Tetrahedron Letters, Vol. 33, No. 25, pp. 3669-3672, 1992
Printed in Great Britain

0040-4039/92 $5 00 + .00
Pergamon Press Ltd

An Unexpected Reaction in the Lactamisation of 13-Azido-13-deoxy-(9*S*)-9-dihydroerythronolide A seco-Acid Derivatives

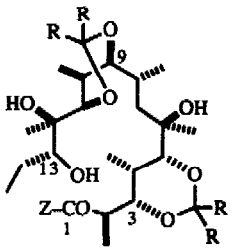
Martí Bartra, Fèlix Urpí, and Jaume Vilarrasa

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona(III), 08028 Barcelona, Catalonia (Spain)

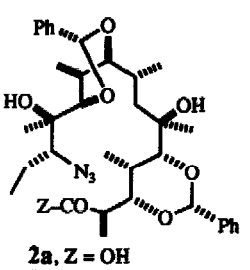
Abstract: *By reduction of the title compounds (azido acid derivatives* **2***) and cyclisation in situ, either the desired lactam* **3** *or unexpected acyl triazene* **4** *can be predominantly obtained, depending on the reaction conditions.*

Yonemitsu et al.[1] have very recently shown that lactonisation of some 9-dihydroerythronolide A seco-acid derivatives (see e.g. **1**), which had posed so many difficulties in the total synthesis of erythromycin A,[2] can be readily accomplished at rt, in surprisingly high yields, by the Yamaguchi activation method (Z = 2,4,6-trichlorobenzoyloxy, see **1**)[3] if excess DMAP is added; the efficiency of this procedure has been confirmed in our lab on similar substrates.[4] We report here on a closely related subject: *the lactamisation of the azido seco-acid derivatives* **2** (obtained from erythromycin A according to **Scheme I**, see overleaf), *by reduction of the azide group and cyclisation in situ of the resulting amino thioesters or mixed anhydrides.*[5]

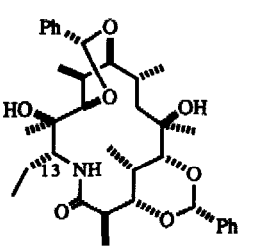
Addition of azido thioester **2b** (0.10 mmol, in 2 ml of CH_3CN) to a mixture of $SnCl_2$/2-thiopyridone/Et_3N (1/4/4 mmol, in 10 ml of CH_3CN) and stirring at rt, until all the azide had been reduced,[6] allowed us to isolate the desired lactam **3**,[7] as well as a related product of higher R_f and unusual structure whose more significant spectral features, as obtained by ^1H-, ^{13}C-, HETCOR 2D-NMR, IR, and UV spectroscopy, were:[8] (i) a NH proton at δ 9.65; (ii) the C13 signal at δ 76.1 (21 ppm at lower field than that of C13 of **3**); (iii) a $\bar{\nu}_{CO}$ band at 1720 cm^{-1}, too high for an amide group; and (iv) a strong absorption band at 244 nm that was shifted to 276 nm by addition of 0.1 M KOH. After ruling out other possibilities, the acyl triazene structure **4** was attributed to that compound, which was then corroborated by microanalysis and, indirectly, CIMS(NH_3).



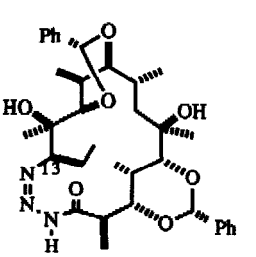
1



2a, Z = OH
2b, Z = S-2-Pyridyl
2c, Z = $OCOC_6H_2Cl_3$
2d, Z = OSO_2Mes



3



4

Apparently, an intramolecular coupling between the azide and COSPy groups has taken place, as if *the thioester group had trapped the 'reduction intermediate'* (C_{13}-N=N-$\bar{N}$-SnX_3). Although acyl triazenes are well-known compounds,[9] there is no precedent, to the best of our knowledge, of such a sort of reaction between azides and activated carboxyl groups. In fact, acyl triazene **4** was the major product in many cases (see the following Table for a summary of the most relevant experiments), especially in those ones in which the reactivity of COZ groups could be higher. However, *the relative yields of 3 and 4 changed clearly in favour of the first one when the cyclisation of 2b was performed at 80 °C.*

Table. Cyclisation of Azido-seco-erythronolides **2** in CH_3CN, under Different Conditions

substrate	reagents (no. equiv.) & conditions	yield, **3**	yield, **4**
2b	$SnCl_2$ (10), Py-2-SH (40), Et_3N (40), rt, 12 h	35%[a]	20%[a]
2b	$SnCl_2$ (10), Py-2-SH (40), DMAP (60), rt, 12 h	10%	55%
2b	PhSeH (20), Et_3N (20), rt, 24 h	5%	55%
2c	$SnCl_2$ (5), *o*-$C_6H_4(CH_2SH)_2$ (10), Et_3N (10), rt, 6 h	trace	50%[b]
2d	$SnCl_2$ (5), *o*-$C_6H_4(CH_2SH)_2$ (10), Et_3N (10), rt, 6 h	trace	55%[b]
2b	$SnCl_2$ (3), Py-2-SH (12), Et_3N (12), 80 °C, 3 h	60%	trace
2b	$SnCl_2$ (3), Py-2-SH (12), Et_3N (12), 80 °C, addn during 6h	65%	trace

[a]The yields of lactam and acyl triazene were similar starting from Mes (mesityl) instead of Ph. In CH_2Cl_2 both the yields of **3** and **4** were slightly lower than in CH_3CN. [b]Overall yield for COOH activation and cyclisation.

Lactam **3**, which is stable under the above reaction conditions, could be deprotected to afford the desired aza analogue of (9*S*)-9-dihydroerythronolide A (mp 185-187 °C, $\tilde{\nu}$ 1650 cm^{-1}, expected NMR spectra, CIMS, and microanalysis) by treatment at rt with several drops of $ClSO_3H$ in 9:1 MeOH/H_2O, for a few days so as to cleave the more 'reluctant' 9,11-*O*-benzylidene group.

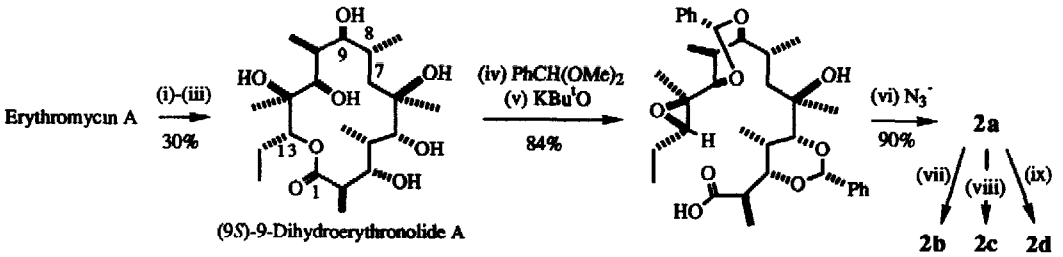
In spite of the possible uses of acyltriazene-containing macrolide antibiotics in chemotherapy, we evaluate humbly the results of the Table, as our lactamisation procedures, which at present are among the most efficient,[5] fail or give only moderate yields when applied on these willing substrates. Nevertheless, that the overall yields (of **3** plus **4**) were only around 60% worried us much more than anything else, since we stopped the reaction after all the starting material had been transformed. For this reason we looked for the 'lost' material: in addition to **3** and **4**, a series of more polar spots were observed on TLC; from the NMR and IR analyses of the byproducts mixture (20-25% w/w, overall) we supposed that they were mainly $CONH_2$-containing open products which could arise from the decomposition of **4** in the reaction medium.

In this connection, it is worth noting that **4** is stable under refluxing CH_3CN or C_6H_6, even in the presence of Et_3N, as well as in NaOH(aq)/CH_3CN at rt for 3 days. However, **4** is sensitive to the excess of the reagents indicated in the Table; for instance, when **4** is treated with 5 equiv. of Sn^{2+}/Py-2-SH/Et_3N in refluxing CH_3CN for 3 h, it disappears completely to afford a complex mixture of polar products very similar to that just mentioned (but not **3**).[10]

There seems that the azide and COSPy groups are relatively close[11] and that, after the attack of Sn(II) species, there is a competition between the loss of N_2 from the triazene intermediate and its direct cyclisation towards **4**. Even though at rt the formation of **4** often predominates, *at 80 °C* nitrogen is extruded more rapidly and **4** (which is now produced in a lower percentage) is decomposed more quickly than at rt by the reagent excess. This explains the better yields of **3** and the lack of **4** in the last experiments shown in the Table. A plausible series of events is represented in **Scheme II**.

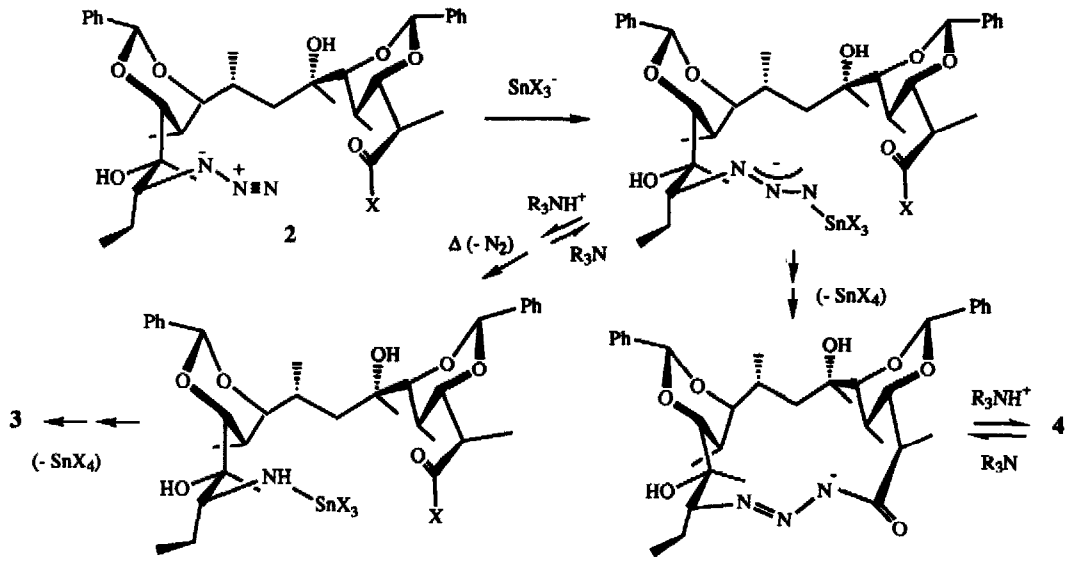
In summary, the method of choice for the macrolactamisation of conformationally free substrates —reduction of azido thioesters with $[R_3NH][Sn(SR)_3]$ and cyclisation in situ— has two *paradoxical disadvantages* when applied to the rigid, cyclisation-prone substrates reported here: (a) reduction of the azide group becomes

Scheme I



(i) $NaBH_4$, MeOH, rt, 48h; (ii) HCl, MeOH, rt, 72h; (iii) 2 M HCl, $CHCl_3$, 60°C, 72h;[12] (iv) $PhCH(OMe)_2$ (5 equiv.), $ClSO_3H$, CH_2Cl_2, 0°C, 5h, 100%; (v) KBu^tO (2.2 equiv.), DMSO, rt, 24h, 84%; (vi) NaN_3, DMSO, 120°C, 72h, 90%; (vii) PySCOCl,[13] Et_3N, CH_2Cl_2, 5°C, 1h, 80%; (viii) $C_6H_2Cl_3COCl$,[3] Et_3N, THF, rt; (ix) $MesSO_2Cl$,[14] Et_3N, THF, rt.

Scheme II



the slow step, a fact we were not used to, and (b) the intermediate triazenides, before losing N_2, may give rise to acyl triazenes. Thus, in spite of the much higher nucleophilicity of aliphatic amines with regard to alcohols, it is easier to obtain lactones than lactams, at least in these cases. Obviously, for the preparation of lactam analogs of macrolide antibiotics the azido acid may be converted to amino acid and this one may be submitted to a more standard lactamisation procedure, but it is not exempt from problems, as we plan to report in due course.

ACKNOWLEDGMENTS.- Financial support from the Comisión Interministerial de Ciencia y Tecnología, CICYT (PB86-0170 and FAR90-0349) is deeply acknowledged. We also thank Abbott Laboratories (Chicago) for a gift of erythromycin B.

REFERENCES AND NOTES

1. Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7 & *Tetrahedron* **1990**, *46*, 4613. Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Letters* **1990**, *31*, 6367.
2. Woodward, R. B. et al., *J. Am. Chem. Soc.* **1981**, *103*, 3213. For related, very recent macrolactonisation studies, see: Kinoshita, M.; Arai, M.; Oshawa, N.; Nakata, M. *Tetrahedron Letters* **1986**, *27*, 1811 & 1815; *Bull. Chem. Soc. Jpn.*

1989, *62*, 2618. Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S.; Kochetkov, N. K. *Tetrahedron Letters* **1987**, *28*, 3835 & 3839; *Tetrahedron* **1991**, *47*, 2291 & 2317. Stork, G.; Rychnovsky, S. D. *J. Am Chem. Soc* **1987**, *109*, 1565. Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569; *Chem Pharm. Bull.* **1989**, *37*, 1167. Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636. Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910. Martin, S. F.; Yamashita, M. *J. Am. Chem. Soc.* **1991**, *113*, 5478.

3. Inanaga, J.; Hirata, K.; Sacki, H.; Katsuki, T.; Yamaguchi, M. *Bull . Chem. Soc. Jpn.* **1979**, *52*, 1989.
4. Bartra, M. *Estudis sobre Macrolactamització i Macrolactonització. Síntesi i Ciclació d'Azido i Hidroxi Acids Derivats de l'Acid 9-Decenoic i l'Eritronolida A* (Tesi Doctoral), Universitat de Barcelona 1991. Six (9*S*)-9-dihydroerythronolide A or B seco-acid derivatives (3,5;9,11-bis-ArCH-protected) were cyclized in 80-95% yields, within a few min, following the Yonemitsu procedure (ref. 1); besides, 3,5;9,11-di-*O*-isopropylidene (9*S*)-9-dihydroerythronolide A seco-acid gave 96% of the corresponding lactone within 2 h, and 9,11-deprotected derivatives afforded ca. 60% of the 14-membered lactones within 1 h.
5. Bartra, M.; Bou, V.; Garcia, J.; Urpí, F.; Vilarrasa, J. *J. Chem. Soc., Chem. Comm.* **1988**, 270. Bartra, M.; Vilarrasa, J. *J Org. Chem.* **1991**, *56*, 5132.
6. The reducing power of Sn(II)/2-thiopyridone is not so strong as that of Sn(II)/PhSH and Sn(II)/RSH (see: Bartra, M.; Urpí, F.; Vilarrasa, J. *Tetrahedron Letters* **1987**, *28*, 5941. Bartra, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 585). Thus, an excess of reagents has to be added to perform within few hours the reduction of the sterically crowded azide group of **2** at rt.
7. Compound **3**: dec. 215 °C; R_f 0.28 (98:2 CH_2Cl_2/MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J=7.5, 3 H, CH_3CH_2), 1.07 (s, 3 H, 12-Me), 1.12 (d, J=6.5, 3 H, 4-Me), 1.28 (d, J=6.5, 3 H, 2-Me), 1.29 (d, J=6.5, 3 H, 8-Me), 1.33 (s, 3 H, 6-Me), 1.36 (dd, J=14.5, J=11.0, 1 H, H7), 1.40 (d, J=6.5, 3 H, 10-Me), 1.52 (br d, J=14.5, 1 H, H7'), 1.53 (ddq, J=14.5, J=11.0, J=7.5, 1 H, CHH'CH_3), 1.82 (br q, J=6.0, 1 H, H4 or H10), 1.88 (br q, J=6.0, 1 H, H10 or H4), 2.03 (dqd, J=14.5, J=7.5, J=2.5, 1 H, CHH'CH_3), 2.54 (dq, J=11.0, J=6.5, 1 H, H2), 2.54 (tq, J=11.0, J=6.5, 1 H, H8), 33.4 (d, J=11.0, 1 H, H9), 3.83 (s, H11), 4.05 (d, J=11.0, 1 H, H3), 4.11 (s, 1 H, H5), 4.14 (ddd, J=11.0, J=9.8, J=2.5, 1 H, H13), 5.24 (br d, J=9.8, 1 H, NH), 5.71 (s, 1 H), 5.92 (s, 1 H), 7.4-7.6 (m, 10 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 8.0 (4-Me), 10.8 (CH_3CH_2), 13.5 (8-Me or 2-Me), 14.7 (10-Me), 14.9 (12-Me), 17.0 (2-Me or 8-Me), 20.5 (CH_2CH_3), 26.8 (6-Me), 26.9 (C8), 28.5 (C10), 31.1 (C4), 39.8 (C7), 43.5 (C2), 55.1 (C13), 74.6 (C11), 74.6 & 75.1 (C6 & C12), 84.7 (C3), 86.4 (C9), 87.0 (C5), 95.5 & 103.5 (2 x O-CH-O), 126.3, 126.4, 128.3, 128.4, 128.9, 129.0, 138.3, 138.6 (C arom), 174.2 (C1); IR ($CHCl_3$) 3600, 1670 cm^{-1}; CIMS(NH_3) m/z 596 ($M+1^+$), 613 ($M+18^+$); $[\alpha]^{25}$ -9.2° (*c* 0.9, $CHCl_3$).
8. Compound **4**: mp 108-110 °C; R_f 0.39 (98:2 CH_2Cl_2/MeOH); ^1H NMR (500 MHz, CDCl3) δ 0.74 (t, J=7.5, 3 H, CH_3CH_2), 1.17 (d, J=6.5, 3 H, 4-Me), 1.19 (s, 3 H, 12-Me), 1.25 (d, J=6.0, 3 H, 8-Me), 1.32 (m, 1 H, H7), 1.34 (s, 3 H, 6-Me), 1.40 (d, J=6.5, 3 H, 2-Me), 1.41 (d, J=7.0, 3 H, 10-Me), 1.52 (br d, J=14.5, 1 H, H7'), 1.75 (br q, J=6.5, 1 H, H4), 1.81 (m, 1 H, CHH'CH_3), 1.85 (br q, J=7.0, 1 H, H10), 2.09 (dqd, J=14.5, J=7.5, J=2.5, 1 H, CHH'CH_3), 2.40 (m, 1 H, H8), 2.71 (dq, J=10.5, J=6.5, 1 H, H2), 3.31 (d, J=2.0, 1 H, H11), 3.34 (d, J=10.0, 1 H, H9), 3.80 (dd, J=11.0, J=2.0, H13), 3.97 (br d, J=10.5, 1 H, H3), 4.12 (d, J=1.5, 1 H, H5), 5.67 (s, 1 H), 5.70 (s, 1H), 7.4-7.6 (m, 10 H), 9.65 (br s, 1 H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 8.4 (4-Me), 11.1 (CH_3CH_2), 12.3 & 15.3 (2-Me & 10-Me), 15.5 (12-Me), 17.3 (8-Me), 19.5 (CH_2CH_3), 27.3 (C8), 27.5 (6-Me), 28.2 (C10), 32.0 (C4), 39.1 (C7), 41.6 (C2), 73.2 (C11), 74.5 & 74.8 (C6 & C12), 76.1 (C13), 84.8 (C3), 85.5 (C5), 87.9 (C9), 95.5 & 103.2 (2 x O-CH-O), 125.9, 126.3, 126.5, 128.4, 128.5, 129.1, 129.3, 138.0, 138.5 (C ar), 170.7 (C1); IR ($CHCl_3$) 1720 cm^{-1}; UV (EtOH) 244 nm (log ε = 3.9); CIMS(NH_3) m/z 596 $[(M+1)^+-28]$, 613 $[(M+18)^+-28]$; $[\alpha]^{25}$ -3.0° (*c* 1, $CHCl_3$). *Anal.* Calcd for $C_{35}H_{49}N_3O_7$: C, 67.38; H, 7.93; N, 6.74. Found: C, 67.03; H, 7.91; N, 6.39.
9. Acyl triazenes are often prepared by reaction of amides with Ar-$N^+{\equiv}N$. See, e.g.: Trappendahl, S.; Jakobsen, P.; Wieczorkowski, J. *Acta Chem. Scand. Ser. B*, **1983**, *37*, 155. Other methods include the reaction of $ArCONHNH_2$ with ArN=O and that of $RCON_3$ with ArMgX.
10. In independent experiments aimed at evaluating the stability of acyl triazenes under our reaction conditions, we have observed that MeC_6H_4-N=N-NH-COPh is relatively stable at rt (provided that small amounts of reagent are used) but gives 80% of $PhCONH_2$, ca. 15% of MeC_6H_4NH-COPh, and several coloured byproducts in refluxing CH_3CN for 3 h.
11. The $^3J_{HH}$ values in **2a** are identical with those of dibenzylidene-protected **1** and, except for $J_{7,8}$, with those of the corresponding lactam (**3**) and lactone (see ref. 1 for a discussion on this question).
12. Sigal, M. V.; Wiley, P. F.; Gerzon, K.; Flynn, E. H.; Quarck, U. C.; Weaver, O. *J. Am. Chem. Soc.* **1956**, *78*, 388.
13. Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875.
14. Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916.

(Received in UK 30 March 1992)