258. Photochemical High-yield Preparation of Tricyclo[3.3.0.$0^{2,8}$]octan-3-ones. Potential Synthons for Polycyclopentanoid Terpenes and Prostacyclin Analogs

Preliminary Communication[1])

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Summary

Three-step syntheses and the resolution into the enantiomers are reported for the tricyclo[3.3.0.$0^{2,8}$]octan-3-ones **7–9**, which are destined to serve as synthons for polycyclopentanoid terpenes and prostacyclin analogs. Routine overall yields of *ca.* 75% for **7**, 40% for **8**, and 46% for **9** are obtained, with 2-chloroacrylonitrile and 1,3-cyclohexadiene (for **7**) and 1-methyl-1,4-cyclohexadiene (for **8** and **9**) as the starting materials. The key step is the triplet-sensitized oxadi-π-methane photorearrangement of the β,γ-unsaturated ketones **1–3** which can be achieved in 80–90% yields of isolated product and quantum yields of 0.5–1.0. The racemates of both ketone **1** and its photoisomer **7** have been resolved *via* chromatographic separation of suitable diastereoisomeric acetal mixtures. On the other hand, sensitization of **1** with an optically active donor, (–)-**14**, gave only an impractical maximum enantiomeric excess of 10% (–)-**7**.

Introduction. – A family of polycyclopentanoid terpenes and prostacyclin analogs has recently attracted increasing attention, both for the synthetic challenge and for the biological activities exhibited by some of these compounds[2]). A retrosynthetic analysis of the structures involved has led us to probe into the usefulness of ketones **7–9** as building blocks. We describe here the preparation of **7–9** in racemic forms, and results on their optical resolution. A previous report [5] has already dealt with some of the transformations of these synthons. In subsequent papers [3] [4] their synthetic potential will be exemplified on a broader scope and in greater depth.

Synthesis of the racemic compounds 7–9. – The key step in the synthesis of **7–9** is the photochemical rearrangement of the respective unsaturated ketones **1–3**, which

[1]) Presented in parts at the ESOC I Conference, Köln 1979 [1], and at the VIII IUPAC Symposium on Photochemistry, Seefeld 1980 [2]. Patent applications have been submitted for major parts of this communication.

[2]) See our following papers [3] [4] for a summary of such target compounds and literature references to the most recent reports on syntheses.

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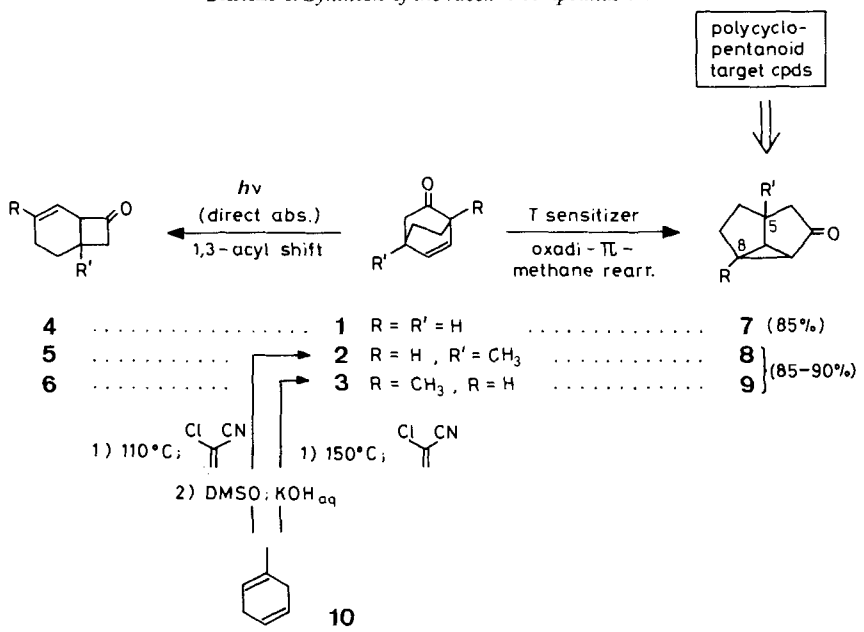
Scheme 1. *Synthesis of the racemic compounds* **7–9**



in turn are readily accessible by the *Diels-Alder* route from the cyclohexadienes *(Scheme 1)*. Preparations of **1** [6] and **3** have already been reported, the latter *via* a stepwise sequence of base-catalyzed isomerization of 1-methyl-1,4-cyclohexadiene (**10**) to the 1,3-diene [7], addition of 2-acetoxy- [7] or 2-chloroacrylonitrile [8], and hydrolysis. We have now found conditions which combine higher overall yields with a regioselective control, steering the [2+4]-addition towards either **2** or **3**. Diene **10** was isomerized *in situ* to the 1,3-isomer and trapped by 2-chloroacrylonitrile[3]) when heated in the presence of catalytic amounts of *p*-hydroquinone. At 110°C, a readily separable 5:1 mixture of **2** and **3** was thus formed after hydrolysis, whereas at 150°C the regioselectivity was entirely in favour of **3**. In either case, overall yields of 50–55% isolated ketone(s) were regularly obtained.

Givens et al. [9] had first described the photochemical rearrangements of **1** which are characteristic of β,γ-unsaturated ketones [10]. On direct irradiation, a 1,3-acyl shift to the cyclobutanone **4** and, on triplet sensitization, an oxadi-π-methane rearrangement to **7** were reported. Using acetone as a sensitizer and light of 254 nm, an isolated yield of 34% **7** was obtained. This latter procedure has now been significantly improved by concentration and wavelength optimization, and routine yields of 80–85% of isolated **7** were achieved when 1% solutions of **1** in acetone were irradiated with 300 nm lamps through quartz[4]). Only at higher concentrations, *e.g.* with a 4% solution of **1**, competitive formation of **4** was still observed.

[3]) In accordance with previous observations [7] the use of the less dienophilic 2-acetoxyacrylonitrile did not afford adducts under these conditions.

[4]) Compound **7** has previously been prepared *via* the diazoketone route [11], which affords much lower yields and is less convenient in large scale preparations.

Table. *Maximum quantum yields of sensitized product* **7** *formation from* **1** *(0.17 mol/l)*

Sensitizer	E_T [kcal/mol]	Concentration [mol/l]	Solvent	λ^{irrad} [nm]	$A_\lambda{}^{irrad}$ [a])	Φ_{max} [b])
Acetone	80 [17]	neat	–	250	*ca.* 100	1.0
exo-1,4-Methano-*cis*-1,2,3,4,4a,9a-hexahydrofluoren-9-one (**14**)	74[c])	0.0204	benzene	> 340	2.66	0.5
Acetophenone	72 [19]	0.0167	benzene	> 340	0.54	0.3

[a]) Absorbance in 1.0-cm cell.

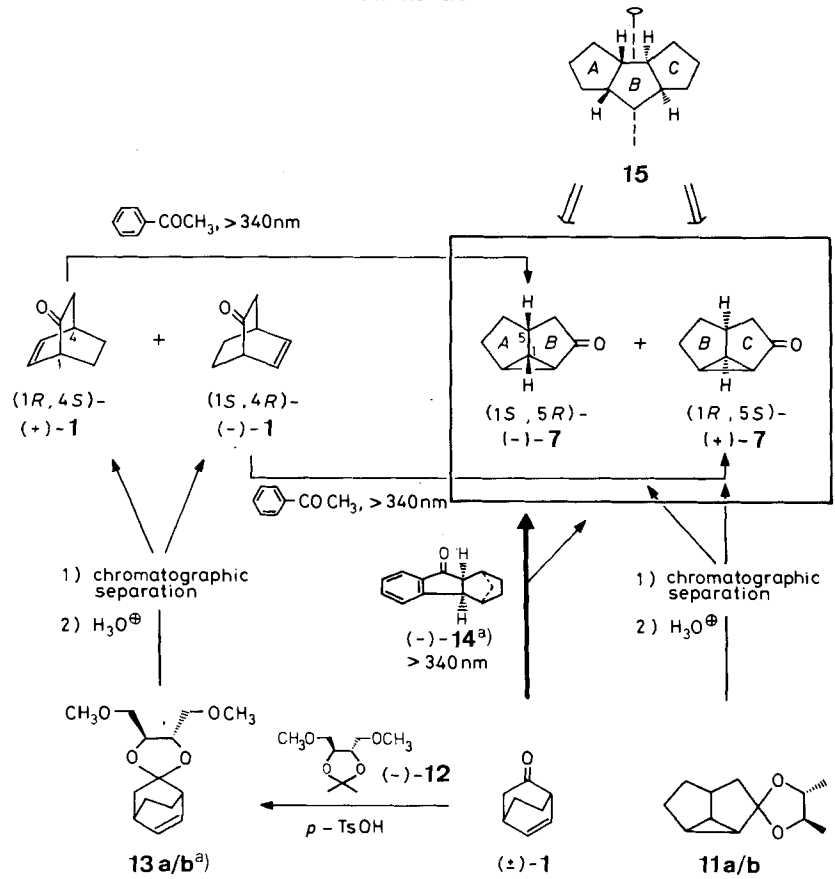
[b]) Reciprocal of intercept in *Stern-Volmer* plot. Experimental error ± 10%. Solutions were degassed in three freeze-pump($< 10^{-3}$ Torr)-thaw cycles. Quantum yields were measured in an electronically integrating actinometer [16], and product formation by glass capillary GLC., using octadecane as an internal standard. The Φ_{max} values for **14** and acetophenone are extrapolations to maximum concentrations of sensitizer.

[c]) Estimated from lowest E_T^{phosph} in ether/isopentane/ethanol 5:5:2 glass at 77 K [18].

When the methyl-substituted ketones **2** and **3** were subjected to the same sensitization conditions, the acyl shift products **5** and **6** were formed in addition to the oxadi-π-methane rearrangement products **8** and **9**, respectively. The ratios were *ca.* 1:4. These undesired side products which were again the only photoproducts on direct irradiation, could be entirely avoided by using acetophenone as a sensitizer. Irradiation of 2% solutions of **2** and **3** in benzene at > 340 nm in the presence of acetophenone thus afforded 85–90% yields of **8** and **9**, respectively.

The wavelength and concentration dependence of the product pattern from **1–3** in acetone shows that the 1,3-acyl shift to **4–6** is exclusively due to reaction initiated by residual direct light absorption. In other words, it is particularly not a consequence of selective sensitization of different triplet states of **1–3**, depending on the donor triplet energies (see *Table*). In analogy to the mechanism elaborated in detail for other β,γ-unsaturated ketones [12], this would leave either or both of the n,π^*-excited states, S_1 and T_2, as the possible reactive species for this process. The oxadi-π-methane rearrangement to **7–9**, on the other hand, should accordingly result from the T_1 (π,π^*) states [12]. Subject to these conditions, sensitization by both acetone and acetophenone should populate only the T_1 states of **1–3**. Again, in analogy to other β,γ-unsaturated ketones [10] [12a] [13], the energy of these lowest-lying triplet states may be expected in the 70–74 kcal/mol range. The drop in quantum yield of product formation from acetone to acetophenone (see *Table*) may possibly reflect near degeneracy in triplet energy of acetophenone and acceptor, and consequently reversible triplet energy transfer between the two. This could, in turn, favour an enantioselective energy transfer from a chiral sensitizer owing to a greater controlling influence of steric factors. With this hypothesis in mind, ketone (–)-**14** [14] was used to sensitize the rearrangement of (±)-**1**. Although asymmetric induction was achieved – for the first time in an oxadi-π-methane photorearrangement –, it was only of a magnitude similar to that reported for other cases [15] and failed to reach a degree of practical utility.

Scheme 2. *Enantioselective energy transfer from* (−)-**14**, *and resolution of* (±)-**1** *and* (±)-**7** *into the enantiomers*

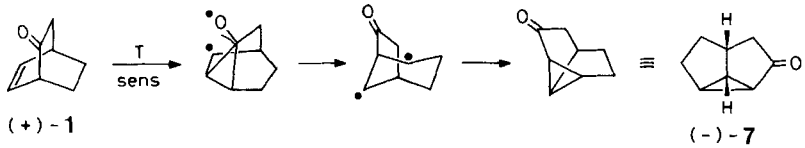


a) The absolute configuration of **13a/b** is chosen assuming retention on the asymmetric C-atoms during the transacetalization from (−)-**12**. The absolute configuration of (−)-**14** is based on a CD. *Cotton* effect of $\Delta\varepsilon_{max}^{337.5\ nm} = +1.01$ (cyclohexane) and the octant rule for indanones [20].

After 7–44% conversions of (±)-**1**, products with 4.5±0.7% enantiomeric excess of (−)-**7** in benzene and ethyl acetate at room temperature, and 10±3% in ethyl acetate at −78° were formed.

Resolution of (±)-1 and (±)-7 into the enantiomers. – The *p*-toluenesulfonic-acid catalyzed acetalization of (±)-**7** with (2*R*,3*R*)-(−)-2,3-butanediol (from *Fluka AG; cf.* [12]) and transacetalization of (±)-**1** with (*S*, *S*)-(−)-**12** [22] gave, quantitatively at *ca.* 80% conversions, the mixtures **11a/b** and **13a/b**, respectively. Chromatographic separation of the diastereoisomers (1.5 g of each mixture) could be achieved on *Merck* ready-made columns (*Li-Chroprep* SI 60, type C) with toluene (for **11a/b**) and toluene/ether 10:1 (for **13a/b**) under 2 atm pressure. Hydrolyses with 1 N HCl (aqueous)/ethanol 1:4 at room temperature quantitatively

Scheme 3. *Stereospecific mechanism of the oxa-di-π-methane photorearrangement*



gave the enantiomers (+)-**1** and (−)-**1**, $[\alpha]_D = 520°$ (±5%; $CHCl_3$)[5]), and (+)-**7** and (−)-**7**, $[\alpha]_D = 56°$ (±5%; $CHCl_3$). The absolute configuration of **7**, as shown in *Scheme 2*, was established by a CD. *Cotton* effect of $\Delta\varepsilon_{max}^{306\,nm} = -2.02$ (isooctane) for (+)-**7** and the octant rule for bicyclo[3.1.0]hexan-2-ones [25].

The chromatographic separation of **11a/b** was superior over that of **13a/b**. The former route, (±)-**7** → (+)-**7** + (−)-**7**, is therefore recommended for large-scale batches.

The stereospecificity of the oxadi-π-methane rearrangement **1** → **7**, as predicted by the mechanism proven for other β,γ-unsaturated ketones [26] and shown in *Scheme 3*, was ascertained by acetophenone-sensitized conversions (> 340 nm) of (+)-**1** and (−)-**1** in benzene at room temperature. Products (−)-**7** and (+)-**7**, respectively, were obtained with full conservation of enantiomeric purity within experimental error.

Conclusion. – The ready access to both enantiomers of **7** provides the necessary pool of synthons for optimum chiral choices in the planning of syntheses. Depending on the structural demands of the target compounds (see **15**)[2]), either one or the other enantiomeric synthon will be more efficiently employed.

We thank Professor *B. Fuchs* for stimulating discussions, and Mrs. *H. Matthäus* and Mr. *P. Ritterskamp* for technical assistance.

Experimental Part

Complete spectral data and physical constants of all new products will be reported in a full paper, including detailed experimental procedures in addition to the following ones.

Synthesis of 1-methyl- (**3**) *and 4-methyl-5-bicyclo[2.2.2]octen-2-ones* (**2**). A mixture of 1-methyl-1,4-cyclohexadiene (**10**), 2-chloroacrylonitrile and a catalytic amount of hydroquinone in an autoclave was heated to 110° for 14 h. The crude material was distilled at 60–65°/0.1 Torr, and the distillate was hydrolyzed in aqueous KOH-solution/dimethylsulfoxide at 120° for 30 min. The mixture was then poured into ice/water. Extraction with pentane and chromatographic separation on a silica gel column gave **2** and **3** in a 5:1 ratio and in a combined overall yield of 50–55%.

When the [2+4] addition was carried out at 150° for 14 h, 54% **3** were isolated after hydrolysis. The regioisomer **2** could not be found under these conditions.

Products **2** and **3** can be stored in degassed solutions in the refrigerator for a few days. In isolated form, however, they readily decompose.

Synthesis of tricyclo[3.3.0.0^{2,8}]octan-3-one (**7**) [9]. A solution of 10 g of **1** [6] in 1 l of acetone was purged with argon and irradiated in a water-cooled quartz vessel placed in a *Rayonet* RPR-208 photoreactor equipped with RUL-3000 Å lamps, until after 72 h 96–98% of **1** were converted into **7** (no other

[5]) All $[\alpha]_D$ measurements at 23°. Previously described attempts of optical resolutions of (±)-**1** by way of fractional recrystallization were only partially successful. The reported $[\alpha]_D$ values for **1** vary from 497° [23] to 670° [24], and the absolute configuration was assigned in [24].

products detected by GLC.). The acetone was distilled off, and the residue chromatographed on a column of 150 g of silica gel (70–230 mesh). Benzene eluted **1**, and benzene/ether 9:1 gave 8.6 g of **7**. Distillation at 50°/1 Torr afforded 8.1 g of **7** (81% yield; 99.5% purity by GLC.).

Synthesis of 5-methyl- (**8**) *and 8-methyltricyclo[3.3.0.0^{2,8}]octan-3-ones* (**9**). Solutions of 2% of **2** and **3**, respectively, and 0.3 mol-equiv. of acetophenone in acetone were purged with argon and irradiated with a 250 W Hg medium-pressure lamp placed in a water-cooled pyrex immersion well, which was surrounded by an additional mantle containing a filter solution (> 340 nm: 750 g of NaBr and 8 g of $Pb(NO_3)_2$ in 1 l of water). At 98% conversion the work-up as described above afforded 85–90% yields of **8** and **9**, respectively.

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