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

Part II

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

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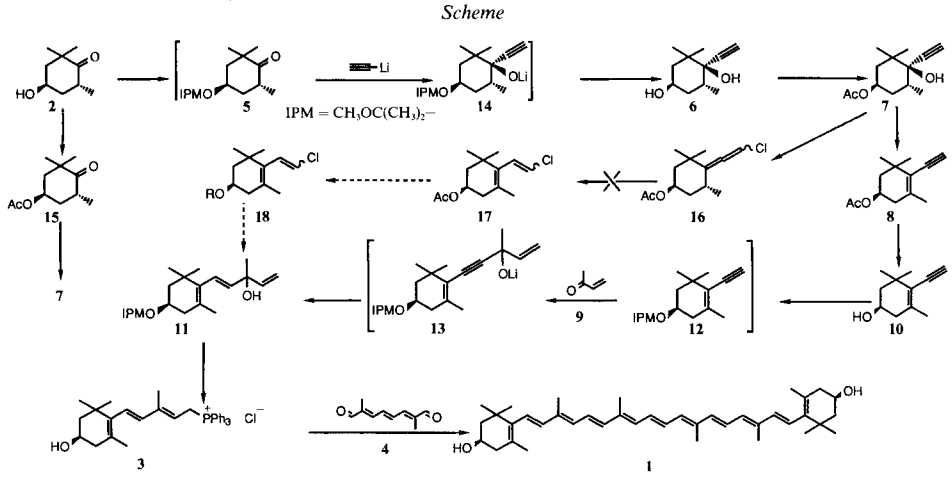
Starting from the readily available, optically active (4*R*)-hydroxy-2,2,6-trimethylcyclohexanone (**2**), a new technical synthesis of (3*R*,3'*R*)-zeaxanthin is described. According to a completely new $C_9+C_2+C_4 = C_{15}$ scheme, the ketone **2** was protected, ethynylated with Li-acetylide, and the C_{11}-intermediate **6** was acetylated, followed by dehydration. The product **10** was protected, deprotonated, and subsequently reacted with methyl vinyl ketone to provide the C_{15}-propargylate **13**. Reduction *in situ* of **13** with *Vitride* yielded the olefinic C_{15}-alcohol **11** which was transformed into the known C_{15}-*Wittig* salt **3**. A double *Wittig* reaction of this salt with the C_{10}-dialdehyde **4** afforded nature-identical zeaxanthin (**1**).

Introduction. – In the foregoing publication [1], we described a new technical synthesis of (3*R*,3'*R*)-zeaxanthin (**1**) starting from the optically active hydroxy-ketone **2** [2] *(cf. Scheme)*. Using this C_9-building block and the vitamin-A intermediate (*E*)-3-methylpent-2-en-4-yn-1-ol (C_6-synthon [3]), we prepared the C_{15}-allyl alcohol **11** which was converted in three additional steps into the known olefinic C_{15}-*Wittig* salt **3** [1] [4–6]. Subsequent 'double *Wittig* reaction' of **3** with the C_{10}-dialdehyde **4** [7] provided (3*R*,3'*R*)-zeaxanthin (**1**).

Scheme



In this publication, we describe a completely new approach to the known C_{15} salt **3** [1] again from ketone **2** but applying a new $C_9+C_2+C_4$ building scheme. In comparison with the former synthesis [1], the overall yield of **3** from **2** was increased from 43% up to 72%. Furthermore, the new approach avoids such problematical steps as the dehydration and hydrogenation of only moderately stable C_{15}-intermediates.

Results and Discussion. – The OH group of **2** was first protected *in situ* with isopropenyl methyl ether, and the resulting THF solution of the IPM-ketone **5** was then treated with 2 equiv. of freshly prepared Li-acetylide in liquid ammonia *(Scheme)*. After an acidic workup, the crude diol **6** [8] [9] was obtained in almost quantitative yield with a purity of more than 98%. GLC analysis of this material revealed the presence of *ca.* 3% of the other C_6-diastereoisomer [10]. After acetylation of this crude material with Ac_2O in pyridine or in the presence of 1% DMAP, the resulting monoacetate **7** [9] was used directly without purification in the following dehydration step. According to a previously described method on a similar vitamin-A intermediate [11] [12], we used as a catalyst 10 mol-% of $CuSO_4$ in boiling *o*-xylene. The catalyst could be easily removed afterwards by simple filtration and recycled. A detailed investigation of this dehydration step showed that, contrary to [11] [12], no reaction took place in boiling toluene, and we were not able to find any other suitable catalyst. All the common catalysts (*Brønsted* or *Lewis* acids *etc.*) gave rise to complex mixtures in which the major products were derived from hydration of the triple bond (*cf. Rupe* reaction).

Efficient purification of the crude but stable en-yne acetate **8** was effected by distillation (72°/0.01 mm). Thus, we now had an excellent approach in 93% overall yield to this new and interesting C_{11}-building block **8** starting from ketone **2**. For the subsequent coupling with the C_4-synthon, methyl vinyl ketone (**9**), it was necessary to cleave the Ac group in **8** (KOH/MeOH). The alcohol **10** could easily be purified by crystallization from pentane (92% recovery), but in the technical process, this purification was not necessary. Therefore, we converted crude **10** directly into the known *tert*-C_{15}-alcohol **11** [4] [9] *via* a three-step sequence carried out as a one-pot procedure. The OH group of **10** was protected with isopropenyl methyl ether, and the resulting THF solution of **12** was treated at $-10°$ with 1.25 equiv. of BuLi to give the corresponding Li salt. After the addition of 1.5 equiv. of dry **9** in the presence of 0.5 equiv. of LiBr [13], the intermediate Li-propargylate **13** was reduced *in situ* [14] with 1.3 equiv. of *Vitride*. The reduction of **13** proceeded quantitatively within 45 min and provided, after basic workup with 30% eq. NaOH, **11** in almost 80% yield from the acetate **8**. A detailed investigation of the entire sequence from **8** to **11** demonstrated that the presence of LiBr (0.5–1.0 equiv.) as well as scrupulous dryness of **9** were essential for the high yield. When the reaction **12** → **11** was carried out without LiBr, the yield dropped to 30–40%. In this case, around 40% of the starting material **12** remained unreacted. Under the above mentioned, optimized conditions, the crude allyl alcohol **11** contained less than 4% of unreacted **12**.

On account of its instability, the crude **11** was directly converted, under standard conditions (HCl/Ph_3P in MeOH), to the known *Wittig* salt **3** [1] [4–6] which could efficiently be purified by a single crystallization from 1,2-dichloroethane/AcOEt. By this new route, the desired *Wittig* salt **3** was obtained in 78% yield from **8** or in 72% yield from **2**. According to HPLC, this material contained *ca.* 5% of the (9*Z*)-isomer of **3**.

The *Wittig* reaction of crude **3** with the C_{10}-dialdehyde **4** [7] using 1,2-epoxybutane as an acid scavenger [1] in boiling EtOH gave the crystalline (all-*trans*)-zeaxanthin (**1**) in

only *ca.* 80% yield. According to our previous findings [1], we endeavoured to gain access to the isomerically pure (9*E*)-Wittig salt **3**. By heating the suspension of the (9*E*/*Z*)-salt **3** in boiling toluene for *ca.* 20 min, (9*E*)-**3** was obtained almost pure in 98% yield. With a content of the undesired (9*Z*)-**3** of less than 1.5%, the final *Wittig* reaction proceeded smoothly as expected [1] with only 2.05 equiv. of **3**, to give the crystalline, nature-identical zeaxanthin (**1**) in 88% yield.

Further efforts were directed towards shortening this synthesis. In a first attempt, direct dehydration of the diol **6**, instead of the acetate **8**, gave only *ca.* 60% **10** due to competitive elimination of the unprotected secondary OH group. The IPM-protected diol derived from **14** provided the corresponding dehydration product in only 30% yield due to the thermal instability of the IPM group.

In a second attempt, we prepared acetate **7** directly from **2** *via* **15**. Treatment of **2** with Ac_2O in the presence of 1 mol-% of DMAP followed by subsequent ethynylation of **15** with 2 equiv. of Li-acetylide gave **7** which was contaminated with *ca.* 10% of the diol **6**. Reacetylation (Ac_2O/DMAP) of the crude mixture led finally to pure **7** [9] in almost quantitative yield. Nevertheless, because of the necessity of reacetylation, this approach is technically unattractive and was, therefore, abandoned. In a third attempt, we treated the acetate **7** according to [15] with $SOCl_2$ (instead of $POCl_3$) in pyridine and obtained, in 85% yield, a mixture of the enyne **8** and the allene chloride **16** [15] in a ratio of 15:85. Experiments to either convert this mixture to pure **8** by elimination of HCl or to isomerize **16** into the conjugated diene **17** failed. Therefore, the C_{15}-allyl alcohol **11** was not accessible from **17** *via* **18** by reaction with methyl vinyl ketone.

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Experimental Part

General. See [16].

1. *Preparation of {(2*E*,4*E*)-5-[(*R*)-4-Hydroxy-2,6,6-trimethylcyclohex-1-enyl]-3-methylpenta-2,4-dienyl}-triphenylphosphonium Chloride ((7*E*,9*E*)-**3**) from Crude* **11**. To a cooled (0°) soln. of Ph_3P (56.6 g, 216 mmol) in MeOH (175 ml) and 37% HCl (19 ml, 190 mmol) was slowly added, over *ca.* 2–4 h, the crude C_{15}-allylalcohol **11** (54.8 g, derived from 181.25 mmol of acetate **8**) dissolved in MeOH (56 ml). The mixture was stirred at r.t. overnight, then diluted with H_2O (90 ml), and extracted with hexane (2 × 300 ml) to remove nonpolar by-products. After treatment of the MeOH/H_2O phase with charcoal (7.5 g) and filtration through *Speedex* (11 g), the filtrate was evaporated to a volume of *ca.* 300 ml, treated with H_2O (250 ml) and brine (90 ml), and extracted with CH_2Cl_2 (3 × 250 ml). The CH_2Cl_2 extract was dried (Na_2SO_4), filtered, and evaporated: 116.5 g of crude **3**. For crystallization, the crude material was dissolved in 1,2-dichloroethane (110 ml) and slowly precipitated at r.t. by the addition of AcOEt (600 ml) over *ca.* 4 h. The slurry was stirred overnight under N_2, then cooled to 0° and filtered. The pure *Wittig* salt was washed with AcOEt (300 ml) and hexane (300 ml), dried overnight at 45° under high vacuum: 81.97 g of **3** (78% resp. to **8**). M.p. 193–195°. HPLC: 85% (7*E*,9*E*)-**3**; 5% (7*E*,9*Z*)-**3**, and 5% solvents. For the isomerization and further purification, the slurry of **3** (43.5 g) was heated and intensively stirred for 25 min in boiling toluene (870 ml), then cooled to 60°, and further stirred for 30 min. After cooling to r.t., pure crystalline **3** was filtered, washed with toluene (3 × 150 ml) and hexane (300 ml), and dried at 50° overnight under high vacuum: 38.82 g of (7*E*,9*E*)-**3** (76% yield from **8**). M.p. 196–198° (dec.). Purity according to HPLC: 96% of (7*E*,9*E*)-**3** and 1.2% of (7*E*,9*Z*)-**3**, solvents: 0.01% hexane, 0.23% toluene, 0,05% 1,2-dichloroethane 0.42% H_2O. $[\alpha]_D^{20} = -57.2$ ($c = 1$, $CHCl_3$). IR and ^{1}H-NMR: identical with those published in [1]. Anal. calc. for $C_{33}H_{38}ClOP \cdot H_2O$: C 76.65, H 7.41, Cl 6.86; found: C 76.24, H 7.63, Cl 7.14.

2. *Preparation of (1S,4R,6R)-1-Ethynyl-2,6,6-trimethylcyclohexane-1,4-diol* (**6**) *from* **2**. 2.1. *Preparation of IPM-Protected Ketone* **5** in situ *from* **2**. To a stirred soln. of **2** (156.20 g, 1 mol [2]) in abs. THF (250 ml) was added pyridinium tosylate (0.25 g) followed by isopropenyl methyl ether (156.5 g, 2.17 mol) over *ca.* 20 min at 15–25°. The soln. was then stirred for 90 min and used directly in the following experiment.

2.2. *Preparation of Li-Acetylide in Liq. NH_3 and Reaction with* **5** *Leading to* **6**. Li-Wire (14 g, 2 mol) was slowly added over *ca.* 40 min to liq. NH_3 (750 ml) cooled to − 40°. Acetylene (*ca.* 150 l, 6.1 mol) was then introduced into the soln. within *ca.* 2–3 h, until the violet colour changed to gray-white. After the careful addition of dried THF (750 ml) and under a steady stream of acetylene, the ammonia condenser was removed and the slurry was warmed with a bath (45°) to *ca.* 0° to allow the bulk of the NH_3 to evaporate. The introduction of acetylene was terminated, and, within *ca.* 30 min, the mixture was slowly treated at 0–2° with the IPM soln. of **5** from *Exper. 6.1* and subsequently stirred at 2° for 30 min. H_2O (400 ml) was carefully added over 10 min (foaming!), and was stirred at r.t. overnight. The product was extracted into hexane (3 × 700 ml) and the org. phase was washed with sat. NH_4Cl soln. (700 ml) and brine (700 ml), then dried (Na_2SO_4), and finally evaporated under reduced pressure at 40°. The residue was dried for 4 h under high vacuum at r.t.: 260 g of **14**.

To cleave the IPM protecting group, the crude material was dissolved in THF/H_2O (1.3 l: 52 ml), and, after the addition of pyridinium tosylate (2.54 g), the solution was stirred at r.t. for 1 h, then treated with AcOEt (2.1 l). The org. phase was washed with sat. $NaHCO_3$- soln. (300 ml) and brine (2 × 500 ml), then dried (Na_2SO_4), and evaporated under reduced pressure at 40°. The residue was dried under high vacuum at r.t. for 30 min: 201 g of crude **6** as colourless crystals ('110% yield'). This material was used directly in the next step (*Exper. 3*). For anal. purposes, a small amount was crystallized from hexane: m.p. 149–150°. GLC (5% *SE-30*): t_R 5.91 min for **6** and t_R 13.27 min for **2**. TLC ((i-Pr)$_2$O, UV detection): R_f 0.16 for **2**, 0.36 + 0.45 for **5**, 0.21 + 0.32 + 0.39 for **14**. TLC (hexane/Et_2O 4:1): R_f 0.55 + 0.64 for **14** and 0.25 for **6**. IR: 3491*s*, 3299*s*, 2969*s*, 2931*s*, 2876*m*, 2100*vw*, 1483*m*, 1456*s*, 1409*s*, 1254*s*, 1062*s*, 1036*s*. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.08 (*d*, *J* = 6,3H); 1.11 (*s*, 3 H); 1.23 (*s*, 3 H); 1.52–1.76 (*m*, 6 H); 2.32–2.45 (*m*, 1 H); 2.48 (*s*, 1 H); 4.04 (*m*, 1 H). MS: 164 (5, $[M - H_2O]^+$), 149 (3), 126 (4), 121 (4), 108 (12), 96 (22), 82 (100). Anal. calc. for $C_{11}H_{18}O_2$ (182.63): C 72.49, H 9.95; found: C 71.97, H 10.12.

3. *Preparation of (1R,4S,5R)-4-Ethynyl-4-hydroxy-3,3,5-trimethylcyclohexyl Acetate* (**7**) *from* **6**. To a stirred soln. of crude **6** (201 g, derived from 1 mol of **2**) in pyridine (380 ml, 4.71 mol) was slowly added Ac_2O (500 ml, 5.28 mol) at 0° within *ca.* 20 min, and the resulting clear soln. was stirred at r.t. overnight. After evaporation of the mixture under reduced pressure at *ca.* 45°, the residue was dissolved in CH_2Cl_2 (1.6 l), washed with 2N HCl (500 ml), brine (400 ml), and sat. $NaHCO_3$ soln. (400 ml). The org. phase was dried (Na_2SO_4, 200 g), evaporated under reduced pressure at 40°, and finally dried at r.t. for 4 under high vacuum: 246.9 g of crude **7** (*ca.* '110% yield'). This material was used directly for the next step (see *Exper. 4*). GLC (5% *SE-30*): t_R 5.9 min for **6** and 7.92 min for **7**. TLC ((i-Pr)$_2$O, UV detection): R_f 0.36 for **6** and 0.70 for **7**. M.p. 68–69°. IR: 3421*s*, 3249*m*, 2974*m*, 2935*m*, 2100*w*, 1711*vs*, 1262*s*, 1230*s*, 1024*m*. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.08 (*d*, *J* = 8,3 H); 1.11 (*s*, 3 H); 1.14 (*s*, 3 H); 1.67–1.75 (*m*, 4 H); 2.04 (*s*, 3 H); 2.07 (*s*, 1 H); 2.19–2.26 (*m*, 1 H); 2.51 (*s*, 1 H); 4.95 (*m*, 1 H). MS: 224 (0.5, M^+), 164 (10), 149 (20), 108 (28), 82 (100). Anal. calc. for $C_{13}H_{20}O_3$ (224.30): C 69.61, H 8.99; found: C 69.73, H 9.03.

4. *Preparation of (R)-4-Ethynyl-3,5,5-trimethylcyclohex-3-enyl Acetate* (**8**) *from* **7**. To a soln. of crude **7** (121.6 g, prepared from 0.429 mol of **2**) in *o*-xylene, $CuSO_4$ (7.9 g, 10 mol-%) was added, and the mixture was stirred intensively under reflux for no longer than 2 h using a *Dean-Stark* apparatus to remove H_2O. After rapid cooling to r.t., the slurry was filtrated through *Speedex* (*ca.* 20 g), and the residue was washed with hexane (2 × 200 ml). The filtrate was diluted with hexane (600 ml) and the solution washed with H_2O (2 × 200 ml) and sat. $NaHCO_3$ soln. (400 ml). The solvent was dried (Na_2SO_4) and evaporated at 40–60° under reduced pressure (80 mm). The concentrate was distilled over a small 20-cm *Vigreux* column to yield (b.p. 83°/0.19 mm): 96.5 g of colourless oil **8** (94.9%) with purity (GLC) of 98.1%. Overall yield from ketone **2**: 93%. GLC (5% *SE30*): t_R 9.07 min for **8** and 10.92 for **7**. TLC ((i-Pr)$_2$O, UV detection): R_f 0.43 for **7**, 0.55 for **8** $[\alpha]_D^{20} = -67.2$ (*c* = 1, EtOH). IR: 3299*m*, 2964*m*, 2927*m*, 2887*m*, 2090*w*, 1738*s*, 1364*m*, 1243*s*, 1029*m*. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.36 (*s*, 3 H); 1.42 (*s*, 3 H); 1.54 (*dd*, *J* = 16, 12,1 H); 1.82 (*ddd*, *J* = 16, 4, 1, 1 H); 1.90 (*s*, 3 H); 2.04 (*s*, 3 H); 2.09 (*dd*, *J* = 16, 8,1 H); 2.41 (*dd*, *J* = 16, 6, 1 H); 3.10 (*s*, 1 H); 5.20 (*m*, 1 H). MS.: 146 (38, $[M - AcOH]^+$), 131 (100), 116 (20), 115 (15), 105 (10), 91 (22), 43 (36). Anal. calc. for $C_{13}H_{18}O_2$ (206.28): C 75.69, H 8.80; found: C 75.42, H 8.74.

5. *Preparation of (R)-4-Ethynyl-3,5,5-trimethylcyclohex-3-en-1-ol* (**10**) *from* **8**. A soln. of **8** (183.8 g, 882 mmol) in MeOH (1 l) was cooled to 0°, and KOH (74.2 g, 1.32 mol) was added slowly in small portions so that the temp. did not exceed *ca.* 11°. The soln. was stirred at 4–8° for 15 min and then at r.t. for 30 min. After the addition of H_2O (2 l) and AcOH (26.5 g, 441 mmol), the product was extracted with CH_2Cl_2 (3 × 500 ml) and the org. phase washed with sat. $NaHCO_3$ soln. (600 ml) and brine (500 ml). The org. phase was dried (Na_2SO_4), filtrated, and evaporated in vacuum at no higher than 30° (otherwise slight decomposition). The crude product **10** was dissolved

in pentane (300 ml) and the soln. evaporated in vacuum as described above, finally dried under high vacuum at r.t. overnight: 146 g of crude **10** (100.1%) as colourless crystalls. M.p. 65–67°. Purity (GLC): 98%. This material was used directly in the next step. For anal. purposes, a small amount was crystallized from pentane. M.p. 67–9°. GLC: ~ 100% pure. TLC ($(i\text{-Pr})_2O$, UV detection): R_f 0.4 for **10** and 0.7 for **8**. GLC (5% *SE30*; 2 min at 160°, 8°/min to 260° for 10 min): t_R 3.75 min for **10** and 5.72 min for **8**. $[\alpha]_D^{20} = -125.3$ ($c = 1$, EtOH). IR: 3412*s*, 3288*s*, 2933*s*, 2080*w*, 1630*w*, 1361*m*, 1045*s*, 1040*s*. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.13, 1.89 (2*s*, 6 H); 1.42 (*t*, $J = 12{,}1$ H); 1.58 (br. *s*, OH); 1.80 (*dd*, $J = 12, 1, 1$ H); 1.91 (*s*, 3 H); 2.04 (*dd*, $J = 16, 10$), 1 H); 2.40 (*dd*, $J = 16, 8, 1$ H); 3.1 (*s*, 1 H); 3.95 (br. *m*, 1 H). MS: 164 (40, M^+), 149 (50), 131 (100), 105 (50), 91 (50). Anal. calc. for $C_{11}H_{16}O$ (164.25): C 80.44, H 9.82; found: C 80.10, H 9.87.

6. *Preparation of 1-[4-(1-Methoxy-1-methylethoxy)-2,6,6-trimethylcyclohex-1-enyl]-3-methylpenta-1,4-dien-3-ol* (**11**) *from* **10**. To a soln. of **10** (30 g, corresponding to 181.2 mmol of **8**) in dry THF (200 ml) were added, at 20–24°, pyridinium tosylate (0.5 g) and, within *ca.* 10 min, isopropenyl methyl ether (43.5 ml, 462 mmol). The soln. was stirred for 1 h at r.t., cooled to – 10°, and then treated over 10 min with 1.56M BuLi soln. in hexane (140 ml, 218 mmol). After stirring for 10 min at – 12°, a soln. of anh. LiBr (15.6 g, 179.6 mmol) in THF (150 ml) was added, followed by carefully dried methyl vinyl ketone (22 ml, 270 mmol). The clear soln. was kept at – 12° for 30 min, then treated at – 10° with 3.5M *Vitride* soln. in toluene (63 ml, 220 mmol). After warming the mixture to 0°, stirring was continued for 40 min. The excess of *Vitride* was destroyed by the careful addition of a mixture EtOH/hexane (40 ml/60 ml), followed by addition of 28% NaOH soln. (300 ml). After extensive stirring of the mixture for 15 min, the org. phase was separated and extracted with hexane (600 ml). The combined hexane phases were dried (Na_2SO_4), filtrated, evaporated under reduced pressure, and finally dried under high vacuum at 60° for *ca.* 4 h: 54.0 g (97%) of crude **11**, which was used directly without purification in the next step (*Exper. 1*). For anal. purposes, a small amount of crude **11** was dissolved in THF/H_2O 1:1, then treated with pyridinium tosylate (5 mol-%), and stirred for 2 h at r.t. After extraction of the mixture with AcOEt, the crude unprotected alcohol was purified by column chromatography. The spectroscopical data of **11** were identical with those given in [4] [9].

7. *Preparation of (1R,5R)-3,3,5-Trimethyl-4-oxocyclohexyl Acetate* (**15**) *from* **2**. The ketone **2** (300 g, 1.92 mol) and DMAP (2.34 g, 19.2 mmol) were dissolved in Ac_2O (900 ml, 9.5 mol), and the soln. was stirred for 3 h at 50°, then distilled through 30-cm *Vigreux* column under high vacuum. The product was collected at 96°/0.10 mm as a colourless oil: 381.7 g of **15** (100% yield). Purity according to GLC: 99.2%. GLC (5% *SE-30*): t_R 6.61 min for **2** and 8.42 min for **15**. $[\alpha]_D^{20} = -86.75$ ($c = 0.4$, MeOH). IR: 2960*s*, 2940*s*, 2880*m*, 1740v*s*, 1710v*s*, 1370*s*, 1300v*s*. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.04 (*d*, $J = 7$, 3 H); 1.06 (*s*, 3 H); 1.30 (*s*, 3 H); 1.65–1.80 (*ddd*, *dd*, $J = 16, 8, 4, 16, 4$, 2 H); 2.07–2.24 (*m* + *s*, 5 H); 3.04 (*sept.*, $J = 6$, 1 H); 5.14 (*m*, 1 H). MS: 156 (10, $[M - C_2H_2O]^+$), 138 (36, $[M - AcOH]^+$), 110 (20), 95 (30), 88 (50) 83 (80), 43 (100). Anal. calc. for $C_{11}H_{18}O_3$ (198.26): C 66.64, H 9.15; found: C 66.71, H 9.39.

8. *Preparation of* **7** *from* **15**. Li wire (14 g, 2 mol) was dissolved, over 40–50 min, in liq. NH_3 (750 ml) maintained at – 40°. Acetylene (150 l, 6.1 mol) was introduced in a slow stream into the soln. over 2–3 h, until the violet colour changed to gray-white. After carefully adding dried THF (750 ml) and under constant introduction of acetylene, the ammonia condenser was removed and the slurry was warmed with a bath (45°) to *ca.* 0° to allow the majority of NH_3 to escape. The introduction of acetylene was terminated and the slurry cooled to – 15° and treated, within *ca.* 30 min, with a soln. of **15** (198.2 g, 1 mol) in THF (250 ml). Stirring was continued at – 15° for further 45 min. After adding 4N H_2SO_4 (850 ml) at *ca.* 0° over 30 min, the two-phase mixture was extracted with AcOEt (3 × 500 ml). The org. phase was washed with 2N H_2SO_4 (600 ml) and sat. $NaHCO_3$ soln. (2 × 300 ml), then dried (Na_2SO_4), filtrated, and evaporated under reduced pressure. The product was dried under high vacuum at 45° for 2 h: 235 g of a mixture **6**/**7** in a ratio of *ca.* 65:35. For the re-acetylation step, the crude material was dissolved in Ac_2O (220 ml) containing DMAP (600 mg, 1 mol-%), and the soln. was heated at 60° for 90 min. The mixture was evaporated under reduced pressure at 50°, and the residue was treated with MeOH (200 ml) and the solvent evaporated again. The product was dried under high vacuum at 45° for 2–3 h: 120.6 g of crude **7** ('107% yield' based on **2**). Purity (GLC): 93,2%. This material was used directly in the next step (*Exper. 4*). The anal. data of **7** were identical with the data described in *Exper. 3*.

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