195. Synthesis, Reactivity, and Application as Chiral Auxiliaries of the Novel (3*R*)- and (3*S*)-4,5-Dihydro-3-hydroxy-4,4,5,5-tetramethyl-3-phenylfuran-2(3*H*)-ones in the *Paterno-Büchi* Reaction

by **Thomas Oppenländer*** and **Peter Schönholzer**

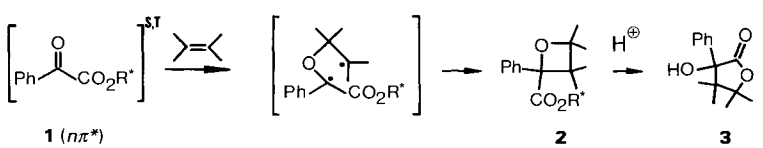
Central Research Units, *F. Hoffmann-La Roche AG*, CH-4002 Basle

(14.IX.89)

Both enantiomers of the novel α-hydroxy-γ-lactone (±)-**3** (4,5-dihydro-3-hydroxy-4,4,5,5-tetramethyl-3-phenylfuran-2(3*H*)-one) have been synthesized *via* hydrolysis of the oxetanes **2** derived from the photochemical [2 + 2] cycloaddition of the ketones **1** and 2,3-dimethylbut-2-ene (*Paterno-Büchi* reaction) involving conventional separation of diastereoisomers (*Schemes 2* and *3*). The absolute configuration of (*R*)- and (*S*)-**3** and of the corresponding oxetane precursors could be assigned on the basis of an X-ray structural analysis of the (–)-(1*S*,4*R*)-camphanoyl derivative (3′*S*)-**5** of (*S*)-**3**. *O*-Acylation of (*S*)- and (±)-**3** to yield a variety of derivatives ((3′*S*)- and (3′*RS*)-**5**, (*S*)- and (±)-**7**, (±)-**8**, (±)-**9**) was accomplished by deprotonation with BuLi at room temperature and subsequent quenching of the Li alcoholate with acyl chlorides or acid anhydrides, demonstrating the extraordinary chemical stability of **3**. Additionally, the course of the temperature-dependent diastereoselective *Paterno-Büchi* reaction of 2,3-dimethylbut-2-ene to the benzoylformate (*S*)-**7** (= (*S*)-**1d**; obtained from (*S*)-**3**) was shown to proceed with 58% de at 60°, leading to a decrease of enantiomeric purity in the hydrolysis product **3**.

1. Introduction. – α-Hydroxy-γ-lactones like (*R*)-pantolactone are extraordinary useful as chiral auxiliaries in the asymmetric *Diels-Alder* reaction explored for the syntheses of various natural products [1]. We now bring into focus the facile synthesis of the novel highly substituted α-hydroxy-γ-lactone **3** in its enantiomerically pure forms (*R*)-**3** and (*S*)-**3**, which may serve as potential chiral auxiliaries in EPC (enantiomerically pure

Scheme 1



1 ($n\pi^*$) **2** **3**

R* = Chiral auxiliary

compound) synthesis. Compound **3** may be formed by hydrolysis of oxetanes **2** (*Scheme 1*). Oxetane formation *via* [2 + 2] cycloadditions of olefins to an electronically excited carbonyl group (see, *e.g.*, **1**) is known as the *Paterno-Büchi* reaction which proceeds usually *via* distinct 1,4-biradical intermediates [2]. Recent investigations concerning the diastereoface differentiation in the *Paterno-Büchi* reaction [3] have shown that the high diastereoselectivities (often ≥ 96% de) using chiral benzoylformates **1** (R* = chiral auxiliary) are probably due to a kinetic selection process occurring on the diabatic reaction

surface with the formation of diastereoisomeric 1,4-biradicals of different kinetic stability [3a]. This was concluded from the dependence of diastereoisomeric excess on the reaction temperature [3c].

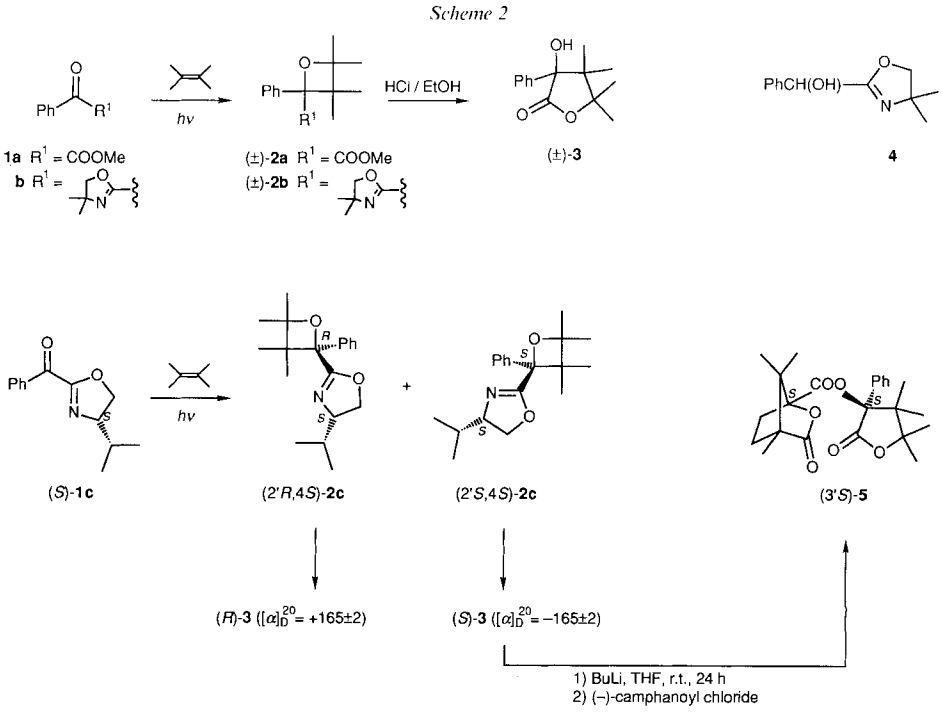
In this study, we describe the synthesis of oxetanes **2** by irradiation of ketones **1** in the presence of 2,3-dimethylbut-2-ene. Conventional chromatographic separation of diastereoisomeric oxetanes **2** (see **2c**) or separation of diastereoisomeric (*R*)-α-methylbenzylammonium salts (see **6**) followed by acidic hydrolysis of the pure diastereoisomers leads to both enantiomers (*S*)- and (*R*)-**3**.

Furthermore, it was our objective to study the diastereoface differentiation in the *Paterno-Büchi* reaction using the novel hydroxylactone (*S*)-**3** as a chiral auxiliary. The course of the [2 + 2] cycloaddition of 2,3-dimethylbut-2-ene to the chiral benzoylformate (*S*)-**7** derived from (*S*)-**3** can be elucidated by the hydrolysis of the mixture (2*R*,3′*S*)-**2e**/(2*S*,3′*S*)-**2e** which should lead to two molecules of **3** (*cf.* [4]). The enantiomeric composition of **3** should then reflect *re*- or *si*-face preference of attack to the C=O group depending on the diastereoface differentiation and the diastereoisomeric excess reached in the [2 + 2] cycloaddition.

The extraordinary chemical stability of the novel hydroxylactone **3** and its *O*-acylation *via* deprotonation by BuLi at room temperature is demonstrated by the synthesis of some acyl derivatives. Additionally, the assignment of the absolute configuration of all optically active compounds described herein is based on an X-ray structural analysis of the pure diastereoisomeric (–)-camphanate (3′*S*)-**5** obtained from (*S*)-**3** [5].

2. Results. – Racemic α-hydroxy-γ-lactone (±)-**3** was easily obtained by a two-step sequence. Irradiation ($\lambda > 300$ nm) of methyl benzoylformate **1a** [6] or dihydrooxazolyl ketone **1b** in benzene or toluene at room temperature in the presence of 2,3-dimethylbut-

Scheme 2



2-ene gave the corresponding oxetanes (±)-**2a** and (±)-**2b**, respectively, the chemical yield of (±)-**2a** being superior *(cf. Exper. Part)*; oxetane (±)-**2b** was accompanied by the photoreduction product **4** (17%; *Scheme 2*). Hydrolysis of (±)-**2a** or (±)-**2b** in refluxing 1N HCl/EtOH 1:1 afforded crystalline (±)-**3** in good chemical yields.

In the case of the chiral dihydrooxazolyl ketone (*S*)-**1c**, the diastereoisomeric oxetanes (2′*S*,4*S*)- and (2′*R*,4*S*)-**2c** were formed in a 1:1 ratio. The pure diastereoisomers were separated by chromatography and hydrolysed to give (*S*)- and (*R*)-**3** in 85 and 67% yield, respectively *(Scheme 2)*.

The optical purity of (*S*)-**3** was confirmed by analysis of its camphanoyl derivative (3′*S*)-**5**, formed by deprotonation with BuLi at room temperature and quenching with (−)-(1*S*,4*R*)-camphanoyl chloride (56% yield). HPLC of the crude reaction mixture using a *Pirkle* stationary phase exhibited only one peak, and the ^{1}H-NMR spectrum unambiguously proved the absence of a second diastereoisomer. Crystallization of (3′*S*)-**5** from Et_2O gave suitable crystals for X-ray analysis *(Fig. 1)* which revealed the (3′*S*)-configuration at the asymmetric center of the lactone moiety and hence the (*S*)-configuration of (*S*)-**3**.

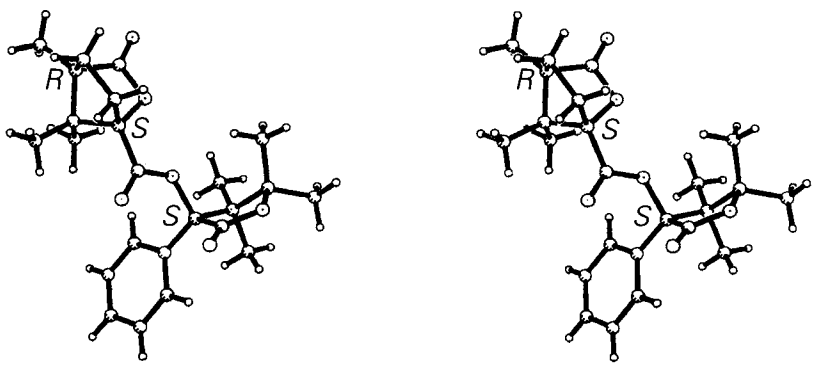


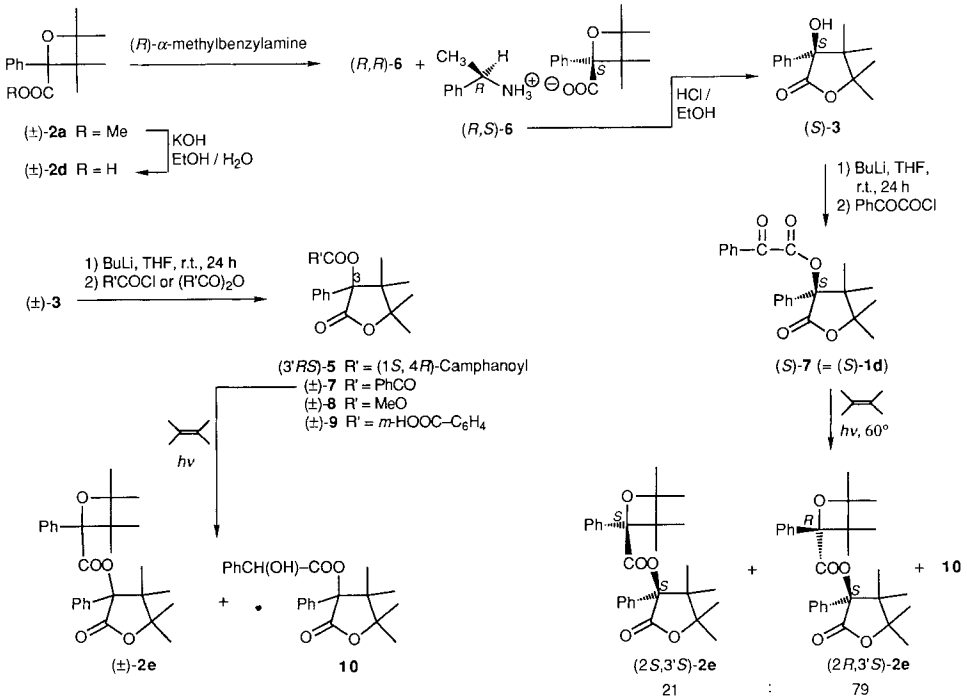
Fig. 1. *X-Ray structure of (3′S)-***5**

In order to obtain synthetically useful quantities of hydroxylactone (*S*)-**3**, we performed a conventional separation of the diastereoisomeric salts **6** derived from the oxetanecarboxylic acid (±)-**2d** and (*R*)-α-methylbenzylamine *(Scheme 3)*. Acid (±)-**2d** was easily accessible by basic hydrolysis (10% aq. KOH/EtOH 1:1) of the crude ester (±)-**2a** followed by acidification (1N HCl, 0°; 80% yield). The diastereoisomeric salt (*R*,*S*)-**6** was hydrolyzed with 1N HCl/EtOH 1:1 to yield the optically pure hydroxylactone (*S*)-**3** (81% yield).

Hydroxylactone **3** could be transformed to a variety of *O*-acylated derivatives, but only after slow deprotonation using BuLi in THF at room temperature and quenching with an acyl chloride or acid anhydride. Thus, (*S*)-**3** was converted to (*S*)-**7** (= (*S*)-**1d**) and (±)-**3** to (±)-**7**, -**8**, and -**9** (*Scheme 3*; see also (*S*)-**3** → (3′*S*)-**5**). Hydroxylactone (±)-**3** was completely inert against hot acids and bases (*e.g.* HCl, H_2SO_4, KOH, and NaOMe), it even survived on treatment with BuLi in boiling abs. THF for 2 h.

Finally, irradiation of benzoylformate (±)-**7** in the presence of 2,3-dimethylbut-2-ene gave the corresponding oxetanes (±)-**2e** which could be isolated from the complex

Scheme 3



photolysate by column chromatography in moderate chemical yields, together with photoreduction product **10** (15%). HPLC and ^{1}H-NMR (0.79 and 0.75 ppm) analyses of the crude photolysate obtained similarly (at 20°) from (*S*)-**7** revealed the formation of the two diastereoisomers (2*R*,3'*S*)- and (2*S*,3'*S*)-**2e** in a ratio of 74:26. This ratio increased to a maximum of 79:21 with increasing photolysis temperature *(Fig. 2)*, corresponding to a

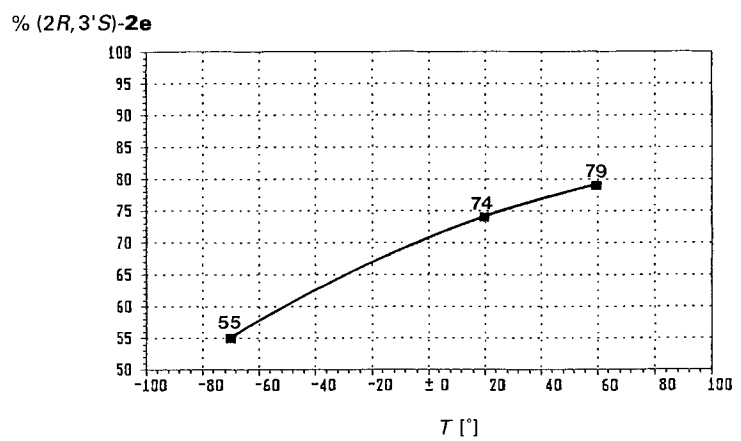
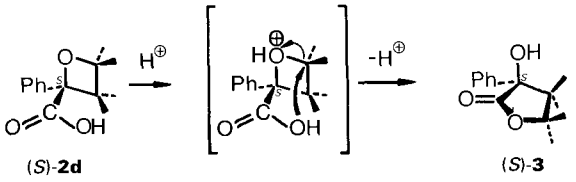


Fig. 2. *Temperature dependence of the diastereoisomeric ratio (2*R,3'S*)-***2e****/(2*S,3'S*)-***2e*** *in the* Paterno-Büchi *reaction*

diastereoisomeric excess (de) of 58%. Chromatographic isolation of the mixture (2*R*,3′*S*)-**2e**/(2*S*,3′*S*)-**2e** 74:26 and its subsequent hydrolysis gave **3** with an optical purity (o.p.) of 65% (measured by its optical rotation), revealing the formation of (*R*)-**3** during this hydrolysis.

3. Discussion. – The formation of the novel α-hydroxy-γ-lactone **3** from oxetanes **2** may be explained mechanistically by acidic saponification (→ **2d**) and protonation of the oxetane O-atom [7] followed by cleavage of the oxetane ring and successive rearrangement of the tetramethyl-substituted side chain *(Scheme 4)*. The extraordinary chemical stability of **3** against acids and bases may be explained in terms of the *'Bürgi-Dunitz'* model [8] describing the angular trajectory of the nucleophilic attack to the sp^2-center of a carbonyl group. In **3**, the non-perpendicular attack of a nucleophile is sterically strongly hindered by the Me groups.

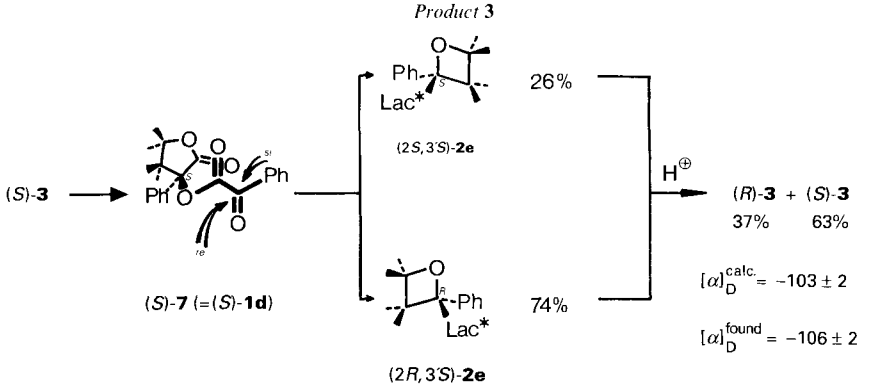
Scheme 4



The configurational assignment of the asymmetric centers of the oxetanes **2e**, **2c**, and **6** is based on the X-ray structure of (3′*S*)-**5** which reveals the (*S*)-configuration for the hydroxylactone (*S*)-**3**, according to the CIP rules [9] (*Schemes 2* and *3*). Accepting the obvious assumption that the configuration of the oxetane C(2)-O bond is not affected during hydrolysis, the (*R*)- and (*S*)-configurated oxetanes rearrange to hydroxylactone (*R*)- and (*S*)-**3** respectively *(Scheme 4)*.

With these facts in mind, the stereochemical outcome of the diastereoselective [2 + 2] cycloaddition of 2,3-dimethylbut-2-ene to the chiral benzoylformate (*S*)-**7** may be explained as outlined in *Scheme 5*. The excess diastereoisomer (2*R*,3′*S*)-**2e** is (*R*)-configurated at the oxetane moiety. Thus, hydrolysis of (2*S*,3′*S*)-**2e**/(2*R*,3′*S*)-**2e** (26:74) leads to

Scheme 5. *Diastereoselective* Paterno-Büchi *Reaction Leading to a Decrease of Enantiomeric Purity of Hydrolysis Product* **3**



the formation of 37% of (*R*)-**3** and 63% of (*S*)-**3**, explaining the low optical purity (65%) of the hydroxylactone **3**.

Therefore, the diastereo-differentiating process with 48% de (at 20°) leads to a large decrease of enantiomeric purity in the hydrolysis product **3**, reflecting the *re*-face preference of the [2 + 2] cycloaddition. The strong temperature dependence of the diastereoisomeric ratio *(Fig. 2)* is in accordance with the hypothesis that the process of stereoselection takes place on the stage of the diastereoisomeric 1,4-biradicals exhibiting different kinetic stability [3a].

In conclusion, we have synthesized the enantiomers of the novel α-hydroxy-γ-lactone **3** which exhibits extraordinary chemical stability against acid and base treatment. Enantiomer (*S*)-**3** was used as readily recoverable chiral auxiliary in the diastereoselective *Paterno-Büchi* reaction, unfortunately leading to a decrease of enantiomeric purity in the hydrolysis product **3**. Nevertheless, (*R*)- and (*S*)-**3** may be used as chiral auxiliaries in EPC synthesis and as chiral agents for the optical resolution of acids.

The authors wish to express their gratitude to Dr. *K.H. Pfoertner* who initiated this work. Furthermore, they thank Mr. *A. Ritter* for performing the large-scale photoreactions, Dr. *W. Arnold* (NMR), Mr. *W. Meister* (MS), Dr. *M. Grosjean* (IR) for the spectroscopic data, Mrs. *J. Kohler* (optical rotation), Mr. *P. Helffer* (HPLC), and the microanalytical laboratory for the elemental analyses.

Experimental Part

1. *General.* X-Ray analysis: data collection on a *Nicolet R3m/V* four-circle diffractometer fitted with a graphite monochromator and *LT1* cooling apparatus. HPLC analyses: *Waters Instrument*, detection at λ 211 nm *(Perkin Elmer LC55)*, equipped with a *Pirkle* column (dinitrobenzoyl-phenylglycine on amine-phase, i-PrOH/hexane 1:1) for the resolution of the diastereoisomers (3′*RS*)-**5**, and a *Perkin Elmer*, Series *1* LC-pump, detection at λ 254 nm *(Perkin Elmer LC75)*, equipped with a *Hyperchrome NC/Spherisorb CN* column (i-PrOH/hexane 6:4) for the resolution of **2e**. Optical rotation: *Perkin Elmer Polarimeter 241*, path length 1 dm, $T = 20°$. IR (cm^{-1}): in KBr or neat; *Nicolet FT/IR 719*. ^{1}H-NMR ($CDCl_3$, unless specified otherwise): *Bruker-Spectrospin WM 250* (250 MHz); δ (ppm) and *J* (Hz). MS: *MS9* from *AEI*, Manchester, updated with *ZAB* console and data system *3000*, *m/z* (rel.-%).

2. *General Irradiation Procedure.* Irradiations were performed at r.t. in benzene or toluene with a high-pressure Hg lamp *TQ 150* or, for scaling up [10], with the medium-pressure Hg lamp *TQ 2020* (*Heraeus*, Hanau, FRG) with light $\lambda \geqslant 300$ nm using a *Pyrex* filter, Ar atmosphere. Workup: evaporation of the solvent at 35°. Flash chromatography or radial chromatography *(Harrison Research Chromatotron 7924T)* on silica gel (AcOEt/hexane 2:8). TLC retention factors (R_f): precoated plastic sheets for TLC (*Macherey-Nagel, Polygram® SIL G(UV$_{254}$)*, 0.25 mm silica gel with fluorescent indicator); separation factor $\alpha = R_f^1/R_f^2$.

Starting Materials. Compounds **1b** and (*S*)-**1c** [11] were synthesized according to the literature using freshly prepared barium manganate [12] for the oxidation of the (4,5-dihydrooxazol-2-yl)phenylmethanols. Methyl benzoylformate (**1a**), 2,3-dimethylbut-2-ene, (+)-(*R*)-α-methylbenzylamine, (−)-camphanoyl chloride, methyl chloroformate, and phthalic anhydride from *Fluka;* benzoylformyl chloride according to [13].

(−)-(S)-4,5-Dihydro-4-isopropyloxazol-2-yl Phenyl Ketone ((*S*)-**1c**): Yield 69%. B.p. 102–104°/0.05 Torr. $[\alpha]_D^{20} = -76.7$ ($c = 0.9$, $CHCl_3$). IR: 3060, 2955, 2930, 2879, 1739, 1678, 1637, 1597, 1167, 985, 732, 688. ^{1}H-NMR: 8.34–8.25 (*m*, 2 H); 7.68–7.58 (*m*, 1 H); 7.54–7.42 (*m*, 2 H); 4.52–4.41 (*m*, 1 H); 4.34–4.14 (*m*, 2 H); 1.94 (*oct.*, $J = 6.4$, 1 H); 1.07 (*d*, $J = 6.8$, 3 H); 0.99 (*d*, $J = 6.8$, 3 H). MS: 217 (2.1, M^+), 189 (2), 175 (5), 146 (1.7), 105 (100), 77 (29). Anal. calc. for $C_{13}H_{15}NO_2$ (217.27): C 71.87, H 6.96, N 6.45; found: C 71.68, H 7.05, N 6.36.

3. Paterno-Büchi *Reaction Using* **1b** *and (S)-***1c**. rac-*4,5-Dihydro-4,4-dimethyl-2-(3,3,4,4-tetramethyl-2-phenyloxetan-2-yl)oxazol* ((±)-**2b**). Irradiation of **1b** (5.0 g, 24.6 mmol) and 2,3-dimethylbut-2-ene (4.25 g, 50 mmol) in benzene (250 ml), 7.5 h. Yield 50%. M.p. 69.0–70.5° (hexane), R_f 0.20. IR: 3064, 2970, 2895, 1652, 1599, 1038, 1014, 760, 699. ^{1}H-NMR: 7.67–7.58 (*m*, 2 H); 7.40–7.22 (*m*, 3 H); 3.92 (*AB* ('*q*'), $J = 9.2$, 2 H); 1.49 (*s*, 3 H);

1.35 (*s*, 3 H); 1.30 (*s*, 3 H); 1.23 (*s*, 3 H); 1.20 (*s*, 3 H); 0.82 (*s*, 3 H). MS: 288 (1, $M^+ + H$), 228 (33), 204 (77), 105 (90), 84 (100), 69 (80). Anal. calc. for $C_{18}H_{25}NO_2$ (287.41): C 75.22, H 8.77, N 4.87; found: C 74.92, H 8.99, N 4.91.

By-product: rac-*4,5-Dihydro-4,4-dimethyl-α-phenyloxazol-2-methanol* (**4**) [11]. Yield 17%. B.p. 132–138°/0.05 Torr. IR, ^{1}H-NMR and MS: in accordance with structure.

*(−)-(2′*R*,4*S*)- and (+)-(2′*S*,4*S*)-4,5-Dihydro-4-isopropyl-2-(3′,3′,4′,4′-tetramethyl-2′-phenyloxetan-2′-yl)-oxazol* ((2′*R*,4*S*)- and (2′*S*,4*S*)-**2c**, resp.). Irradiation of (*S*)-**1c** (10.88 g, 50.08 mmol)/14.18 g 2,3-dimethylbut-2-ene (0.17 mmol) in 500 ml benzene, 24 h. $\alpha = 1.22$.

*(2′*R*,4*S*)-***2c***: Yield 21%. $[\alpha]_D^{20} = -68.4$ ($c = 0.8$, $CHCl_3$). R_f 0.28. IR: 3061, 2961, 2874, 1659, 1599, 1082, 757, 707. ^{1}H-NMR: 7.65–7.62 (*m*, 2 H); 7.33–7.25 (*m*, 3 H); 4.26–4.19 (*m*, 1 H); 4.02–3.95 (*m*, 1 H); 2.92–2.77 (*m*, 1 H); 1.90–1.67 (*m*, 1 H); 1.50 (*s*, 3 H); 1.33 (*s*, 3 H); 1.23 (*s*, 3 H); 1.0 (*d*, $J = 6.8$, 3 H); 0.89 (*d*, $J = 6.7$, 3 H); 0.83 (*s*, 3 H). MS: 243 (7, $M^+ - C_3H_6O$), 218 (100), 105 (56), 84 (50), 69 (33). Anal. calc. for $C_{19}H_{27}NO_2$ (301.43): C 75.71, H 9.03, N 4.65; found: C 75.10, H 9.18, N 4.76.

*(2′*S*,4*S*)-***2c***: Yield 16%. $[\alpha]_D^{20} = +10.9$ ($c = 1.0$, $CHCl_3$). R_f 0.23. IR: 3056, 2957, 2924, 1657, 1598, 1081, 757, 703. ^{1}H-NMR: 7.66–7.57 (*m*, 2 H); 7.39–7.19 (*m*, 3 H); 4.26–4.13 (*m*, 1 H); 4.04–3.91 (*m*, 2 H); 1.90–1.68 (*m*, 1 H); 1.47 (*s*, 3 H); 1.36 (*s*, 3 H); 1.24 (*s*, 3 H); 0.87 (*d*, $J = 6.8$, 3 H); 0.83 (*s*, 3 H); 0.71 (*d*, $J = 6.8$, 3 H). MS: 243 (7, $M^+ - C_3H_6O$), 218 (86), 105 (78), 84 (100), 69 (53). Anal. calc. for $C_{19}H_{27}NO_2$ (301.43): C 75.71, H 9.03, N 4.65; found: C 75.20, H 9.10, N 4.63.

4. *(±)-, (+)-(*R*)-, and (−)-(*S*)-4,5-Dihydro-3-hydroxy-4,4,5,5-tetramethyl-3-phenylfuran-2(3*H*)-one* ((±)-, (*R*)-, and (*S*)-**3**, resp.). 4.1. *Acidic Hydrolysis of (±)-***2b** *and (2′*R*,4*S*)- and (2′*S*,4*S*)-***2c***. The dihydrooxazol was refluxed with 1N HCl/EtOH 1:1 for 24 h. Extraction with Et_2O, washing of the org. phase with H_2O and brine, drying (K_2CO_3), and evaporation gave crude colourless **3** which was recrystallized from pentane or hexane.

*(±)-***3**: Yield 84%. M.p. 124–125° (hexane). IR: 3292, 3055, 2961, 2938, 1761, 1110, 1058, 768, 707. ^{1}H-NMR: 7.48–7.31 (*m*, 5 H); 2.90 (br. *s*, OH); 1.63 (*s*, 3 H); 1.31 (*s*, 3 H); 1.14 (*s*, 3 H); 0.59 (*s*, 3 H). MS: 190 (36, $M^+ - CO_2$), 175 (40), 148 (15), 105 (100), 84 (86), 69 (43). Anal. calc. for $C_{14}H_{18}O_3$ (234.30): C 71.77, H 7.74; found: C 71.52, H 7.89.

*(S)-***3**: Yield 85%. M.p. 92–93° (pentane). $[\alpha]_D^{20} = -164.4$ ($c = 0.8$, $CHCl_3$). Anal. calc. for $C_{14}H_{18}O_3$ (234.30): C 71.77, H 7.74; found: C 71.55, H 7.81.

*(R)-***3**: Yield 67%. $[\alpha]_D^{20} = +164.1$ ($c = 0.6$, $CHCl_3$).

4.2. Paterno-Büchi *Reaction Using* **1a**. Irradiation of **1a** (58 g, 0.35 mol)/2,3-dimethylbut-2-ene (71 g, 0.84 mol) in 5 l of toluene, 2.5 h. Evaporation gave a viscous yellow oil of (±)-**2a** (81.6 g, 93%). This material was heated to reflux in 1N HCl/EtOH 1:1 (1 l) for 16 h. After cooling to r.t., the mixture was extracted with Et_2O (4 × 400 ml), the org. phase washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried (K_2CO_3), and evaporated: pale yellow oil. Crystallization from heptane gave 53.8 g (65%) of (±)-**3**.

4.3. *Separation of the Enantiomers of (±)-***2d** *by Formation of Diastereoisomeric Salts.* rac-*3,3,4,4-Tetramethyl-2-phenyloxetane-2-carboxylic Acid* ((±)-**2d**). A soln. of (±)-**2a** (81.2 g, 0.33 mol) in EtOH 10% aq. KOH 1:1 (600 ml) was refluxed for 16 h. After cooling to r.t., the clear soln. was poured onto 500 ml of ice/H_2O and acidified with conc. HCl soln. (pH 2). Extraction with CH_2Cl_2 (3 × 500 ml), washing of the org. phase with H_2O (until pH 7), drying ($MgSO_4$), and evaporation gave 61 g of a colourless powder of (±)-**2d**. Yield 80%. M.p. 120° (H_2O). IR: 3700–2200, 3094, 2995, 2966, 2882, 1761, 1598, 1484, 1040, 1012, 761, 695. ^{1}H-NMR: 10.0–8.5 (br., 1 H); 7.64–7.60 (*m*, 2 H); 7.42–7.29 (*m*, 3 H); 1.49 (*s*, 3 H); 1.36 (*s*, 3 H); 1.34 (*s*, 3 H); 0.84 (*s*, 3 H). MS: 189 (31, $M^+ - COOH$), 158 (3), 105 (100), 84 (30), 69 (28). Anal. calc. for $C_{14}H_{18}O_3$ (234.30): C 71.77, H 7.74; found: C 71.82, H 7.88.

(R)-α-Methylbenzylammonium (S)-3,3,4,4-Tetramethyl-2-phenyloxetane-2-carboxylate ((*R*,*S*)-**6**). A soln. of 39.8 g of (±)-**2d** (0.17 mol) in MeOH (800 ml) was treated with (+)-(*R*)-α-methylbenzylamine (20.58 g, 0.17 mol). The clear soln. was heated to reflux for 30 min and H_2O (800 ml) added. The crystals formed after 24 h at r.t. were recrystallized again from 800 ml of MeOH/H_2O 1:1 to yield 20 g of pure (*R*,*S*)-**6**. Yield 66% rel. to 1 diastereoisomer. M.p. 218–220°. IR: 3680–2200, 2989, 2869, 2669, 1641, 1614, 1538, 1482, 1449, 1048, 1013, 742, 701. ^{1}H-NMR ((D$_6$)DMSO): 8.00–7.10 (br. *m*, 2 H); 7.66–7.54 (*m*, 2 H); 7.48–7.38 (*m*, 2 H); 7.38–7.13 (*m*, 6 H); 4.16 (*q*, $J = 6.5$, 1 H); 3.78–3.00 (br. *m*, 1 H); 1.36 (*d*, $J = 6.7$, 3 H); 1.29 (*s*, 3 H); 1.25 (*s*, 3 H); 1.10 (*s*, 3 H); 0.73 (*s*, 3 H). MS: 189 (12, $M^+ - C_9H_{12}NO_2$), 105 (100), 84 (17), 77 (21), 69 (18), 43 (11). Anal. calc. for $C_{22}H_{29}NO_3$ (355.48): C 74.33, H 8.22, N 3.94; found: C 74.44, H 8.05, N 3.93.

A soln. of (*R*,*S*)-**6** (18.0 g, 50.6 mmol) in 400 ml of 1N HCl/EtOH 1:1 was heated to reflux for 16 h. After cooling to r.t., extraction with Et_2O (4 × 300 ml), washing the org. phase twice with sat. aq. $NaHCO_3$ soln. (100 ml) and H_2O, drying (K_2CO_3), and evaporation, a pale yellow oil was obtained. Crystallization from pentane yielded 9.58 g (81%) of (*S*)-**3**. $[\alpha]_D^{20} = -164.63$ ($c = 0.8$, $CHCl_3$).

5. *Acylation of* **3**. *General Procedure.* The soln. of **3** in abs. THF was treated with 1.2 equiv. of BuLi (1.6M in hexane) at r.t. and stirred under Ar. After 24 h, a colourless precipitate was formed, and the mixture was quenched with 1.5 equiv. of an acyl chloride or acid anhydride at 0°. After further stirring for 18 h at r.t., the soln. was treated with a sat. aq. soln. of NH_4Cl and extracted with Et_2O. The org. phase was washed with H_2O, $NaHCO_3$, and dried (K_2CO_3). Evaporation of the solvent gave pale yellow oils which were crystallized to yield the crystalline products.

(3'RS)-Tetrahydro-4',4',5',5'-tetramethyl-2'-oxo-3'-phenylfur-3'-yl (1S,4R)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate ((3'*RS*)-**5**): Yield 45%. HPLC (1*S*,4*R*,3'*S*) and (1*S*,4*R*,3'*R*) diastereoisomer at t_R 14.4 and 12.5 min, resp. (3'*RS*)-**5**: M.p. 255–256° (Et_2O). IR: 3060, 2970, 2939, 1789, 1701, 1495, 1269, 1099, 1059, 768, 741, 703. ^{1}H-NMR: 7.46–7.29 (*m*, 5 H); 2.41–2.22 (*m*, 1 H); 2.10–1.84 (*m*, 2 H); 1.76–1.63 (*m*, 1 H); 1.67 (br. *s*, 3 H); 1.35 (*s*, 1.5 H); 1.33 (*s*, 1.5 H); 1.28 (*s*, 1.5 H); 1.27 (*s*, 1.5 H); 1.10 (*s*, 3 H); 1.00 (*s*, 1.5 H); 0.98 (*s*, 1.5 H); 0.96 (br. *s*, 3 H); 0.59 (*s*, 1.5 H); 0.58 (*s*, 1.5 H). MS: 414 (2.8, M^+), 399 (2), 370 (3.6), 355 (1), 313 (11), 172 (36), 105 (100), 83 (77), 43 (91). Anal. calc. for $C_{24}H_{30}O_6$ (414.50): C 69.55, H 7.30; found: C 69.21, H 7.14.

(3'*S*)-**5**: Yield 56%. HPLC of the crude reaction mixture: 1 peak, t_R 14.4 min. M.p. 255–256° (Et_2O). $[\alpha]_D^{20} = -173 \pm 2$ (*c* = 0.15, $CHCl_3$). ^{1}H-NMR: 7.47–7.33 (*m*, 5 H); 2.40–2.27 (*m*, 1 H); 2.10–1.84 (*m*, 2 H); 1.76–1.63 (*m*, 1 H); 1.67 (*s*, 3 H); 1.35 (*s*, 3 H); 1.27 (*s*, 3 H); 1.10 (*s*, 3 H); 0.98 (*s*, 3 H); 0.96 (*s*, 3 H); 0.58 (*s*, 3 H).

*X-Ray Analysis of (3'S)-***5**. *Crystal data:* orthorhombic $P2_12_12_1$; *a* = 7.696(9), *b* = 15.516(6), *c* = 18.429(6) Å; *D* = 1.251 Mg/m^3, *Z* = 4. *Data collection:* crystal size, 0.17 × 0.17 × 0.5 mm^3; temp., 183 K; wavelength, λ 0.71069 Å; $\theta_{min}/\theta_{max}$, 0/56°; peak/background ratio; 5:1; total data measured 3039, excluding standards; total data observed, 2015. The structure was determined by direct methods using the SHELXS-86 package; the refinement was performed using SHELXTL PLUS (MicroVAX II) package of the *R3m*[1]). Refinement proceeded to convergence at *R* = 4.95%, *wR* = 5.19% with anisotropic refinement of all non-H-atoms.

rac-*Tetrahydro-4,4,5,5-tetramethyl-2-oxo-3-phenylfur-3-yl 2-Oxo-2-phenyl acetate* ((±)-**7**): Yield 56%. M.p. 126–127° (AcOEt/hexane 1:1). IR: 3060, 2979, 1781, 1710, 1594, 1498, 1193, 1168, 741, 709, 682. ^{1}H-NMR: 8.00–7.96 (*m*, 2 H); 7.70–7.61 (*m*, 1 H); 7.48–7.41 (*m*, 7 H); 1.64 (*s*, 3 H); 1.36 (*s*, 3 H); 1.24 (*s*, 3 H); 0.63 (*s*, 3 H). MS: 217 (6.5, $M^+ - C_8H_5O_3$), 189 (5.8), 159 (3.6), 105 (100), 77 (28), 43 (81). Anal. calc. for $C_{22}H_{22}O_5$ (366.41): C 72.12, H 6.05; found: C 71.92, H 6.23.

(*S*)-**7** (= (*S*)-**1d**): Yield 77%. M.p. 133–134° (AcOEt/hexane 1:1). $[\alpha]_D^{20} = -179.1$ (*c* = 0.7, $CHCl_3$).

rac-*Tetrahydro-4,4,5,5-tetramethyl-2-oxo-3-phenylfur-3-yl hydrogen Benzene-1,2-dicarboxylate* ((±)-**9**): Yield 55%. M.p. 216–217° (EtOH/hexane 1:1). IR: 3600–2400, 3031, 2938, 2666, 1774, 1688, 1570, 1495, 1447, 1280, 1252, 757, 702. ^{1}H-NMR ((D_6)DMSO): 14.10–12.25 (br. *s*, 1 H); 7.86–7.62 (*m*, 4 H); 7.50–7.34 (*m*, 5 H); 1.45 (*s*, 3 H); 1.29 (*s*, 3 H); 1.12 (*s*, 3 H); 0.49 (*s*, 3 H). MS: 234 (4.8, $M^+ - C_8H_4O_3$), 219 (1.4), 190 (27), 175 (36), 149 (27), 105 (100), 84 (86), 69 (46), 43 (29). Anal. calc. for $C_{22}H_{22}O_6$ (382.41): C 69.10, H 5.80; found: C 68.75, H 6.08.

Methyl rac-*Tetrahydro-4,4,5,5-tetramethyl-2-oxo-3-phenylfur-3-yl Carbonate* ((±)-**8**): Yield 72%. M.p. 138–139° (Et_2O). IR: 3020, 2981, 1790, 1755, 1440, 1258, 784, 709. ^{1}H-NMR: 7.42–7.37 (*m*, 5 H); 3.69 (*s*, 3 H); 1.65 (*s*, 3 H); 1.34 (*s*, 3 H); 1.19 (*s*, 3 H); 0.57 (*s*, 3 H). MS: 292 (2.3, M^+), 277 (3.6), 248 (1.9), 233 (3.0), 217 (1.3), 189 (16), 172 (40), 157 (84), 105 (100), 77 (45), 43 (80). Anal. calc. for $C_{16}H_{20}O_5$ (292.33): C 65.74, H 6.90; found: C 65.83, H 7.11.

6. *Diastereoselective* Paterno-Büchi *Reaction Using (S)-***7**. 6.1. *(3'S)-Tetrahydro-4',4',5',5'-tetramethyl-2'-oxo-3'-phenylfur-3'-yl (2R)- and (2S)-3,3,4,4-Tetramethyl-2-phenyloxetane-3-carboxylate* ((2*R*,3'*S*)- and (2*S*,3'*S*)-**2e**, resp.). Irradiation of (*S*)-**7** (1.0 g, 2.73 mmol)/2,3-dimethylbut-2-ene (2.0 g, 23,8 mmol) at −75° (external cooling, dry ice/acetone), 20° or 60° (external heating with an oil bath) in toluene (250 ml) for 2.5 h; α = 1.19. HPLC of the crude photolysate: (2*S*,3'*S*)- and (2*R*,3'*S*)-**2e** at t_R 7.93 and 8.51 min, resp., ratio: −75° 45:55, 20° 26:74, 60° 21:79.

*(2R,3'S)-***2e**: Main diastereoisomer: Yield 25%. M.p. 176–177° (heptane), R_f 0.26. IR: 3065, 2976, 2921, 1771, 1745, 1219, 1030, 765, 704. ^{1}H-NMR: 7.53–7.49 (*m*, 4 H); 7.38–7.22 (*m*, 6 H); 1.46 (*s*, 3 H); 1.27 (*s*, 3 H); 1.18 (*s*, 3 H); 1.17 (*s*, 3 H); 1.15 (*s*, 3 H); 1.06 (*s*, 3 H); 0.75 (*s*, 3 H); 0.51 (*s*, 3 H). MS: 217 (2), 189 (10), 105 (100), 84 (7). Anal. calc. for $C_{28}H_{34}O_5$ (450.58): C 74.64, H 7.61; found: C 74.49, H 7.73.

*(2S,3'S)-***2e**: Minor diastereoisomer: Yield 7%. M.p. 217–219° (heptane). R_f 0.31. ^{1}H-NMR: 7.58–7.51 (*m*, 4 H); 7.40–7.28 (*m*, 6 H); 1.63 (*s*, 3 H); 1.38 (*s*, 3 H); 1.33 (*s*, 3 H); 1.28 (*s*, 3 H); 1.27 (*s*, 3 H); 1.02 (*s*, 3 H); 0.79 (*s*, 3 H); 0.46 (*s*, 3 H).

6.2. *By-product of (±)-***7** → *(±)-***2e** *and of (S)-***7** → *(2S,3'S)-***2e**/*(2R,3'S)-***2e**: rac-*Tetrahydro-4,4,5,5-tetramethyl-2-oxo-3-phenylfur-3-yl α-Hydroxybenzeneacetate* (**10**): Yield 15%. M.p. 228–230° (EtOH/hexane 2:8). R_f 0.19. IR: 3481, 3061, 2979, 2940, 1778, 1719, 1497, 1248, 1015, 758, 701. ^{1}H-NMR: 7.68–7.52 (*m*, 2 H); 7.51–7.42

[1]) Coordinates and thermal parameters have been deposited at the *Cambridge Crystallographic Data Centre.*

(*m*, 1 H); 7.36–7.24 (*m*, 4 H); 7.22–7.05 (*m*, 8 H); 7.04–6.86 (*m*, 5 H); 5.45 (*s*, 1 H); 5.42 (*s*, 1 H); 1.39 (*s*, 3 H); 1.24 (*s*, 3 H); 1.14 (*s*, 3 H); 1.07 (*s*, 3 H); 0.91 (*s*, 3 H); 0.85 (*s*, 3 H); 0.50 (*s*, 3 H); 0.42 (*s*, 3 H). Anal. calc. for $C_{22}H_{24}O_5$ (368.43): C 71.72, H 6.57; found: C 71.89, H 6.40.

6.3. *Acidic Hydrolysis.* For 16 h, 0.26 g (0.58 mmol) of (2*R*,3'*S*)-**2e**/(2*S*,3'*S*)-**2e** (74:26) in 10 ml of 1N HCl/EtOH 1:1 were heated to reflux. Extraction of the resulting mixture with Et_2O (3 × 50 ml), washing of the org. phase with sat. aq. $NaHCO_3$ soln. and H_2O, drying (K_2CO_3), and evaporation gave 240 mg (89%) of a colourless oil of (*S*)-**3**. $[\alpha]_D^{20} = -106.8$ ($c = 0.5$, $CHCl_3$).

REFERENCES

[1] G. Helmchen, A.F. Abdel Hady, H. Hartmann, R. Karge, A. Krotz, K. Sartor, M. Urmann, *Pure Appl. Chem.* **1989,** *61,* 409.

[2] M. Demuth, G. Mikhail, *Synthesis* **1989,** 145.

[3] a) R. Pelzer, P. Jütten, H.-D. Scharf, *Chem. Ber.* **1989,** *122,* 487; b) M. Weuthen, H.-D. Scharf, J. Runsink, R. Vaßen, *Chem. Ber.* **1988,** *121,* 971; c) H. Koch, H.-D. Scharf, J. Runsink, H. Leismann, *ibid.* **1985,** *118,* 1485; d) H. Koch, J. Runsink, H.-D. Scharf, *Tetrahedron Lett.* **1983,** *24,* 3217; e) R. Pelzer, H.-D. Scharf, H. Buschmann, J. Runsink, *Chem. Ber.* **1989,** *122,* 1187; f) H. Buschmann, H.-D. Scharf, N. Hoffmann, M.W. Plath, J. Runsink, *J. Am. Chem. Soc.* **1989,** *111,* 5367.

[4] A. Roloff, K. Meier, M. Riediker, *Pure Appl. Chem.* **1986,** *58,* 1267.

[5] a) H. Gerlach, *Helv. Chim. Acta* **1968,** *51,* 1587; b) W. Tochtermann, G.-R. Schröder, G. Snatzke, E.-A. Peters, K. Peters, H.G. von Schnering, *Chem. Ber.* **1988,** *121,* 1625.

[6] H. Gotthardt, W. Lenz, *Angew. Chem.* **1979,** *91,* 926.

[7] H.A.J. Carless, in 'Photochemistry in Organic Synthesis', Ed. J.D. Coyle, The Royal Society of Chemistry, Burlington House, London, 1986, Chapt. 6.

[8] H.B. Bürgi, J.D. Dunitz, J.M. Lehn, G. Wipf, *Tetrahedron* **1974,** *30,* 1563.

[9] R.S. Cahn, C. Ingold, V. Prelog, *Angew. Chem. Int. Ed.* **1966,** *5,* 385.

[10] K.H. Pfoertner, in [7], Chapt. 13.

[11] L.N. Pridgen, G. Miller, *J. Heterocycl. Chem.* **1983,** *20,* 1223.

[12] H. Firouzabadi, E. Ghaderi, *Tetrahedron Lett.* **1978,** 839.

[13] M.S. Kharasch, H.C. Brown, *J. Am. Chem. Soc.* **1942,** *64,* 329.