = C_{40}$ construction scheme, the ketone **1** was first transformed with (*E*)-3-methylpent-2-en-4-yn-1-ol (**5**) into a C_{15}-intermediate which, by a three-step sequence, could be converted into the known olefinic C_{15}-*Wittig* salt **4**. Optimized conditions for the final *Wittig* reaction of **4** with the C_{10}-dialdehyde **3** are discussed. Based on **1**, the overall yield of the entire technical process is *ca.* 40%.

1. Introduction. – In [1], we described a new synthesis of the chiral hydroxy-ketone **1** which can now be produced on an industrial scale. Having this interesting intermediate in hand, our next target was the development of a technically feasible synthesis of (3*R*,3'*R*)-zeaxanthin (**2**). In the past, various approaches to **2** have been published [2–18], but, for practical reasons, we adopted a concept which had already proved successful in the

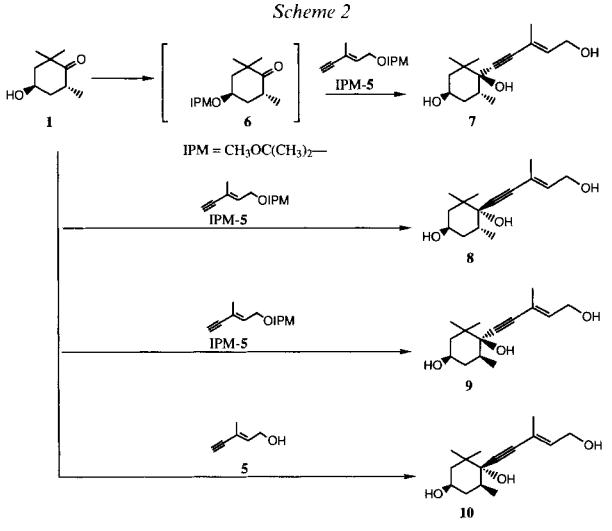
Scheme 1



technical syntheses of other C_{40}-carotenoids [19]. Accordingly, in the final step, the carotenoid is procured by a double *Wittig* reaction of the C_{10}-dialdehyde **3** [20] with the C_{15}-phosphonium salt **4** [11] [16] [21–23] which was obtained from the optically active hydroxy-ketone **1** (C_9-building block) and the vitamin-A intermediate, (*E*)-3-methylpent-2-en-4-yn-1-ol (**5**; a C_6-building block [24]). We now delineate in detail this approach to the C_{15}-*Wittig* salt **4** from **1** *(Scheme 1)* as well as the subsequent *Wittig* reaction which leads to the nature-identical zeaxanthin (**2**). In the following publication [22], we report a completely new access to the *Wittig* salt **4** starting again from **1** but using a new $C_9 + C_2 + C_4$ building scheme.

2. Results and Discussion. – The OH group in **1** was protected as a ketal through reaction with isopropenyl methyl ether. The resulting THF solution of IPM-protected **6** was then treated with the Li salt of IPM-protected (*E*)-3-methylpent-2-en-4-yn-1-ol IPM-**5** [24]. After an acidic workup, the crude triol **7** was obtained in almost quantitative yield *(Scheme 1)*. From the crude material, we were also able to isolate *ca.* 3% of the C(6)-diastereoisomer **8** [25] *(Scheme 2)*. For the synthesis, the separation of **7** and **8** was not necessary, since, in the subsequent step, both isomers could be dehydrated under the same conditions to give an identical product. A detailed investigation of the alkynylation step revealed that BuLi was the most suitable base for the deprotonation of IPM-**5**. Other bases such as EtMgBr, $LiNH_2$, $NaNH_2$, *t*-BuOK, MeONa, and KOH were less efficient.

Scheme 2



The variation of the reaction conditions as well as the form of protection of the starting materials allowed us finally to determine the conditions for the selective preparation of the four possible diastereoisomers of **7** *(Scheme 2)*. Thus, alkynylation of unprotected **1** with 2 equiv. of the Li salt of IPM-**5** yielded the C(6)-isomer **8** [25] in *ca.* 86% yield. On the other hand, treatment of **1** with IPM-**5** in THF using KOH as a base gave the isomer **9** in 81% yield, because, under these conditions, the Me group at C(5) [25] in **1** epimerized rapidly [1]. In contrast, under the same conditions, the use of the unprotected **5** led to the new isomer **10** in 70% yield.

In the following step, the dehydration of crude **7** in a two-phase system (*e.g.* 1,2-dichloroethane/aqueous HCl or H_2SO_4) gave the diol **11** in *ca.* 85% yield. In the course of this dehydration, the acid-labile (9*E*)-configurated C=C bond partially isomerized giving rise to a mixture of the (9*E*)- and the (9*Z*)-diols **11** in a ratio of *ca.* 85:15. No reaction conditions could be found to prevent this isomerization. In particular, prolonged reaction times, higher temperatures, or concentrated acids promoted the formation of the (9*Z*)-isomer. Since the (9*E*/*Z*)-diols **11** were not particularly stable, purification was not easy on a technical scale, and the crude dehydration product was converted directly into the acetylenic (9*E*/*Z*)-*Wittig* salt **12** by reaction with HCl and Ph_3P under standard conditions (*ca.* 80% yield based on **7**). As expected from previous findings [16] [19], the mixture **12** could easily be purified by crystallization.

The partial hydrogenation of the C≡C bond in **12** proved to be the most critical step of the synthesis. The pure (9*E*)-*Wittig* salt **12** could be cleanly reduced to the (9*E*)-salt **4** in 75% yield [26] using either *Raney*-Ni or *Lindlar* catalyst. Significant from the technical point of view was the fact that the catalyst could be easily recovered and recycled in this case. However, hydrogenation of the (9*Z*)-isomer of **12** was very slow, less selective, and eventually it led to poisoning of the catalyst. According to these results, the pure (9*E*)-**12** had to be isolated by careful crystallization from the (9*E*/*Z*)-mixture **12**. Thereby, the overall yield of the dehydration and *Wittig*-salt formation sequence was only 58% compared to 80% for the (9*E*/*Z*)-mixture **12**. The partial hydrogenation of (9*E*)-**12** yielded (7*Z*,9*E*)-**4** as expected, but this could be isomerized with catalytic amounts of $Pd(OAc)_2$ in boiling MeOH to the isomerically pure (7*E*,9*E*)-**4** in an overall yield of *ca.* 75% from (9*E*)-**12**. The pathway described above leads to the known *Wittig* salt **4** in *ca.* 43% overall yield from ketone **1**.

In the course of our investigation of the $C_9 + C_6$ approach, we evaluated additionally the following three variations. In the first case, we attempted to avoid (9*E*) → (9*Z*) isomerization in the side chain of **7** so as to prevent the formation of the undesired (9*Z*)-acetylenic *Wittig* salt **12**. Since this could not be achieved by simply modifying the conditions for the acidic dehydration of the triol **7**, we developed a new dehydration method [27]. Accordingly, the intermediate Li-alcoholate **13** was treated sequentially with ethyl chloroformate and pyridinium tosylate to generate the tertiary carbonate **14** in virtually quantitative yield. Direct treatment of the crude **14** with 2 equiv. of *t*-BuOLi [27] in toluene/hexane (1:1) for 5 min at 70° led to (9*E*)-**11** in 90% overall yield from **1**. GLC analysis indicated that the crude product **11** contained less than 1% of the unwanted (9*Z*)-isomer **11**. Conversion of **11** into the corresponding allylic halide or (9*E*)-*Wittig* salt **12** was difficult to accomplish without affecting the unprotected secondary OH group or isomerizing the (9*E*)-configurated C=C bond. Acidic conditions (HCl, HBr, or HCl/Ph_3P) induced isomerization of the (9*E*)-configurated C=C bond and gave rise to a (*E*/*Z*)-mixture (85:15) of isomers. The only reagent which demonstrated adequate selectivity was $Ph_3P \cdot Cl_2$/*sym*-collidine in CH_2Cl_2. However, after treatment with Ph_3P, the purity and the overall yield of the resulting *Wittig* salt (9*E*)-**12** turned out to be too insufficient to warrant any further investigation of this approach.

In the second case, we tried to overcome the difficulties encountered with **12** by effecting partial hydrogenation of the (9*E*/*Z*)-diol **11** instead, but yet no conditions could be found to give the (7*Z*,9*E*/*Z*)-olefinic diol **15** in higher than 40% yield.

In the third case, attempts were made to replace *Lindlar* hydrogenation by a reduction with a complex hydride reagent. With *Vitride* for example, propargyl alcohols have been successfully reduced to allyl alcohols. In contrast to the procedures described in the literature, we directly reduced the intermediate **13**, prepared *in situ* [28], instead of the free alcohol. Thus, the addition of the Li salt of IPM-**5** to the IPM-ketone **6** followed by treatment of the reaction mixture with 1.5 equiv. of *Vitride* at –10° afforded the olefinic triol **16**, after an acidic workup, in *ca.* 75% overall yield from **1**. Dehydration of **16** to the diol **15** was unsuccessful due to poor stability of both **15** and **16**. Only the diacetate **17** (*ex* **16**) could be dehydrated to **18** in *ca.* 40% yield by treatment with $KHSO_4$ in boiling toluene; other acids were even less efficient. A partial breakthrough was finally achieved with a completely new catalytic dehydration system [29] consisting of 5 mol-% of $MgBr_2$ or $CaBr_2$ in boiling acetone or better in isopropenyl acetate. Yields of up to 80% were attained, but, due to its instability, diacetate **18** was directly saponified to the diol **15** and further transformed into the *Wittig* salt **4**. After purification, only a 40–60% yield of **4** was obtained and as a consequence, this approach also was discontinued.

The initially described pathway **1** → **7** → **12** → **4** allowed the preparation of the olefinic *Wittig* salt **4** in *ca.* 43% overall yield from **1**. Careful optimization of the economically important, final double *Wittig* reaction was essential. Using 1,2-epoxybutane as an acid scavenger in boiling EtOH with only 2.05 equiv. of **4**, an excellent yield of 90% of (all-*trans*)-zeaxanthin (**2**) could be achieved. When the *Wittig* reaction was carried out with the mixture of isomers (7*E*,9*E*/*Z*)-**4**, the yield drastically dropped to *ca.* 75%, but only to *ca.* 85%, if 1–5 mol-% of $Pd(OAc)_2$ was added to the reaction mixture.

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Experimental Part

General. See [30].

1. *Preparation of (3*R,*3'*R*)-Zeaxanthin* (**2**). A soln. of phosphonium salt **4** (0.50 kg, 0.97 mol), 2,7-dimethyl-octa-2,4,6-trienedial (**3** [20]; 0.077 kg, 0.47 mol) and 1,2-epoxybutane (0.34 l, 3.9 mol) in EtOH (1.3 l) was stirred at reflux for 20 h. The suspension was cooled to –10° and the product was filtered, washed with EtOH (1.5 l, –15°), and recrystallized by gradual solvent exchange from $CHCl_3$ (7.5 l containing 1% of Et_3N) to EtOH (10 l) (by distillation at normal pressure). The suspension was refluxed for 1 h, cooled to r.t., filtered, and the product was washed with EtOH (2 l) and dried at 60°/0.1 mm for 3 days: 249 g of **2** (90% from **4**, 93% from **3**). M.p. 207–208°. HPLC: > 99% (all-*E*)-isomer. UV ($CHCl_3$): 462 (2298). The IR, ^{1}H-NMR, and MS data were identical with those already published [11] [16] [31] [32].

2. *Preparation of {(2*E,*4*E*)-5-[(*R*)-4-Hydroxy-2,6,6-trimethylcyclohex-1-enyl]-3-methylpenta-2,4-dienyl}-triphenylphosphonium Chloride* (**4**). A slurry of *Raney*-Ni (93 g; *Degussa*, type *B 113 W*) and 1,2-bis(2-hydroxy-ethylthio)ethane (1.03 g) in MeOH (1 l) was deoxygenated by repeated evacuation/hydrogenation. The phosphonium salt (9*E*)-**12** (320 g, 0.613 mol) in MeOH (2.1 l) was added, and hydrogenation was carried out at ambient temp. and pressure. After 2 h, H_2 take-up had ceased, and the catalyst was removed by filtration and washed with MeOH (0.5 l). $Pd(OAc)_2$ (0.32 g) was added to the filtrate and the mixture stirred for 4 h at 65° under Ar. The mixture was evaporated at 45°/15 mm and dry MeOH (182 ml) was added followed by AcOEt (4 l). Additional AcOEt (6 l) was slowly added over 2 h, leading to the crystallization of the product. After 3 h, the suspension was filtered, and the product was washed with AcOEt/MeOH (0.5 l; 97:3) and dried at 60°/0.01 mm for 48 h: 239 g (75%) of (7*E*,9*E*)-**4**. M.p. 200–201°. $[\alpha]_D^{20} = -58.5$ ($c = 1$, $CHCl_3$). HPLC: 99.3%. Combustion analysis of metal

traces (in ppm): Pd(41), Ni(265), Zn(16). *Data of* **4**. IR: 3477*s*, 3425*s*, 1585*w*, 1434*w*, 1438*s*, 1112*s*. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.99 (*s*, 6 H); 1.41 (*d*, *J* = 4, 3 H); 1.62 (*s*, 3 H); 1.80–2.50 (*m*, 4 H); 2.78 (br. *s*, 1 H); 3.75–4.05 (*m*, 1 H); 4.80 (2*d*, *J* = 8, 2 H); 5.15–5.60 (*q*, *J* = 8, 1 H); 5.85, 6.07 (2*d*, *J* = 18, 2 H); 7.50–8.20 (*m*, 15 H). Anal. calc. for $C_{33}H_{38}OClP \cdot X$ MeOH · Y H_2O: C 75.94, H 7.50, Cl 6.73; found: C 75.75, H 7.52, Cl 6.95.

*Data of (7Z,9E)-***4**. M.p. 2.10–2°. IR: 3320*s*, 3265*s*, 1590*w*, 1484*w*, 1440*s*, 1118*s*, 760*s*, 752*s*, 742*s*, 697*s*. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.94 (*s*, 6 H); 1.35 (*s*, 3 H); 1.48 (*d*, *J* = 4, 3 H); 1.65–2.30 (*m*, 4 H); 2.88 (br. *s*, 1 H); 3.75–4.20 (*m*, 1 H); 4.78 (2*d*, *J* = 8, 2 H); 5.30–5.65 (*q*, *J* = 8, 1 H); 5.65, 5.93 (2*d*, *J* = 13, 2 H); 7.50–8.25 (*m*, 15 H). Anal. calc. for $C_{33}H_{38}ClOP \cdot 0.3$ AcOEt · 0.05 CH_2Cl_2 (547.77): C 75.10, H 7.45, Cl 7.12; found: C 75.14, H 7.34, Cl 7.15.

3. *Preparation of the Triols* 7, **8**, **9**, *and* **10** *from* **1**. 3.1. *Preparation of IPM-Ketone* **6** *from* **1**. Isopropenyl methyl ether (0.48 kg, 5.14 mol) was added slowly to a soln. of **1** [1] (0.52 kg, 3.3 mol) and TsOH (0.5 g) in THF (0.5 l) at 15°. After 1 h, the reaction was quenched by the addition of Et_3N (1 ml). The soln. was directly used in the preparation of **7** *(Exper. 3.2)*.

3.2. *Preparation of (1S,4R,6R)-1-[(E)-5-Hydroxy-3-methylpent-3-en-1-ynyl]-2,2,6-trimethylcyclohexane-1,4-diol* (**7**). BuLi (2.8 l, 4.5 mol) was slowly added to a soln. of IPM-**5** [24] [30] (4.7 mol) in THF (0.5 l) at −15°. To this mixture, the soln. of **6** (from *Exper. 3.1*) was added over 30 min at the same temp. The mixture was stirred for 4 h at r.t., cooled again to −15°, and the intermediate **13** was hydrolyzed by the careful addition of 10% H_2SO_4 (1.5 l), followed by stirring at r.t. overnight. The product was extracted with AcOEt (3 l), the org. phase was washed with dil. $NaHCO_3$ soln. (3 l) and concentrated to a volume of 2.5 l, whereby the product began to crystallize. The solvent was exchanged by addition of toluene under distillation, and the crystalline product was isolated at r.t. and dried at 50°/1 mm: 0.80 kg (95%) of **7**. The product contained 3% of **8** (see *Exper. 3.3*). M.p. 126–128°. GLC: 99%. $[\alpha]_D^{20} = -19.2$ (*c* = 1.0, dioxane). TLC (Et_2O): R_f 0.21 for **7**. GLC (5% *SE-30*): t_R 20.2 min for **7**. IR: 3396*s*, 2220*w*, 1390*w*, 1380*w*, 1368*w*, 1358*w*, 1036*w*, 1010*w*. ^{1}H-NMR (220 MHz, (D_6)DMSO): 0.95 (*d*, *J* = 6, 3 H); 1.00, 1.10 (2*s*, 6 H); 1.35–1.90 (*m*, 4 H); 1.72 (*d*, *J* = 1, 3 H); 1.80–2.30 (*m*, 1 H); 3.65–3.85 (*m*, 1 H); 4.00 (*dd*, *J* = 6, 6, 2 H); 4.20 (*d*, *J* = 3, 1 H); 4.60 (*t*, *J* = 6, 1 H); 4.72 (*s*, 1 H); 5.77 (*td*, *J* = 6, 2, 1 H). MS.: 252 (14, M^+), 234 (8), 166 (100), 148 (96). Anal. calc. for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found: C 71.26, H 9.76.

3.3. *Preparation of (1R,4R,6R)-1-[(E)-5-Hydroxy-3-methylpent-3-en-1-ynyl]-2,2,6-trimethylcyclohexane-1,4-diol* (**8**). To a soln. of IPM-**5** [24] [30] (0.44 mol) in THF (200 ml) at −10° was slowly added BuLi (284 ml, 0.44 mol) followed by **1** (31.2 g, 0.20 mol) in THF (200 ml). After 3 h at r.t., the intermediate was hydrolyzed with 3N H_2SO_4 (200 ml) in acetone (20 ml) for 1.5 h at r.t. Extraction with AcO(i-Pr), evaporation, and two crystallizations from $(i\text{-Pr})_2O$/hexane (250 ml, 4:1) gave a mixture **8**/**7** (43.6 g, 86%) with a ratio of 85:15. Two further crystallizations from the same solvents system led finally to the pure **8**: 14.3 g (28%). M.p. 129–130°. $[\alpha]_D^{20} = -28.2$ (*c* = 1, dioxane). IR: 3388*s*, 2224*w*, 1384*m*, 1361*m*, 1097*s*, 1079*s*, 1027*m*, 1006*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.95, 1.18 (2*s*, 6 H); 1.00 (*d*, *J* = 6, 3 H); 1.25–1.82 (*m*, 4 H); 1.75 (*d*, *J* = 1.5, 3 H); 1.90–2.85 (*m*, 1 H); 3.72–3.90 (*m*, 1 H); 4.05 (*dd*, *J* = 6, 6, 2 H); 4.20 (*d*, *J* = 2.5, 1 H); 4.65 (*s*, 1 H); 4.68 (*t*, *J* = 6, 1 H); 5.82 (*td*, *J* = 6, 1.5, 1 H). MS: 252 (14, M^+), 234 (8), 166 (100), 148 (96). Anal. calc. for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found: C 71.35, H 9.66.

3.4. *Preparation of (1S,4R,6S)-1-[(E)-5-Hydroxy-3-methylpent-3-en-1-ynyl)-2,2,6-trimethylcyclohexane-1,4-diol* (**9**). IPM-**5** [24] [30] (113.9 g, 0.65 mol) was slowly added to a well-stirred slurry of KOH powder (109.4 g, 1.95 mol) in THF (525 ml) at 0°. After 20 min, a soln. of **1** (78.1 g, 0.50 mol) in THF (100 ml) was added over 15 min. The mixture was stirred at r.t. for 22 h and treated with 3N H_2SO_4 (750 ml) at 0°. The product was extracted with AcO(i-Pr) (1.5 l), and upon subsequent concentration, the residue recrystallized from AcO(i-Pr) (800 ml) at −10°: 102.2 g (81%) of pure **9**. M.p. 121–122°. $[\alpha]_D^{20} = +23.5$ (*c* = 1, dioxane). IR: 3370*s*, 2230*w*, 1385*m*, 1370*m*, 1030*s*, 980*s*, ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.00 (*d*, *J* = 6); 1.00 (*s*, 6 H); 1.10–1.55 (*m*, 3 H); 1.73 (*d*, *J* = 1, 3 H); 1.80–2.20 (*m*, 1 H); 3.30–3.75 (*m*, 1 H); 4.00 (*dd*, *J* = 6, 6, 2 H); 4.21 (*d*, *J* = 5, 1 H); 4.63 (*t*, *J* = 6, 1 H); 4.67 (*s*, 1 H), 5.77 (*td*, *J* = 6, 2, 2 H). MS: 252 (12, M^+), 234 (7), 166 (100), 148 (86). Anal. calc. for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found: C 71.55, H 9.69.

3.5. *Preparation of (1R,4R,6S)-1-[(E)-5-Hydroxy-3-methylpent-3-en-1-ynyl]-2,2,6-trimethylcyclohexane-1,4-diol* (**10**). *3-Methylpent-2-en-4-ynol* (**5**) [24] (12.6 g, 0.13 mol) was added to a well-stirred slurry of KOH powder (65.6 g, 1.17 mol) in THF (70 ml) at −10°. After 10 min, a soln. of **1** (15.6 g, 0.10 mol) in THF (20 ml) was added over 20 min. After 2 h at r.t., the mixture was cooled to −20° and treated carefully with H_2O (100 ml) at 5°. The product was extracted with AcO(i-Pr) (600 ml), the extract evaporated, and the residue crystallized from EtOH (20 ml) and $(i\text{-Pr})_2O$ (100 ml) at −18°: 17.8 g (70%) of pure **10**. M.p. 148–149°. $[\alpha]_D^{20} = +24.7$ (*c* = 1, dioxane). IR: 3370*s*, 2220*w*, 1390*m*, 1370*m*, 1034*s*, 984*s*. ^{1}H-NMR (80 MHz, (D_6)DMSO): 0.98 (*d*, *J* = 6, 3 H); 0.93, 1.00 (2*s*, 6 H); 1.10–1.90 (*m*, 4 H); 1.87 (*d*, *J* = 1, 3 H); 1.90–2.25 (*m*, 1 H); 3.35–3.85 (*m*, 1 H); 4.01 (*dd*, *J* = 6, 6, 2 H); 4.31 (*d*, *J* = 5, 1 H); 4.66 (*t*, *J* = 6, 1 H); 4.80 (*s*, 1 H); 5.81 (*td*, *J* = 6, 2, 1 H). MS: (252, M^+), 234 (15), 166 (100), 148 (96). Anal. calc. for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found: C 71.42, H 9.93.

4. *Preparation of (*R*)-4-[(*E/Z*)-5-Hydroxy-3-methylpent-3-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enol (E/Z-***11***).* A mixture of **7** (0.77 kg, 3.05 mol) in 1,2-dichloroethane (3.85 l) and 0.1N HCl (3 l) was stirred intensively at 70° for 6–8 h. The mixture was cooled to 50°, when GLC revealed the reaction had proceeded with 85% conversion (with 15% of unreacted **7** remaining). The phases were separated at 50°, the aq. phase was extracted with 1,2-dichloroethane (1 l), and the combined org. extracts were directly used for the preparation of **12** *(Exper. 5)*.

*Isolation of Pure (*E*)-***11***.* An aliquot of the above 1,2-dichloroethane soln. was evaporated and the residue crystallized repeatedly from $(i\text{-}Pr)_2O$ at −20° to yield pure (9*E*)-**11**. M.p. 92–3°. TLC (Et_2O): R_f 0.44. GLC (5% *SE-30*): t_R 19.2 for (*E*)-**11**. $[\alpha]_D^{20} = -105.4$ (*c* = 0.5, dioxane). IR: 3298*s*, 2187*w*, 1613*m*, 1370*m*, 1361*m*, 1056*s*, 1006*s*. ^{1}H-NMR (220 MHz, $CDCl_3$): 1.10, 1.14 (2*s*, 6 H); 1.20–2.20 (*m*, 4 H); 1.82 (2*s*, 6 H); 3.50–3.90 (*m*, 1 H); 3.90–4.20 (*m*, 2 H); 4.60 (*d*, *J* = 4, 1 H); 4.63 (*t*, *J* = 6, 1 H); 5.85 (*td*, *J* = 1.5, 1 H). MS: 234 (100, M^+), 201 (39), 183 (10), 173 (25), 105 (34), 91 (34). Analy. calc. for $C_{15}H_{22}O_2$ (234.34): C 76.88, H 9.46; found: C 76.63, H 9.56.

5. *Preparation {(*E*)-5-[(*R*)-4-Hydroxy-2,6,6-trimethylcyclohex-1-enyl]-3-methylpent-2-en-4-ynyl}triphenylphosphonium Chloride ((*E*)-***12***).* The 1,2-dichloroethane soln. obtained from the preparation of the crude **11** *(Exper. 4)* was cooled to −5° and stirred intensively with conc. HCl (1.3 l) at −2° for 30 min. H_2O (1.5 l) and ice (1.5 kg) were added to dark violet mixture. The aq. phase was separated and extracted with 1,2-dichloroethane (3 l), and the combined org. extracts were washed three times with ice-water (2 l) and immediately transferred to a 10-l round-bottom flask. After the addition of Ph_3P (0.97 kg, 3.7 mol) and Na_2SO_4 (1.0 kg), the slurry was concentrated under reduced pressure at 30° to a volume of *ca.* 6 l and filtered. The filtrate was stirred for 16 h at r.t., and the precipitated product was filtered, washed with 1,2-dichloroethane (3 l, −15°), and dried at 75° for 20 h: 0.926 kg (58%) isomerically pure (*E*)-**12**. M.p. 195–196°.

Evaporation of the mother liquid yielded virtually pure (*Z*)-**12**. *Data of (*E*)-***12***.* M.p. 197–99°. $[\alpha]_D^{20} = -49{,}1$ (*c* = 1, $CHCl_3$). TLC (AcOBu/HCO_2/H_2O 40:9:1): R_f 0.40 for **12**. IR: 3414*s*, 2796*m*, 2183w, 1614*w*, 1586*w*, 1484*w*, 1374*w*, 1360w, 1113*s*, 1058*m*. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.00, 1.02 (2s, 6 H); 1.32 (*d*, *J* = 12, 1 H); 1.50–2.20 (*m*, 9 H); with 1.55 (*d*, *J* = 4), 1.75 (*s*); 3.50–4.00 (*m*, 1 H); 4.70 (*dd*, *J* = 16, 7, 2 H); 4.65 (*d*, *J* = 5, 1 H); 5.40–5.80 (*m*, 1 H); 7.70–8.20 (*m*, 15 H). Anal. calc. for $C_{33}H_{36}ClOP \cdot 0.25\ CH_2Cl_2 \cdot 0.25\ CH_2Cl_2$ (515.08): C 74.48, H 6.86, Cl 9.92; found: C 74.47 H 6.87, Cl 9.43.

*Data of (7*E*,9*Z*)-***12***.* M.p. 197–8°. TLC (AcOBu/HCO_2H/H_2O 40:9:1). R_f 0.35. $[\alpha]_D^{20} = -45.7$ (*c* = 1, EtOH). HPLC: 99.6%. IR: 3392*s*, 2764*w*, 2181*w*, 1611*w*, 1586*w*, 1484*w*, 1373*w*, 1358*w*, 1113*s*, 1056*s*. ^{1}H-NMR. (250 MHz, $CDCl_3$): 0.92, 0.95 (2*s*, 6 H); 1.30 (br. *d*, *J* = 11, 1 H); 1.55–2.30 (*m*, 9 H); 1.68 (*s*, 3 H); 1.85 (*d*, *J* = 7, 3 H); 3.60–4.00 (*m*, 1 H); 4.15 (br. *s*, 1 H); 4.60 (*dd*, *J* = 16, 8, 2 H); 5.50–5.88 (*m*, 1 H); 7.60–8.15 (*m*, 15 H). Anal. calc. for $C_{33}H_{36}ClOP \cdot 0.5\ CH_2Cl_2$ (515.08): C 72.17, H 6.69, Cl 12.72; found: C 72.45, H 7.06, Cl 12.55.

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