Pergamon

Tetrahedron Letters 40 (1999) 4655–4658

TETRAHEDRON
LETTERS

Concurrent Ring Opening and Halogenation of Spiroketals[1]

Thomas G. LaCour* and P. L. Fuchs*

Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA

Received 2 April 1999; accepted 16 April 1999

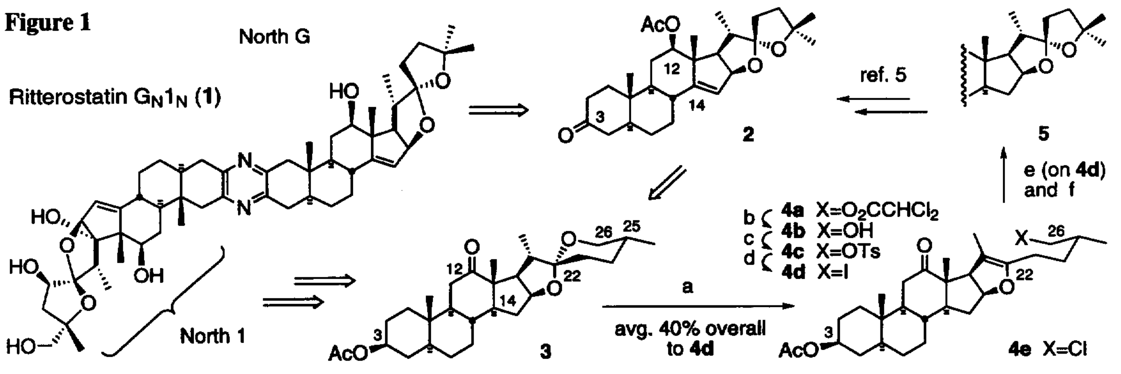
Abstract: Ring opening of various spiroketals with triphenylphosphine dihalides under neutral conditions produced ω-halo-enolethers in good to excellent yield. The method transformed even the very stable spiroketal of hecogenin acetate at temperatures below any previously reported for such isomerative opening. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Acetals, steroids and sterols, phosphonium salts, enol ethers

The structural challenges and extreme antitumor activities displayed by the cephalostatins[2] and ritterazines[3] render them of interest.[4] Recently, we reported the first syntheses of cephalostatin 1 (GI_{50} 1.2 nM)[2] and a very potent "interphylal" hybrid analogue of these marine products, ritterostatin G_N1_N **1** (GI_{50} 14 nM),[5] which incorporated the North G (**2**) subunit of ritterazine G.[3] Derivation of all subunits of these antineoplastics from commercially available hecogenin acetate **3** included an acid catalyzed isomerative spiroketal opening[5,6] with a carboxylic anhydride (ex. **3**→**4a**, Fig. 1, wherein esterification traps the fleeting intermediate pseudosapogenin **4b**). The otherwise efficient synthesis of **2** (13 steps, 15% overall) suffered somewhat in the **3**→**5** sequence. Conversion of **3** to **4a** proved particularly capricious, difficult to scale, required a demanding chromatographic separation and involved subsequent conversion of the sensitive alcohol **4b** to obtain **4c**, **4d** and finally **5**.

Use of dichloroacetic anhydride[6a,b] originally offered an improvement for steroid spiroketal opening in that the C3 acetate is retained, whereas traditional anhydride methods[7] result in C3 transesterification and identical C3/C26 functionality in the derived pseudosapogenins. These positions show surprisingly similar reactivity, and differentiation of C3 and C26 of 5,6-saturated sapogenins has therefore proven historically nontrivial.[8,9] Herein we report a general method that affords *one-step* access to useful **4d/e** type intermediates from spiroketals in good to excellent yields by application of a phosphine dihalide under *neutral conditions, at temperatures below any previously reported for isomerative openings*, followed by filtration through silica.

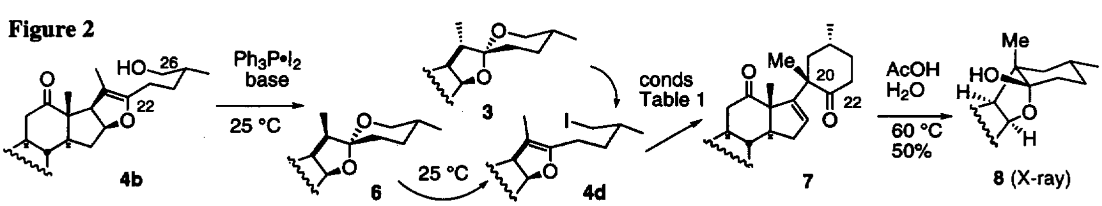
Figure 1



(a) $(Cl_2HCCO)_2O$, PPTs, 35-70%; (b) $KHCO_3$, 80-99%; (c) TsCl, 70-91%; (d) NaI, 99%; (e) DBU, 91%; (f) aq. AcOH, 98%

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00827-8

Figure 2



The new method sprang from attempts to bypass tosylate **4c** by direct conversion of alcohol **4b** to iodide **4d** ($Ph_3P•I_2$, imidazole, 2-12 h).[10] These reactions returned mainly spiroketals **3** (thermodynamic product) and **6** (kinetic product, Fig. 2),[11] by acid-catalyzed cyclization. The lability of alcohols such as **4b** to even trace acid was also evident during tosylation, which gave **4c** (70-90%, 40% if run in CH_2Cl_2 instead of pyridine solvent) accompanied by **3** and **6**. However, a $Ph_3P•I_2$ run allowed to stand 4 days delivered **4d** (40%) and **3** (55%). Although **6** was found to slowly afford mainly **4d** at 25 °C with this reagent system, spiroketal **3** was inert.

Persistent experimentation revealed that transformation of **3** to halides **4** occurred under these essentially neutral conditions at temperatures (130-140 °C) still well below those required by anhydride-mediated openings (180-240 °C),[6,7] *without loss of the 3-acetate or C25 epimerization*[12] (Table 1). Further transformation of **4d** to **7**, obtained as a single diastereomer (confirmed by X-ray of hydrate **8**, Fig. 2)[13] was accomplished by merely extending the reaction time or by resubjecting **4d** to the reaction conditions. Heating **4d** (alone or with base, TCE, 150 °C, 2 h) returned only starting iodide with no trace of **7**.

Table 1. Conditions[a] for isomerative opening of spiroketal **3** with concurrent C26-halogenation.

entry	reagent	base[b]	temp.	time	**4**[c] (halide ratio)[13]	**7**[c]
1	1.1 eq $Ph_3P•I_2$	2.2 eq imidazole	140 °C	2 h	trace	-
2	2.2 eq $Ph_3P•I_2$	4.4 eq imidazole	140 °C	2 h	60% (1:6 **d/e**)	30%
3	2.2 eq $Ph_3P•I_2$	4.4 eq DBMP	140 °C	2 h	62% (1:6 **d/e**)	29%
4	2.2 eq $Ph_3P•I_2$	2.2 eq imidazole	140 °C	1 h	67% (5:1 **d/e**)	25%
5	2.2 eq $Ph_3P•I_2$	2.2 eq imidazole	125 °C	2.5 h	30% (2:1 **d/e**)	62%
6	2.2 eq $Ph_3P•I_2$	2.2 eq 2,6-lutidine	140 °C	1 h	69% (5:1 **d/e**)	24%
7	2.2 eq $Ph_3P•I_2$	0.8 eq 2,6-lutidine	140 °C	0.5 h	75% (8:1 **d/e**)	18%
8	2.2 eq $Ph_3P•I_2$	0.8 eq 2,6-lutidine	140 °C	20 min[d]	60% (25:1 **d/e**)[d]	5%
9	2.2 eq Ph_3P	2.2 eq imidazole	140 °C	2 h	85% (e only)	9%
10	2.2 eq $Ph_3P•Cl_2$	0.8 eq imidazole	140 °C	1 h	90% (e only)	5%
11	2.2 eq $Ph_3P•I_2$	0.8 eq 2,6-lutidine	140 °C	3 h	8% (e only)	87%

[a] 2 mmol **3**, 0.1 M in TCE. [b] DBMP = 2,6-di-*t*-butyl-4-methylpyridine. [c] Isolated yields. [d] 25% unreacted **3**.

Since aliphatic chlorinated solvents, which dissolve the reagent,[10c] were by far superior for the transformation, some chloride **4e** accompanied iodide **4d**. Tetrachloroethane (TCE) permitted sufficient temperature for smooth conversion, but no reaction occurred below 125 °C. Inferior reaction or decomposition was observed in other solvents, including bromo and iodoalkanes, DMF, aliphatic and aromatic hydrocarbons, ethers, nitriles, and aromatic halides. Every soluble "non-nucleophilic" amine base examined served equally well, regardless of steric demand or base strength. Insoluble bases (PVP, alkali carbonates and hydrides) proved unsatisfactory.[14] Minimizing the amount of base decreased reaction time and reduced formation of chloride **4e**. The coproduct Ph_3PO may sequester some HI as $Ph_3P(OH)I$[15] but use of less than 0.8 eq amine base resulted in HI-catalyzed reactions.[14] Chloride formation may arise from dissociation of the phosphine diiodide (free I_2 was noted upon heating) and reaction of liberated Ph_3P with solvent to give chlorophosphonium salts. Indeed, heating **3** with Ph_3P in TCE afforded **4e** in high yield, and use of $Ph_3P•Cl_2$ delivered an excellent yield of **4e**. Cyclization of **4e** to give **7** was very slow. Amine bases may promote $Ph_3P•I_2$ dissociation by forming unrproductive amine diiodides (unlike $Ph_3P•Br_2$, pyridine•Br_2 does not convert acetals to RBr).[17a] Bulky base-induced solvent elimination, releasing chloride ion for S_N2 reaction with **4d**, seems less probable.

Figure 3

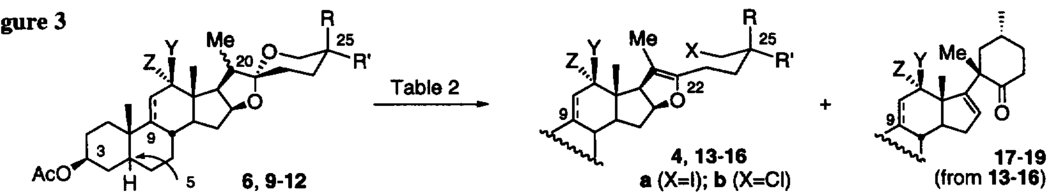


Table 2. Isomerative opening with concurrent halogenation of various steroidal spiroketals.

	spiroketal	eq $Ph_3P{\bullet}I_2$; eq. base	solvent, temp, time[a]	yields (I / Cl ratio)[b]	
1	**6** - 5α,9α,20β; Y=Z=O, R=H, R'=Me	1.1; 1.1 imidazole	CH_2Cl_2, 42 °C, 36 h	82% **4** (17:1 **a**/**b**)	12% **3**
2	**6**	1.1; 1.1 imidazole	CH_2Cl_2/CH_3CN, 70 °C, 5 h	86% **4** (14:1 **a**/**b**)	7% **3**
3	**9** - 5β,9α,20α; Y=Z=H, R=Me, R'=H	1.1; 1.1 imidazole	CH_2Cl_2/CH_3CN, 70 °C, 5 h	89% **13** (15:1 **a**/**b**)	-
4	**10** - 5α,9α,20α; Y=Z=R=H, R'=Me	2.2; 0.8 lutidine	TCE, 140 °C, 0.5 h	82% **14** (8:1 **a**/**b**)	15% **17**
5	**11** - 5α, $\Delta^{9(11)}$,20α; Y=Z=O, R=H, R'=Me	2.2; 0.8 lutidine	TCE, 140 °C, 0.5 h	76% **15** (8:1 **a**/**b**)	14% **18**
6	**12** - 5α,9α,20α; Y=OAc, Z=R=H, R'=Me	2.2; 0.8 lutidine	TCE, 140 °C, 0.5 h	83% **16** (8:1 **a**/**b**)	15% **19**

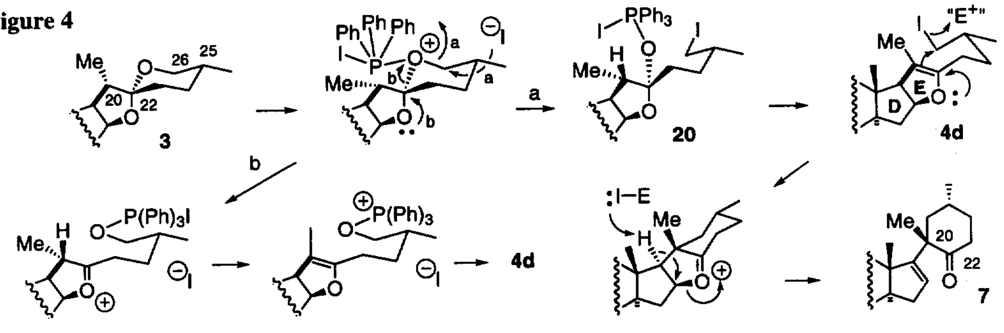
[a] All reactions run at 0.1 M. [b] Isolated yield; halide ratio determined by integration of the HNMR signals for the 26-CH_2 protons.[13]

The scope of the reaction was briefly examined (Fig. 3 and Table 2). Less stable spiroketal types (e.g. **6** or **9**)[11] reacted smoothly at much lower temperatures (25-70 °C). Compatible functionality was found to include ester, ketone, and enone (and, of course, enolether and halide) moieties. Isolated alkenes are evidently also tolerated, as resubjection of compounds **7** and **18** returned starting materials unchanged. The absence of α-halogenated ketone products indicates that R_3NHX_3 or R_4PX_3 type reagents[16] are probably not produced.

Plausible mechanistic rationales for formation of ω-halo-enolethers **4**, **13-16** under these neutral conditions are postulated in Fig. 4. Path "a" differs from that of the anhydride methods and the (acidic) $Ph_3P{\bullet}Br_2$ reaction of THP-protected alcohols and other acetals.[17] In the latter protocol, initial formation of an enolether, acid (HBr) and an oxophosphonium salt is observed. In a spiroketal system, this scenario (path b) would furnish a tethered C26-oxophosphonium salt prior to iodide incorporation at C26. The increased reactivity of substrates **6** and **9** is consistent with the alternative (path a) sequence conjectured in Fig. 4. Complexation by $Ph_3P^{+}I$ of the equatorial lone pair[18] in **6** (20β-Me) to activate the O-C26 bond, and backside attack by iodide at C26 of the activated spiroketal from **9** (axial 25-Me), should each be more facile than for **3** based on steric considerations. Unimolecular elimination of the elements of Ph_3PO and HI from an intermediate phosphorane **20** is consistent with the lack of effect of steric demand or strength of bases employed.

Intramolecular alkylation at C20 of **4**, **13-16** provided C22 ketones **7**, **17-19** as single diastereomers. Thus, alkylation likely occurs from the convex side of the *intact* D/E [3.3.0] system. Electrophilic assistance for the alkylation is implied by the failure to produce **7** from **4d** in the absence of the $Ph_3P^{+}X\text{-}X^{-}$ reagent. No products of the type seen when free mineral acid is present[14] were noted even though production of **7** entails net elimination of a second equivalent of HI. Rupture of the E-ring may proceed after alkylation via *anti*

Figure 4



elimination of the oxacarbenium ion, as iodide attack at C16 followed by *syn* HI elimination seems inconsistent with the observed complete regioselectivity of alkene formation.

Immediate benefits of this new method include a more efficient, reliable and scaleable route via **4d** to **5** (3 steps, 70% vs. 6 steps, 35-45%) as well the potential for rapid access to other antitumor steroids. North G (**2**) is now available in 10 steps (25% overall yield) from **3**.

Typical Procedure. To a solution of **3** (10.00 g, 21.15 mmol), Ph$_3$P (11.1 g, 42.3 mmol, 2.0 eq), and 2,6-lutidine (1.9 mL, 16.3 mmol, 0.8 eq) in TCE (200 mL) was added iodine (10.75 g, 42.3 mmol, 2.0 eq) with vigorous stirring.[19] After 5 min the orange solution was heated to 145 °C for 30 min and then rapidly cooled. The deep red mixture was diluted with 1:3 toluene/hexane (400 mL), washed with ice-cold sat. NaHSO$_3$ and then with sat. NaHCO$_3$, dried (Na$_2$SO$_4$), and suction filtered through a short column of silica gel. The silica plug was washed with hexane to remove residual TCE, then rapidly eluted with 3-5 volumes of 75% hexane/EtOAc. The eluent was concentrated to afford 9.21 g (76%) of **4** as offwhite low-melting solids (6:1 ratio of **4d/e** by NMR).[13] Further elution with 65% hexane/EtOAc provided 1.60 g (17%) of diketone **7**.

Acknowledgements: We thank the Purdue Cancer Center (TL fellowship) and the NIH (CA 60548) for funding, Arlene Rothwell for MS data, and Phil Fanwick for X-ray analysis.

References and Notes

1. Cephalostatin Synthesis 17. Paper 16: Guo, C.; LaCour, T.G.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 419.
2. Pettit, G. R.; Tan, R.; Xu, J.-P.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 953 & refs therein.
3. Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484 & references therein.
4. (a) Smith, S. C.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 6379; (b) Heathcock, C. H.; Smith, S. C. *J. Org. Chem.* **1994**, *59*, 6828; (c) Drogemuller, M.; Jautelat, R.; Winterfeldt, E. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1572; (d) Guo, C.; Bhandaru, S.; Boyd, M.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 10672.
5. LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692 & refs therein..
6. (a) Jeong, J. U.; Fuchs, P. L., *J. Am. Chem. Soc.* **1994**, *116*, 773; (b) Jeong, J. U.; Guo, C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2071; (c) Kim, S.; Sutton, S.; Guo, C.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2056.
7. (a) Dauben, W. C.; Fonken, G. J. *J. Am. Chem. Soc.* **1954**, *87*, 4618; (b) Cameron, A.F.B.; Evans, R.M.; Hamlet, J.C.; Hunt, J.S.; Jones, P.G.; and Long, A.G. *J. Chem. Soc.* **1955**, 2807.
8. Unsuccessful attempts to regioselectively hydrolyze 3,26-diesters or functionalize 3,26-diols have been described (ref 9). In our hands, tosylation of the 3,26-diol corresponding to **4b** (91% from **3** via octanoic acid/Ac$_2$O followed by hydrolysis, ref 7b) proved similarly unrewarding, with only ditosylate being produced. Partially selective hydrolysis of a 3,26-ditosylate (40% yield of 3-OH,26-OTs, the rest being diol) was previously judged to be a useful advance (ref 9b). A single report of direct C26 halogenation detailed a 10% yield of C26-chloride (as the 16-OAc-22-ketone, i.e. scission of ring E also occurred) using HCl/Ac$_2$O (ref 9c). However, mineral acids have been found to be generally unsuitable as catalysts for opening steroidal spiroketals due to redox-mediated epimerization at C25 (ref 12).
9. (a) Fieser, L. F. and Fieser, M. *Steroids*; Rheinhold:NY, **1959** and references therein; (b) Uhle, F. C. *J. Am. Chem. Soc.* **1961**, *83*, 1460; the homoallylic 3-OTs of a Δ^5-3,26-ditosylate was selectively (80%) hydrolyzed; (c) Uhle, F. C. *J. Org. Chem.* **1962**, *27*, 656.
10. (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. I* **1982**, 681; (b) Garegg, P. J.; Johansson, R.; Samuelsson, B. Synthesis **1984**, *84*, 168; (c) Lange, G. L. and Gottardo, C. *Syn. Comm.* **1990**, *20*, 1473.
11. Wall, M. E.; Serota, S. *J. Am. Chem. Soc.* **1957**, *79*, 6481.
12. (a) Woodward, R. B.; Sondheimer, F.; Mazur, Y. *J. Am. Chem. Soc.* **1958**, *80*, 6693; (b) Deslongchamps, P.; Rowan, D. D.; Pothier, N. *Can. J. Chem.* **1981**, *59*, 2787.
13. X-ray data for **8** has been deposited in the Cambridge Crystallographic database. All new compounds gave satisfactory NMR, MS, HRMS and/or combustion. ^{1}H NMR [300 MHz, CDCl$_3$, δ ppm (Hz)] for 26CH$_2$: **4d** (see ref 5 Supp. Info.): 3.23 (1H, dd, J=9.6, 4.3), 3.14 (1H, dd, J=9.6, 5.7); **4e**: 3.47 (1H, dd, J=10.6, 5.1), 3.40 (1H, dd, J=10.6, 6.1).
14. LaCour, T. G. and Fuchs, P. L. manuscript in preparation.
15. Dorta, R. L.; Rodriguez, M. S.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1997**, *38*, 4675.
16. (a) Arrieta, A.; Ganboa, I.; Palomo, C. *Syn. Comm.* **1984**, *14*, 939; (b) Armstrong, V. W.; Chisti, N. H.; Ramage, R. *Tetrahedron Lett.* **1975**, *16*, 373.
17. (a) Sonnet, P. E. *Syn. Comm.* **1976**, *6*, 21; (b) Wagner, A.; Heitz, M.-P.; Mioskowki, C. A. *Chem. Comm.* **1989**, 1619. (c) The cyclic THP C-O bond is not cleaved. The dihydropyran product may arise via an α-bromo-THP.
18. Deslongchamps, P. R. *Stereoelectronics in Organic Chemistry*; Oxford:Pergamon Press, **1985**: 53-60.
19. Identical results were obtained using commercial or premade Ph$_3$P•I$_2$.