199. Total Synthesis of (±)-2-Pupukeanone[1])

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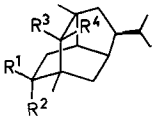
Summary

(±)-2-Pupukeanone (**4**) has been synthesized, the key step being the intramolecular *Diels-Alder* reaction of the intermediate **13** to **14** (42%) and **15** (14%). The bromodiene **12** has been obtained from the reaction of α-isopropylidene-γ-lactone *(Scheme 2)* with sodium phenylselenide and subsequent esterification to **9**, oxidation and thermal elimination of which furnished **10**. Reduction of **10** with diisobutylaluminium hydride and treatment of the resulting alcohol **11** with PBr_3 led to the required bromodiene **12**. Finally, hydrogenation of **14** on Pt(C) in CH_3OH gave a 4:1 mixture of 2-pupukeanone (**4**) and epi-2-pupukeanone **16**.

Introduction. – *Scheuer et al.* isolated 9-isocyanopupukeane (**1**) [1] and 2-isocyanopupukeane (**2**) [2], two defense allomones, from the nudibranch *Phyllidia varicosa* and from its prey, a sponge, *Hymeniacidon sp.* Three groups reported lately the synthesis of **1** and of its degradation product 9-pupukeanone (**3**) [3]. A synthesis of **2** was also achieved [4].



1 R^1 = –NC R^2, R^3, R^4 = H
2 R^3 = –NC R^1, R^2, R^4 = H
3 R^1, R^2 = O R^3, R^4 = H
4 R^3, R^4 = O R^1, R^2 = H

In this report, we describe a short synthesis of 2-pupukeanone (**4**) which has been intermediate in the synthesis of **2** [4]. The key step of the present synthesis is an intramolecular *Diels-Alder* addition based on the smooth ring closure of 2,6-dimethyl-6-(2,4-pentadienyl)cyclohexa-2,4-dien-1-one as observed by *Schmid et al.* [5]. Of particular importance is the fact that heating **5** with 2-bromomethyl-1,3-butadiene in benzene gives a 1:3,5 mixture of **6** and **7** in 58% yield *(Scheme 1)* [5c].

Results. – For our synthesis, the side chain 3-bromomethyl-4-methyl-1,3-pentadiene (**12**) was used *(Scheme 2)*. Reaction of α-isopropylidene-γ-butyrolactone (**8**) [6] with sodium phenylselenide [7] and subsequent esterification of the intermediate acid with

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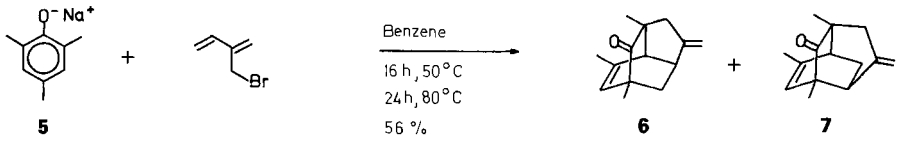
Scheme 1



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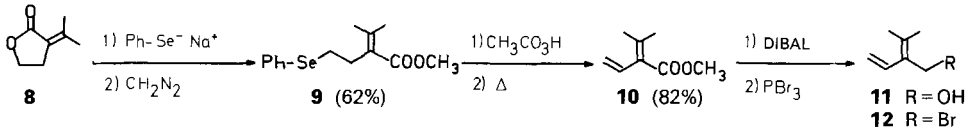
CH_2N_2 yielded **9**. Oxidation of the seleno-ester with peracetic acid and thermal elimination of the selenoxide [8] furnished the diene-ester **10**[3]). Reduction of **10** with diisobutylaluminium hydride (DIBAL) to the corresponding alcohol **11**[4]) and conversion of the alcohol to the bromide **12** were achieved in virtually quantitative yield.

Scheme 2



8 **9** (62%) **10** (82%) **11** R = OH **12** R = Br

Reaction of sodium 2,6-dimethylphenolate in benzene with **12** at 0–5 °C yielded the dienone **13**, which, without isolation, was heated at 80 °C for six hours. A 3:1 mixture of the two easily separable tricyclic ketones **14** and **15** was obtained in 58% yield *(Scheme 3)*. The reaction **13**→**14** + **15** is kinetically controlled, the products being stable under the reaction conditions. However, **15** can be converted in 85% yield to the thermodynamically more stable isomer **14** by heating at 250 °C for five minutes (see also [5c]). Unambiguous assignment of the structures **14** and **15** is possible on grounds of the ^{1}H-NMR spectra. Decoupling experiments proved the sequence of protons H–C(9), H–C(8), H–C(7), H–C(6), H–C(10), H′–C(10) for **14** and H–C(4), H–C(5), H–C(6), H–C(7), H′–C(7), H–C(8) for **15**.

The regioselectivity of the intramolecular *Diels-Alder* addition of **13** is reversed compared to the example in *Scheme 1* (see for discussion of sense I (modus I) and sense II (modus II) additions [5b] [12] [13]). In our opinion, the reason for this change in regioselectivity is the severe steric interaction between the isopropylidene group and the C(2)-methyl group in the transition state leading form **13** to **15.**

The final step of the synthesis, a stereoselective hydrogenation of **14** to **4** turned out to be more difficult than originally anticipated. The best catalyst of those tried[5]) was Pt

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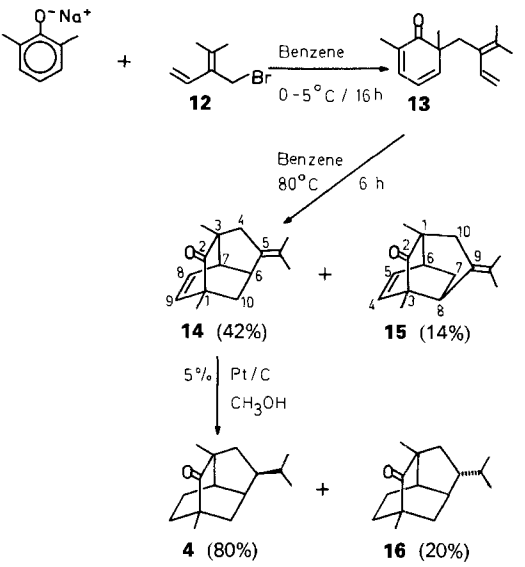
[3]) The probably most obvious preparation of **10**, the reaction of the α-anion of methyl 2-butenoate with acetone and subsequent dehydration of the tertiary alcohol ($SOCl_2$, pyridine, Et_2O) leads in 60% overall yield to a *ca.* 2:1 mixture of methyl 2-isopropenyl-3-butenoate and **10**, which are tedious to separate. Attempts to isomerize the unwanted isomer into **10** exclusively furnished methyl 2-isopropenyl-2-butenoate.

[4]) Alcohol **11** was also synthesized starting with bromomethyl isopropyl ketone [9]. The latter reacted with vinyl $MgBr_2$ [10] in THF to 1-isopropyl-1-vinylethylenoxide (80%), which was converted to **11** with the magnesium derivative of isopropylcyclohexylamine (MICA) [11] in 50% yield.

[5]) $(Ph_3P)_3RhCl$ and Ir-black only hydrogenated the C(8), C(9) double bond. Pd(5% on C) in Et_2O at 100 psi gave a 1:3 mixture of **4** and **16**. PtO_2 in AcOH at 1 atm furnished a 1:1 mixture of the two epimers.

Scheme 3



(5% on charcoal) in MeOH, yielding a 4:1 mixture of 2-pupukeanone (**4**)[6]) and epi-2-pupukeanone (**16**).

From the study of *Dreiding* models of **4** and **16**, one can expect two major detectable differences between the two epimers in their ^{1}H- and ^{13}C-NMR spectra. First in **16** two dihedral angles (H–C(6)/H–C(5) and/H_{endo}–C(10)) are close to 90°. Therefore couplings with only two vicinal H-atom (H–C(6)/H–C(7) and H–C(6)/H_{exo}–C(10)) is expected to be observable. In contrast, in **4** coupling with three vicinal H-atoms is expected. This was actually observed. H–C(6), which is at lowest field in both spectra, appears as *dd* (2.15 ppm) in **16** and as *ddd* (2.32 ppm) in **4.** Second, in **4**, in contrast to **16**, one would expect a strong γ-effect in the ^{13}C-NMR spectra on C(10) due to the nearly eclipsed position of C(10) relative to the i-Pr group. The four triplets in **16** appear at 42.1, 41.6, 31.8, and 17 ppm, while in **4** their position is at 42.1, 34.0, 30.1, and 17.7 ppm. Therefore, three of the triplets appear at similar field in both compounds. Only one is shifted to higher field in **4** by at least 7 ppm.

In conclusion, we described a seven-step synthesis of 2-pupukeanone (**4**) starting with 2,6-dimethylphenol. This represents also a new approach to 2-isocyanopupukeanone (**2**), since the conversion of **4** into **2** has already been demonstrated [4].

We thank Mr. *U. Müller* very much for skilled experimental work and Dr. *E. Billeter* for many stimulating and critical discussions of the NMR spectra. Thanks are also due to Mr. *R. Kaiser* and Dr. *M. Hrivnac* for performing the prep. GC separations.

[6]) Unfortunately we were not able to receive a sample of authentic material for comparison.

Experimental Part

General. Melting points (m.p.) were determined in a *Büchi* melting point apparatus (type Dr. *Tottoli*) in a capillary tube and are uncorrected. GC analyses were run on a *Carlo Erba* Model *HRGC*, with a capillary column (*Ucon HB 5100* 50 m, 0.31 mm diameter), or on a *Carlo Erba* Model *180*, using a packed column (3 m, 2%, *XE 60* on *Chromosorb G, AWDMCS*, 80–100 mesh). Prep. gas chromatography on a *Carlo Erba* Model *GC*, using a packed column (3 m, 15 mm, 15–10% *Carbowax 20 M on Chromosorb G, AWDMCS*, 80–100 mesh). IR spectra were measured on a *Perkin-Elmer 147* and *247* spectrometer. ^{1}H-NMR spectra were measured on *Varian EM 360, Bruker WH 360* and *Bruker WH 400* spectrometers. ^{13}C-NMR spectra were measured on a *Bruker WH 400*. Mass spectra (MS) were determined on an *EC 21-110 B* apparatus or on a *MAT 212* (*Finnigan Incos* Data System), at 70 eV (rel. intensities in %).

α-Isopropylidene-γ-butyrolactone (**8**). To a suspension of 27.0 g (1.125 mol) of NaH (96%) in 250 ml benzene, 250 g (1.125 mol) of α-(*0,0*-diethylphosphono)-γ-butyrolactone [6] were added dropwise. When the H_2-evolution ceased, 83.3 ml (1.135 mol) acetone were added and the reaction was refluxed for 2 h. The brownish slurry was decanted. The benzene phase was evaporated and the residue distilled in high vacuum: 102.8 g (81%) of **8**: b.p. 90°/0.04 Torr. IR (neat): 1755, 1680. ^{1}H-NMR ($CDCl_3$): 1.88 and 2.28 (2 br. *s*, 6H); 2.90 (*m*, 2H), 4.25 (*t*, 2H).

Methyl 3-Methyl-2-[2-(phenylseleno)ethyl]-2-butenoate (**9**). Diphenyl diselenide (12.5 g, 40 mmol) in 100 ml abs. THF was added dropwise to a dispersion of 1.84 g (77 mmol) of Na in 50 ml refluxing THF within ½ h. The reaction was maintained at reflux for 2 h, cooled and charged with 4.5 ml HMPA. Lactone **8** (8.82 g, 70 mmol) was added to the reddish-brown solution, and the mixture was refluxed for 6 h. The reaction mixture was cooled, quenched with a few ml of MeOH, poured into H_2O and extracted with AcOEt to remove excess diphenyl diselenide. The aq. phase was acidified with 2N HCl and extracted with Et_2O. The ethereal extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was dissolved in 50 ml aq. MeOH (90%); 90 ml of a 0.85 molar ethereal CH_2N_2 solution were added slowly to avoid foaming. The reaction mixture was evaporated. Chromatography of the residue (hexane/AcOEt 7:3) gave 12.8 g (61.4%) of **9** as an oil. IR (neat): 1720, 1640. ^{1}H-NMR ($CDCl_3$): 1.7 and 2.0 (*2s*, 6H); 2.5–3.1 (*m*, 4H); 3.6 (*s*, 3H); 7.3–7.6 (*m*, 5H). MS: 298 (2, M^+), 171 (9), 157 (22), 141 (100), 109 (31), 93 (19), 91 (32), 81 (78), 73 (23), 67 (25), 41 (30), 26 (43).

Methyl 3-Methyl-2-vinyl-2-butenoate (**10**). Compound (**9**) (12.0 g, 40 mmol) in 25 ml THF was dissolved in $CHCl_3$; 11.4 g of a 40% CH_3CO_3H in AcOH were added within 5 to 10 min, and the mixture was stirred for 15 min. The reaction mixture was poured into H_2O and extracted with 50 ml $CHCl_3$. The $CHCl_3$-phase was washed with H_2O, dried (Na_2SO_4) and refluxed for 15 min. The solvent was evaporated and the residue distilled in a *Kugelrohr* apparatus (16 Torr; 60–80°): 4.6 g (82%) of **10.** IR (neat): 1740, 1650. ^{1}H-NMR ($CDCl_3$): 1.8 (*s*, 6H); 3.8 (*s*, 3H); 4.9–5.2 (*m*, 2H); 6.3–6.8 (*dd*, 1H). MS: 140 (100, M^+), 125 (15), 109 (70), 108 (39), 97 (11), 81 (58), 73 (23), 59 (7).

3-Methyl-2-vinyl-2-buten-1-ol (**11**). Compound **10** (4.0 g, 28.5 mmol) in 25 ml abs. THF was cooled to 0°; 60 ml of a 20% solution of DIBAL in hexane were added dropwise with a syringe. The reaction mixture was stirred at r.t. for 15 min, poured into cold 2N HCl and extracted with Et_2O. The Et_2O-phase was washed with H_2O, dried (Na_2SO_4) and the solvent evaporated. The residue was distilled in a *Kugelrohr* apparatus (0.01 Torr; 40–50°): 3.0 g (97%) of **11**. ^{1}H-NMR ($CDCl_3$): 1.7 (*s*, D_2O-exchangeable, 1H); 1.9 (*2s*, 6H); 4.4 (*s*, 2H), 5.0–5.3 (*m*, 2H); 6.5–7.0 (*dd*, 1H).

3-Bromomethyl-4-methyl-1,3-pentadiene (**12**). Compound **11** (3.0 g, 26 mmol) was dissolved in a mixture of 10 ml pentane and 0.1 ml of pyridine. The solution was cooled to −20°, and 2.5 g (9 mmol) PBr_3 were added dropwise. After the addition, the mixture was stirred for 15 min, poured into H_2O, extracted three times with pentane. The org. phase was washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4) and the solvent evaporated under reduced pressure at 10°: 4.4 g (99%) of **12**, which was used without further purification. ^{1}H-NMR ($CDCl_3$): 1.9 (*s*, 6H); 4.2 (*s*, 2H); 5.0–5.3 (*m*, 2H); 6.4–6.9 (*dd*, 1H).

5-Isopropylidene-1,3-dimethyltricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (**14**) *and 9-Isopropylidene-1,3-dimethyltricyclo[4.4.0.0^{3,8}]dec-4-en-2-one* (**15**). 2,6-Dimethylphenol (3.35 g, 27.5 mmol) was added to a suspension of 0.66 g (27.5 mmol) NaH in 70 ml benzene. After 1 h, the H_2-evolution ceased and 4.7 g (27 mmol) of **12** were added. The mixture was stirred overnight at 0°. The red solution containing the intermediate dienone **13** was washed with 2N NaOH and H_2O and dried (Na_2SO_4). 2,6-Dimethylphenol (3.35 g, 27.6 mmol) was added and the mixture refluxed for 6 h, the solution turned light yellow. The reaction mixture is poured into 2N NaOH, extracted with Et_2O. The org. phase was washed with H_2O, dried (Na_2SO_4) and evaporated. The residue was chromatographed over 50 g silica gel (hexane/AcOEt 9:1): 2.49 g (41.9%) of **14** as an oil and 0.83 g (13.9%) of **15**.

14: IR: 1710. ^{1}H-NMR (360 MHz, $CDCl_3$): 1.10 and 1.19 (2*s*, CH_3–C(1), CH_3–C(3)); 1.21 (*d*, *J* (10*endo*, 10*exo*) = 12, H_{endo}–C(10)); 1.54 and 1.64 (2 br. *s*, = $C(CH_3)_2$); 1.68 (*dd*, *J* (10*endo*, 10*exo*) = 12, *J* (10*exo*, 6) = 10, H_{exo}–C(10)); 2.10 (*dm*, *J* (4a, 4b) = 16, H_a–C(4)); 2.30 (br. *d*, *J* (4a, 4b) = 16, H_b–C(4')); 2.69 (*ddd*, *J* (8, 7) = 6, *J* (6, 7) = 5.5, *J* (9, 7) = 2 H–C(7)); 2.86 (br. *dd*, *J* (6, 7) = 5.5, *J* (6, 10*endo* = 10, *J* (6, 10*endo* ≈ 0, H–C(6)); 5.95 (*dd*, *J* (9, 8) = 8, *J* (9, 7) = 2, H–C(9)); 6.26 (*dd*, *J* (8, 9) = 8, *J* (8, 7) = 6, H–C(8)). All single proton signals were irradiated and the respective decouplings observed. MS: 216 (51.8, M^+), 188 (23.3), 173 (65.3), 159 (11.4), 145 (100), 131 (58.9), 119 (42.4), 105 (29.2), 91 (33.0), 79 (18.9), 57 (21.9).

15: m.p. 81–82° (pentane). IR ($CHCl_3$): 1720. ^{1}H-NMR (360 MHz, $CDCl_3$): 1.06 and 1.25 (2*s*, CH_3–C(1) and CH_3–C(3)); 1.41 (*dd*, *J* (7*endo*, 7*exo*) = 11.5 Hz, *J* (7*endo*, 6) = 7, *J* (7*endo*, 8) ≈ 0, H_{endo}–C(7)); 1.53 (*d*, *J* (CH_3–C(11), 10) ≈ 1, CH_3–C(11)); 1.69 (*d*, *J* (CH_3–C(11), 10) ≈ 2, CH_3–C(11)); 1.92 (*dd*, *J* (7*endo*, 7*exo* = 11.5, *J* (7, 8) = 6, *J* (7*exo*, 6) ≈ 0, H_{exo}–C(7)); 2.12 (br. *d*, *J* (10a, 10b) = 15, H_a–C(10)); 2.26 (br. *dm*, *J* (10a, 10b) = 15, H_b–C(10)); 2.58 (*m* of overlapping signals, H–C(6) and H–C(8)); 5.60 (*dd*, *J* (4, 5) = 8, *J* (4, 6) = 2, H–C(4)); 6.63 (*dd*, *J* (4, 5) = 8, *J* (5, 6) = 6, H–C(5)). All signals except CH_3-groups were irradiated and the respective decoupling observed. MS: 216 (30, M^+), 173 (14), 145 (11), 122 (100), 105 (8), 95 (23), 77 (9).

Isomerisation of **15** *to* **14.** Compound **15** (0.83 g, 3.8 mmol) was heated to 250° under Ar for 5 min. The reaction product was purified from small amounts of 2,6-dimethylphenol and tars by chromatography over 10 g silica gel (hexane/AcOEt 9:1): 0.71 g (85.5%) of **14**.

Hydrogenation of **14.** To 50 mg Pt(C) (5%) in MeOH under H_2, 50 mg of **14** was added. After 24 h, the reaction mixture was filtered through *Celite*, the solvent evaporated and the residue added to 50 mg of Pt(C) (5%) in MeOH and shaken under H_2 for another 24 h. The catalyst was filtered off as mentioned above and the solvent evaporated: 47 mg of a 4:1 mixture of **4** and **16**, which were separated by prep. gas chromatography.

2-Pupukeanone (**4**). IR ($CHCl_3$): 1710, 1470, 1450. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.83 and 0.85 (2*d*, 6H); 0.92 and 1.13 (2*s*, 6H); 1.31 (*dd*, J_1 = 14, J_2 = 7, 1H); 1.38–1.43 (*m*, $CH(CH_3)_2$); 1.52–1.85 (*m*, 9H), 2.32 (*ddd*, H–C(6)). ^{13}C-NMR ($CDCl_3$): 17.7 (*t*); 19.1 (*q*); 20.4 (*q*); 21.6 (*q*); 21.7 (*q*); 29.4 (*d*); 30.1 (*t*); 34.0 (*t*); 38.9 (*d*); 41.5 (*s*); 42.1 (*t*); 47.4 (*d*); 49.5 (*d*); 53.9 (*s*); 222.5 (*s*). MS: 220 (33, M^+), 205 (3), 202 (6), 189 (13), 159 (90), 149 (44), 132 (9), 121 (34), 107 (24), 93 (100), 81 (2), 77 (14), 69 (14), 55 (21), 43 (15), 41 (30).

Epi-2-pupukeanone (**16**). IR ($CHCl_3$): 1706, 1470, 1450. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.82 and 0.89 (2*d*, 6H); 0.91 and 1.12 (2*s*, 6H); 1.06 (*dd*, *J* (10*endo*, 10*exo*) = 13, J_2 = 2, H_{endo}–C(10)); 1.09–1.19 (*m*, 2H); 1.38–1.48 (*m*, $CH(CH_3)_2$); 1.49–1.59 (*m*, 2H); 1.70–1.78 (*m*, 3H); 1.84–1.92 (*m*, 1H); 1.96 (*dd*, *J* (10*endo*, 10*exo*) = 13, *J* (10*exo*, 6) = 9, H_{exo}–C(10)); 2.15 (*dd*, *J* (6, 10*exo*) = 9, *J* (6, 7) = 5, H–C(6)). ^{13}C-NMR ($CDCl_3$): 17.0 (*t*); 19.0 (*q*); 20.2 (*q*); 20.4 (*q*); 21.3 (*q*); 32.8 (*t*); 33.1 (*d*); 40.5 (*d*); 41.6 (*t*); 42.1 (*t*); 42.2 (*s*); 44.3 (*d*); 54.1 (*d*); 54.5 (*s*); 222.1 (*s*). MS: 220 (40, M^+), 205 (5), 202 (4), 189 (34), 177 (29), 159 (16), 149 (52), 135 (10), 121 (30), 107 (27), 93 (100), 81 (28), 55 (20) 41 (28).

REFERENCES

[1] *B.J. Burreson, P.J. Scheuer, J.S. Finer & J. Clardy*, J. Am. Chem. Soc. *97*, 4763 (1975).

[2] *M.R. Hagadone, B.J. Burreson, P.J. Scheuer, J.S. Finer & J. Clardy*, Helv. Chim. Acta *62*, 2484 (1979).

[3] a) *E.J. Corey, M. Behforouz & M. Ishiguro*, J. Am. Chem. Soc. *101*, 1608 (1979); b) *H. Yamamoto & H.L. Sham*, ibid. *101*, 1609 (1979); c) *G.A. Schiehser & J.D. White*, J. Org. Chem. *45*, 1864 (1980); d) *E. Piers & M. Winter*, Justus Liebigs Ann. Chem. *1982*, 973.

[4] *E.J. Corey & M. Ishiguro*, Tetrahedron Lett. *1979*, 2745.

[5] a) *H. Greuter, G. Frater & H. Schmid*, Helv. Chim. Acta *55*, 526 (1972); b) *H. Greuter, H. Schmid & G. Frater*, ibid. *60*, 1701 (1977); c) *H. Greuter & H. Schmid*, ibid. *55*, 2382 (1972).

[6] a) *W. Walter & H.L. Weidemann*, Liebigs Ann. *685*, 29 (1965); b) *T. Minami, I. Niki & T. Agawa*, J. Org. Chem. *39*, 3236 (1974).

[7] a) *D. Liotta & H. Santiesteban*, Tetrahedron Lett. *1977*, 4369; b) *R.M. Scarborough, Jr. & A.B. Smith*, ibid. *1977*, 4361.

[8] *T.R. Hoye & A.J. Caruso*, Tetrahedron Lett. *1978*, 4611.

[9] *M. Gaudry & A. Marquet*, Org. Synthesis, Vol. *55*, 24 (1976).

[10] *K.G. Golodova & S.I. Yakimovich*, Khim. Geterotsikl. *1974*, 19.

[11] *E.J. Corey, A. Marfat, J.R. Falck & J.O. Albright*, J. Am. Chem. Soc. *102*, 1433 (1980).

[12] *A. Krantz & C.Y. Lin*, J. Am. Chem. Soc. *95*, 5662 (1973).

[13] *W. Oppolzer*, Angew. Chem. Int. Ed. *16*, 10 (1977).