Tetrahedron Vol 45, No 6, pp 1703 to 1710, 1989
Printed in Great Britain

0040-4020/89 $3 00+ 00
Pergamon Press plc

AN APPROACH TO BUFADIENOLIDES FROM DEOXYCHOLIC ACID.[1]

UV, CD, AND X-RAY DATA OF SOME 22,23-DIHYDROBUFADIENOLIDES

ULRICH WERNER[a], HANS-WOLFGANG HOPPE[a], PETER WELZEL*[a],
GÜNTHER SNATZKE*[a], and ROLAND BOESE*[b]

[a]Fakultät für Chemie der Ruhr-Universität
Postfach 102148, D-4630 Bochum (FRG)

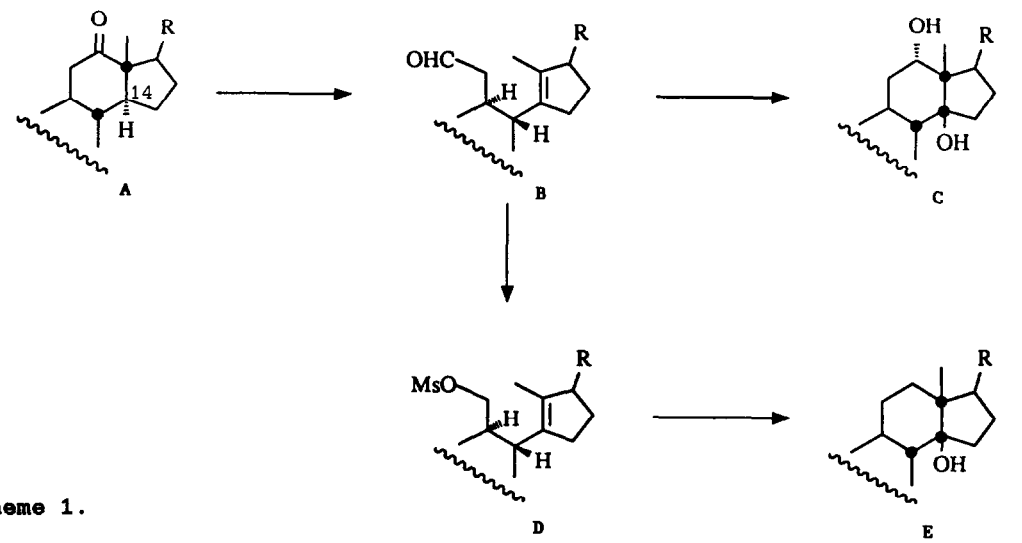
[b]Institut für Anorganische Chemie der Universität-GH Essen
Universitätsstr. 3-5, D-4300 Essen 1 (FRG)

(*Received in Germany* 16 *December* 1988)

Abstract - The electronic transitions of the various chromophores of enol lactones **3a** - **3e** are assigned. The configuration at C-23 of the α-sulfanyl substituted lactones **3b** - **3e** is determined.

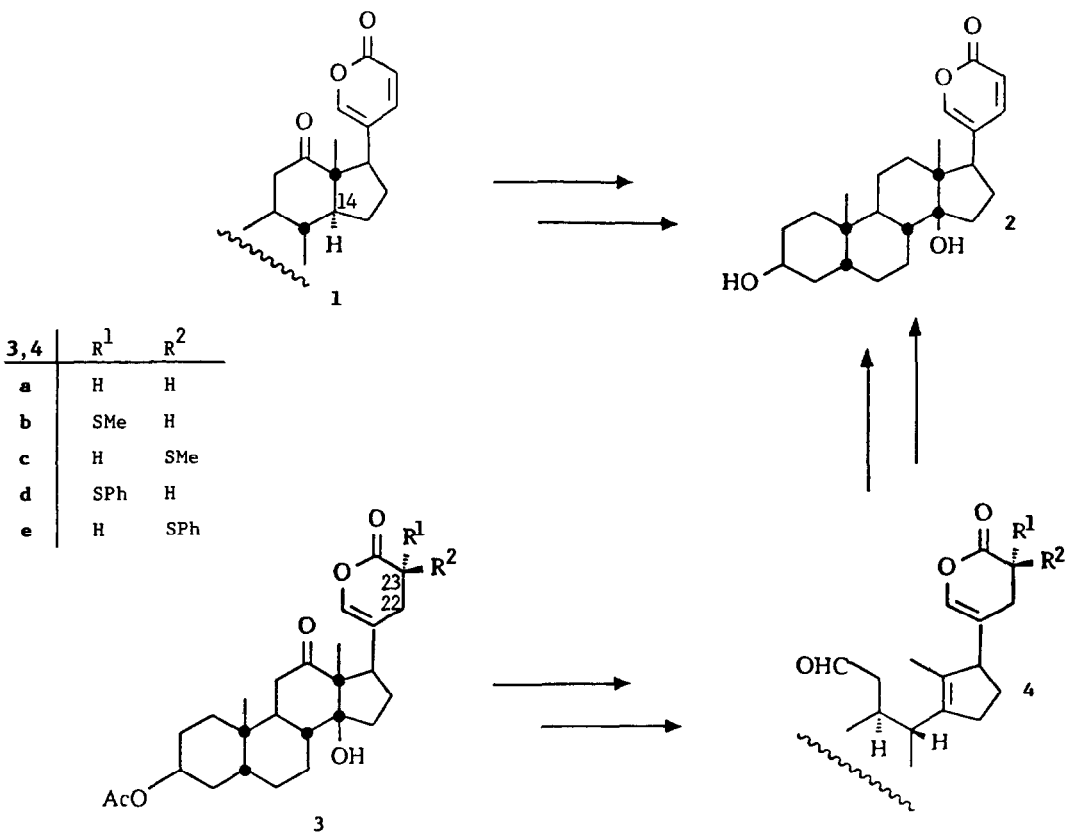
Introduction.

One of the main problems associated with the synthesis of medicinally important cardioactive steroids, e.g. bufalin (**2**), from normal 14α-H steroids is the introduction of the 14β-OH group.[3] Recently, we have shown (see Scheme 1) that photochemical isomerization of 12-oxo-14α-steroids (partial structure **A**) to unsaturated secoaldehydes of type **B**, followed by Prins cyclization opens up a simple access to 12,14β-diols (partial structure **C**), whereas mesylates of type **D** furnish 12-unsubstituted compounds of type **E** under solvolytic conditions.[4,5]



Scheme 1.

This methodology has successfully been exploited for the synthesis of cardenolides.[4] For the extension of this approach to the synthesis of bufalin (**2**) via **1** emerges, however, the problem that it appears impossible to effect selectively the photochemical rearrangement (**A** -> **B**) of a 12-oxo-bufadienolide such as **1** by irradiation into the weak n -> π^* band of the keto group (λ_{max} 300 nm, ϵ < 50) in the presence of the much stronger absorbing 2-pyrone moiety (λ_{max} 300 nm, ϵ = 5500[6]), which is known to react from the excited state(s) to ring-opened products.[7] To circumvent this difficulty we planned to use for the photochemical rearrangement (**A** -> **B**) 23-substituted bufenolides such as **3b** - **3e** and to introduce the missing 22,23 double bond at a later stage of the synthesis (see **4** -> **2**).[2,8,9] In the present study we assign the electronic transitions of the various chromophores in **3a** - **3e** (the synthesis of which has been described elsewhere[2]) on the basis of their UV and CD spectra. We also deduce the configuration at C-23 in **3b** - **3e** by ^{1}H NMR, CD, and X-ray methods.



3,4	R^1	R^2
a	H	H
b	SMe	H
c	H	SMe
d	SPh	H
e	H	SPh

Scheme 2.

UV and CD Spectra of 12-Oxo-bufenolides 3a - 3e

The 23-unsubstituted bufenolide **3a** as well as the methylsulfanyl and the phenylsulfanyl compounds **3b** and **3e** show rather ill-defined UV spectra with a maximum in the 220-240 nm region (Fig.1). The enol lactone chromophore has been reported to absorb at 230-245 nm.[10] Fig.2 reproduces the 300 nm part of the UV spectra (approximately $2x10^{-3}$ mol/l solutions in acetonitrile) . A shoulder around 300 nm in the spectra of both **3a** and **3b** is considered to mark the n -> π^* band of the 12-oxo group. In the spectrum of **3e** this band is hidden by stronger absorptions in this region.

More information about the overlapping absorption bands is furnished by the CD spectra of **3a** - **3e** (Fig. 3-5). The absorption band of the enol lactone chromophore around 240 nm is easily identified in the spectra of **3a**, **3b**, and **3c**, as well as the carbonyl n -> π^* band at 300 nm. Due to the additional presence of the aromatic chromophore, the CD spectra of the phenylsulfanyl compounds **3d** and **3e** display a greater number of Cotton effects, and in this case the enol lactone band can not be assigned with certainty. Furthermore, even in the CD spectra the carbonyl band at 300 nm is masked by other absorptions. The latter observation is in accord with chemical results: Whereas from **3b/3c** upon photolysis a secoaldehyde of type **B** was obtained which was ultimately converted into bufalin (**2**), we have been unable to rearrange the phenylsulfanyl compounds **3d/3e** into the corresponding secoaldehyde.[8]

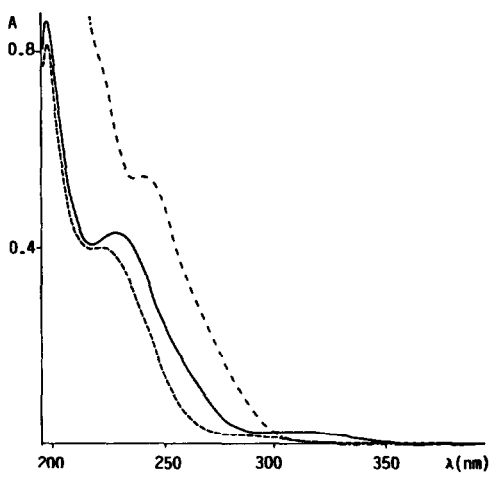


Fig.1.UV spectra of

3a (0.16 mmol/l, - -)
3b (0.15 mmol/l, ——)
3e (0.09 mmol/l, -·-)
in CH_3CN, d = 1 cm

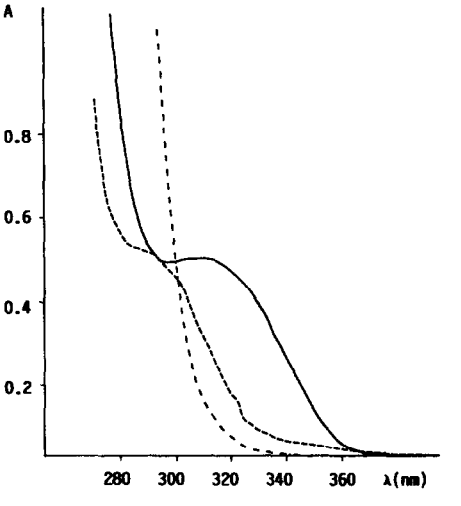


Fig.2.300 nm region of the UV spectra of

3a (3.27 mmol/l, - -)
3b (2.28 mmol/l, ——)
3e (1.88 mmol/l, -·-)
in CH_3CN, d = 1 cm

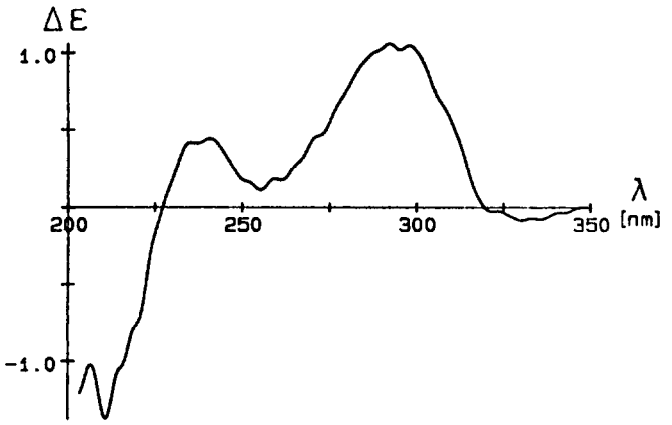


Fig.3. CD spectrum of **3a**.

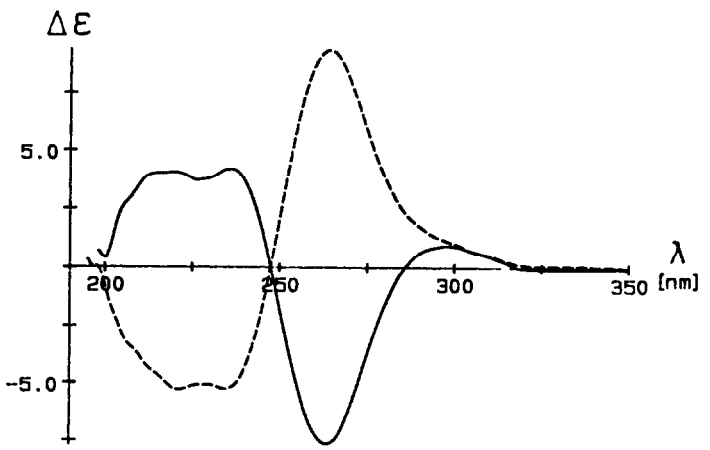


Fig.4. CD spectra of **3b** (--) and **3c** (·).

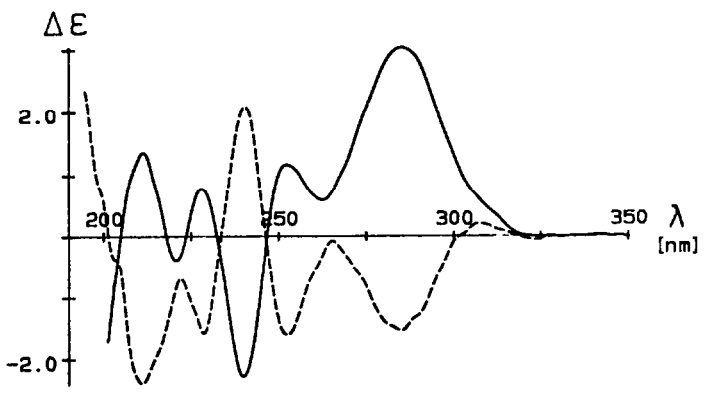
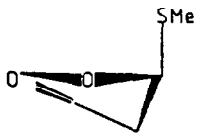


Fig.5. CD spectra of **3d** (--) and **3e** (···).

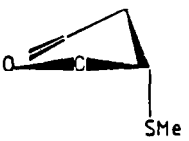
Configuration of 3b and 3c at C-23

From the 400 MHz ^{1}H NMR spectra of **3b** and **3c** it has been concluded that in both compounds the methylsulfanyl substituent adopts an axial orientation (**3b**: $J_{22,22'}$ = 18.1 Hz, $J_{22,23}$ = 6.2 Hz, $J_{22',23}$ = 3.4 Hz; **3c**: $J_{22,22'}$ = 18.1 Hz, $J_{22,23}$ = 6.2 Hz, $J_{22',23}$ = 2.7 Hz). A similar situation has been observed for α-sulfanylated ketones.[11] At the axial position of the hetero substituent dipolar interactions with the carbonyl group are diminished.

For ketones, axially α-substituted with Cl, Br, I, NR_2, or SR, the configuration at the α-carbon can be derived from the sign of the Cotton effect.[12] This "axial haloketone rule" has been found to give the correct configuration for α-amino and α-halo acids, too.[13] From an application of this rule to the methylsulfanyl compounds **3b** and **3c** (see projections **3b'** and **3c'**and Fig. 4) the 23S configuration is deduced for **3c** and 23R for **3b**.



3b'



3c'

Configuration of 3d and 3e at C-23

As in **3b** and **3c**, an axial position of the sulfanyl substituent at C-23 is indicated for **3d** and **3e** by 400 MHz ^{1}H NMR results (**3d**: $J_{22,22'}$ = 17.9 Hz, $J_{22,23}$ = 4.0 Hz, $J_{22',23}$ = 6.0 Hz; **3e**: $J_{22,22'}$ = 17.9 Hz, $J_{22,23}$ = 4.9 Hz, $J_{22',23}$ = 6.0 Hz).[2] Since the enol lactone band in the CD spectra could not be identified with certainty, recourse was made to an X-ray analysis for establishing the configuration at C-23. Fig.6 shows the X-ray structure of the 23S isomer **3e**. The axial position of the phenylsulfanyl substituent which was inferred from the ^{1}H NMR spectra is also clearly visible in the crystal structure. The torsional angle H_R(22)-C(22)-C(23)-H(23) and H_S(22)-C(22)-C(23)-H(23) are 51° and 72°, respectively. In Fig. 7, a standard projection of the X-ray model from O towards C of the lactone (C=O) is represented. Provided that the axial haloketone rule holds in this type of compounds, too, **3e** should display a positive enol lactone Cotton effect. Since the broken-line curve in Fig. 5 was obtained from **3e**, it is the 240 nm band which can be assigned to the enol lactone absorption.

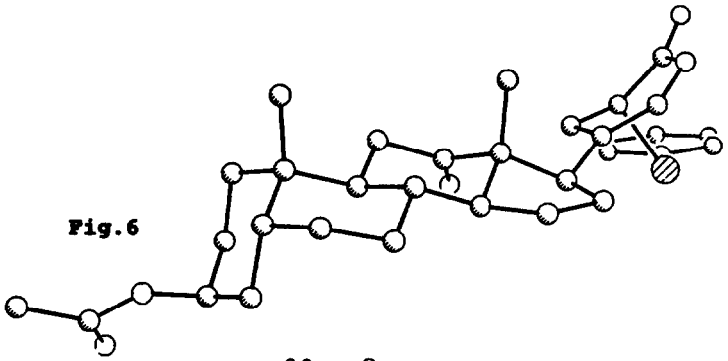


Fig.6

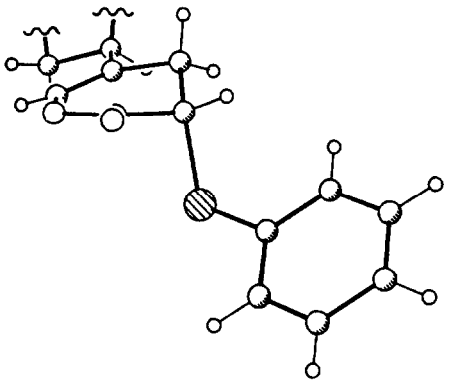


Fig.7

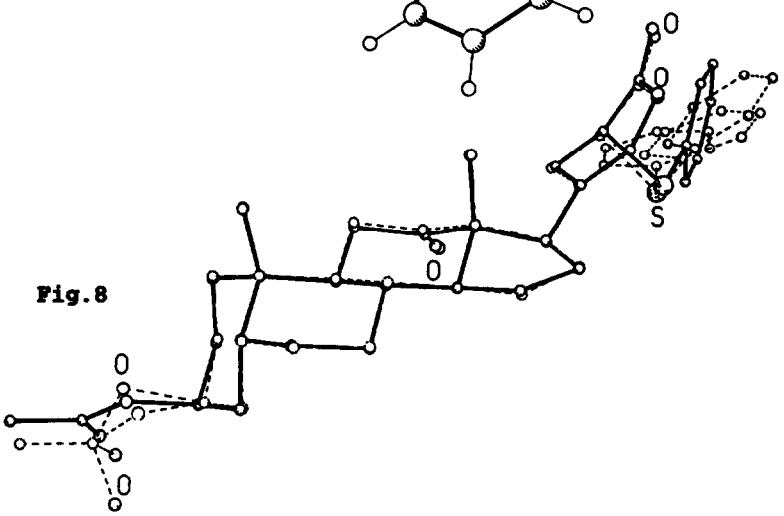


Fig.8

Fig.6. X-ray crystal structure of **3e**.

Fig.7. Projection from O towards C of the lactone-(C=O) of **3e** using X-ray data.

Fig.8. Superpositioning of the two independent molecules of **3e** and the two disordered structures in the unit cell (for further explanations, see Experimental: X-ray structure analysis of **3e**).

Experimental

UV spectra were recorded on a Philips Ph 8740 UV/Vis scanning spectrometer.

CD spectra were measured at 20°C with a Jobin-Yvon-ISA dichrograph Mark III, using 0.5 mmol/l solutions in CH_3CN. Data were collected on-line with a PDP/8-e (5 or 10 data points per nm), and curve smoothing made use of the Golay-Savitzky algorithm. The results are collected in Table 1.

X-ray Structure Analysis of **3e**.
Crystal data: Crystals of **3e** for X-ray analysis were obtained from CH_2Cl_2-hexanes.[2] $C_{32}H_{40}O_5S$ (536.7). Data collection and cell determination were performed at 100K using a Nicolet R3/mV diffractometer with graphite monochromized Mo-K_α radiation. The cell dimensions were derived from the diffractometer angles of 40 centered reflections ($20° \leq 2\theta \leq 25°$). a = 10.968(4)Å, b = 11.739(4)Å, c = 12.354(4)Å, α = 64.44(3)°, β = 77.44(3)°, γ = 89.68(3)°, V = 1393.4(9)Å^3, Z = 2, D_x = 1.28 g/cm^3, μ = 0.15 mm^{-1}. 3739 unique reflections, $2\theta_{max}$ = 45°, 3508 of which observed ($F_o \geq 4\sigma(F)$).
Structure solution and refinement:
Using SHELXTL-Plus software on a MicroVax IIa, the structure solution was performed with direct methods and refined with full matrix least squares. With two independent molecules in the unit cell and the space group P1, only slight conformational differences of both molecules were found with most of the deviations in the S-phenyl group and the ester fragment. These groups were found to be disordered and refined with site occupation factors of 0.5 at each independent molecule, resulting in four conformations. These are shown in Fig. 8, with one conformation outlined, demonstrating the high flexibility of the two functional groups, even in the solid state at low temperature.
With rigid group refinement for the phenyl groups, riding hydrogen atoms with fixed isotropic U of 0.05 and anisotropic U only for the sulfur atoms, least squares converged with 440 parameters at R = 0.082, R_w = 0.086, $w^{-1} = \sigma^2(F_o) + 0.000314\text{-}F_o^2$ and a residual electron density of 0.75e/Å^3 of the final model.
Further details of the of the crystal structure investigation may be obtained from Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshafen 2 (FRG), on quoting the depository number CSD 53601. Any request should be accompanied by the full literature citation for this paper.

Tab.1. CD data (λ_{max} ($\Delta\varepsilon$)) of bufenolides **3a** -**3e**

3a	329 (-0.07), 297 (+1.25), 238 (+0.88)
3b	297 (+0.96), 263 (-7.66), 235 (+4.07)
3c	264 (+9.34), 234 (-5.30)
3d	310 (+0.20), 286 (+3.04), 252 (+1.70), 240 (-2.28), 228 (+0.79), 220 (-0.37), 211 (+1.35)
3e	310 (+0.23), 284 (-1.58), 252 (-1.69), 241 (+1.77), 228 (-1.57), 211 (-2.40)

Acknowledgements - We wish to thank U.Wagner for running the CD spectra. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

[1] For previous work, see ref.[2,4,8]
[2] H.W.Hoppe, M.Kaiser, D.Müller, and P.Welzel, Tetrahedron **1987**, *43*, 2045.
[3] Review: P.Welzel, Proceedings of the 1st International Conference on Chemistry and Biotechnology of Biologically Active Natural Products, Vol.1, Bulgarian Academy of Sciences, Sofia 1981, p.180.
[4] P.Welzel, H.Stein, and Ts.Milkova, Liebigs Ann.Chem. **1982**, 2119, and references therein.
[5] For a different recent approach towards 14ß-OH steroids, see S.Lociuro, Th.Y.R.Tsai, and K.Wiesner, Tetrahedron **1988**, *44*, 35.
[6] Review: L.Dorfman, Chem.Rev. **1953**, *53*, 47.
[7] J.P.Guthrie, C.L.McIntosh, and P.De Mayo, Canad.J.Chem. **1970**, *48*, 237; Y.Kamano and M.Komatsu, Chem.Pharm.Bull. **1969**, *17*, 1698; Y.Kamano, Y.Tanaka, and M.Komatsu, Ibid. **1969**, *17*, 1706.
[8] H.-W.Hoppe and P.Welzel, Tetrahedron Lett. **1986**, *27*, 2459.
[9] For previous routes to 14α-H bufadienolides via 22,23-dihydro derivatives, see W.Haede, W.Fritsch, K.Radscheit, U.Stache, and H.Ruschig, Liebigs Ann.Chem. **1970**, *741*, 92; G.R.Pettit and J.R.Dias, J.Org.Chem. **1971**, *36*, 3207; Ch.R.Engel, R.Bouchard, A.F.de Krassny, L.Ruest, and L.Lessard, Steroids **1969**,*14*, 637; Y.Takeuchi, Y.Makino, K.Maruyama, and E.Yoshii, Heterocycles **1980**, *14*, 163, and references therein. See also, A.Bélanger, P.Brassard, G.Dionne, and Ch.R.Engel, Steroids **1974**, *24*, 377.
[10] A.Yogev and Y.Mazur, Tetrahedron **1966**, *22*, 1317, and references therein.
[11] B.M.Trost, T.N.Salzman, and K.Hiroi, J.Am.Chem.Soc. **1976**, *98*, 4887.
[12] Review: D.N.Kirk, Tetrahedron **1986**, 42, 777.
[13] G.Snatzke and S.H.Doss, Tetrahedron **1972**, *28*, 2539 ; J.Cymerman Craig and W.E.Pereira,Jr., Tetrahedron **1970**, *26*, 3457; W.Gaffield and W.G.Galetto, Tetrahedron **1971**, *27*, 915.