Structural Requirements for the Thallium(III)-mediated Cyclisation of Unsaturated Alcohols. A Novel Fragmentation Reaction Producing 19-Norsteroids

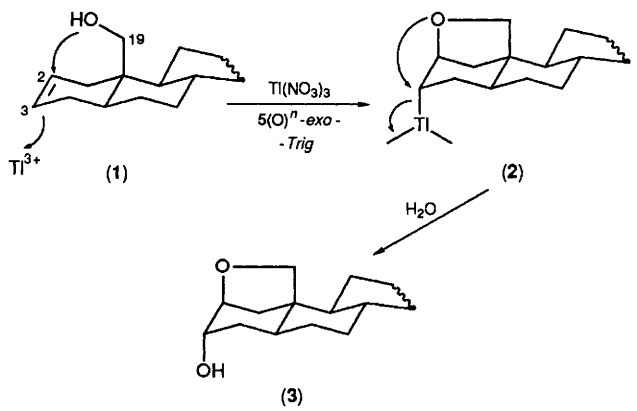
Pavel Kočovský,*[a] Vratislav Langer,[b] and Adolf Gogoll[a]

[a] *Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden*
[b] *Department of Inorganic Chemistry, Chalmers University of Technology and University of Göteborg, S-412 96 Göteborg, Sweden*

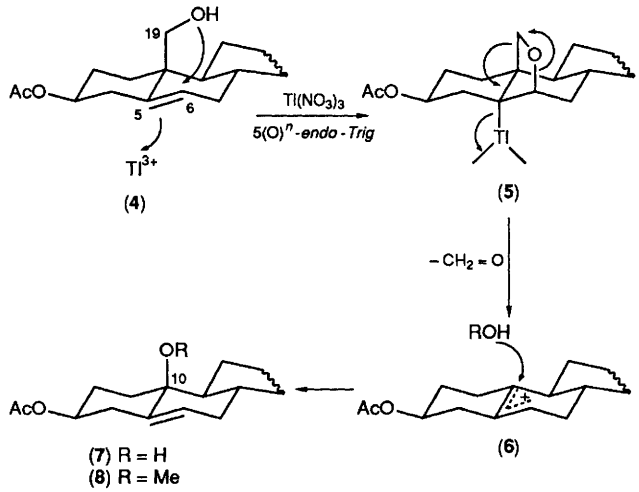
The unsaturated alcohol (**1**) is readily cyclised to the hydroxytetrahydrofuran (**3**) by means of thallium(III), whereas its congener (**4**) has been found to give (**7**) as the product of a novel, stereoelectronically controlled, fragmentation; the scope of the tandem electrophilic cyclisation/solvolysis is discussed; the structure of (**7**) has been determined by *X*-ray crystallography.

Unsaturated alcohols are known to produce cyclic hydroxy-ethers on reaction with thallium(III) salts[1–3] and this method has been applied successfully to the construction of various building blocks for the synthesis of polyether antibiotics.[1] Accordingly, 19-hydroxy-5α-cholest-2-ene (**1**) readily affords the hydroxytetrahydrofuran (**3**) in 93% yield (Scheme 1) as the result of an electrophilic 5(O)^n-*exo*-*Trig* ring closure,[4] (**1**) → (**2**), followed by a stereoselective replacement of thallium by water, (**2**) → (**3**). Retention of configuration in the latter step can be attributed to the anchimeric assistance by the oxygen atom of the newly formed heterocycle.

This reaction parallels the silver(I)-promoted iodination of (**1**) which gives the same product (**3**) in a similar way employing a push–pull mechanism in the solvolysis of the intermediate iodotetrahydrofuran.[5] However, we have recently shown that, in certain instances, the iodination can stop at the iodotetrahydrofuran stage. This was, for example, the case for another steroidal unsaturated alcohol (**4**), which on treatment with I_2/Ag^+ gave a quantitative yield of the 5α-iodo-6β,19-epoxide[5,6] rather than the corresponding hydroxyether. We have rationalized this striking difference as follows.[5] The unsaturated alcohol (**1**) initially gives an



Scheme 1



Scheme 2

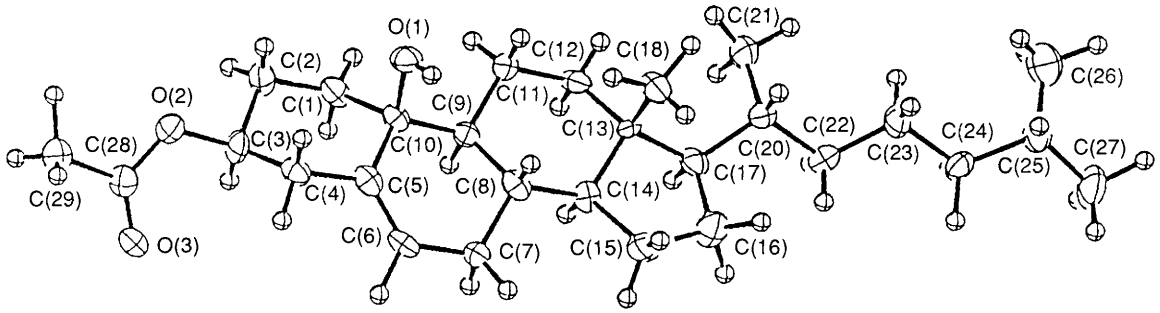
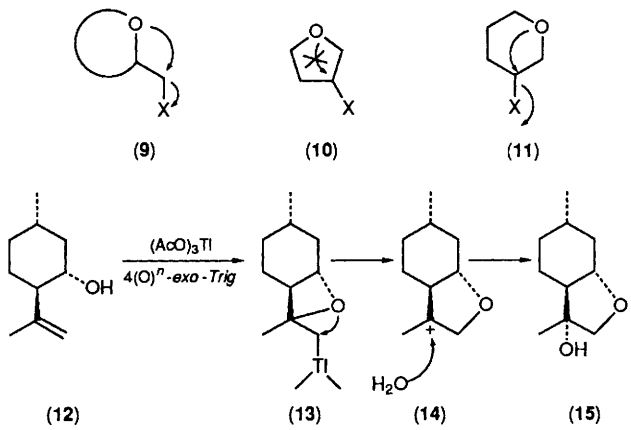


Figure 1. The molecular structure of (**7**).

intermediate in which the halogen atom is anchored *exo* to the tetrahydrofuran ring; anchimeric assistance in subsequent solvolysis is then easily available. By contrast, the unsaturated alcohol (**4**) is cyclised to a product in which the halogen atom is riveted *endo* with respect to the tetrahydrofuran ring. The next step, anchimerically assisted solvolysis, would lead to a highly strained intermediate, a process which appears to be energetically too expensive so that the reaction stops at the stage of the iodo-derivative.

Since the thallium(III)-mediated cyclisation is also believed[1] to require anchimeric assistance for the second step (as shown in Scheme 1) it was of interest to explore the reactivity of (**4**) for which this assistance was precluded for the silver-assisted iodination.† Hence, 19-hydroxy-5-cholestene (**4**) was treated with $Tl(NO_3)_3 \cdot 3H_2O$ in 1,2-dimethoxyethane (DME) and, surprisingly, an instantaneous reaction occurred even at −20 °C producing essentially a single compound in an 81% isolated yield, later identified as the 10β-hydroxy-10-nor-steroid (**7**) by a single-crystal *X*-ray analysis (Figure 1).‡ Similarly, when the reaction was carried out with anhydrous $(CF_3CO_2)_3Tl$ in MeOH, the corresponding methoxy-derivative (**8**) was obtained, although in an appreciably lower yield (27%).§



This unique degradation can be rationalized as follows (Scheme 2): the 5,6-double bond in (**4**) first undergoes an electrophilic attack by Tl^{3+} followed by an expected anti-Markovnikov 5(O)^n-*endo-Trig* ring closure furnishing a diaxial organothallium intermediate (**5**).[10] Then, instead of the bridge oxygen-assisted solvolysis of the C–Tl bond, another competing pathway operates in which a molecule of formaldehyde is lost leaving allylic cation (**6**). The latter is then trapped by the solvent to afford a thermodynamically more stable *trans*-annulated product (**7**) or (**8**), respectively.¶ This fragmentation is obviously boosted by a stereoelectronic effect, since all the bonds involved [C(5)–Tl, C(10)–C(19), and C(6)–O] are perfectly aligned.

In view of these and previous[1,5,6] results it appears that the anchimerically assisted solvolysis in the second step can occur readily and stereospecifically with the intermediates arising by electrophilic *exo-Trig* ring closure, regardless of the size of the ring initially formed (**9**). By contrast, this type of solvolysis is highly disfavoured for the heterocycles formed in a 5-*endo-Trig* fashion. The primary ring-closure product (**10**) is then either stable enough to be isolated (X = Br, I)[5] or suffers another consecutive reaction rather than a simple substitution (X = Tl). However, a six-membered heterocycle resulting from a 6-*endo-Trig* cyclisation (**11**)[1] seems to be the smallest ring size which allows for the anchimerically assisted solvolysis.‖

† Generally, disubstituted alkenes are known to react with Tl^{III} with the formation of various products.[3,7] In contrast, trisubstituted double bonds seem generally unreactive at room temperature, unless neighbouring group participation is provided.[2,8]

‡ *Crystal data* for (**7**): $C_{28}H_{46}O_3$, M = 430.67, monoclinic, space group $P2_1$, a = 11.276(4), b = 9.832(8), c = 12.892(3) Å, β = 112.82(2)°, Z = 2, D_c = 1.086 g cm^{-3}, μ(Mo-K_α) = 0.64 cm^{-1}, crystal size 0.3 × 0.2 × 0.5 mm. Crystals suitable for *X*-ray analysis were grown by slow evaporation from methanol solution at room temperature. Data were collected at 23 °C on a Rigaku AFC6R diffractometer using Mo-K_α radiation (λ = 0.71069 Å). Total number of reflections measured was 2610, R_{int} = 0.016, correction for Lorentz–polarization effects. The structure was solved by direct methods and refined by a full-matrix least-squares method to R = 0.041 and R_w = 0.042, from 1372 observed reflections. Neutral scattering factors and anomalous dispersion coefficients were taken from ref. 9. Hydrogen atoms were located in a difference map and isotropically refined. Maximum and minimum peaks in the final difference map were 0.16 and −0.13 e Å^{-3}, respectively. Since the absolute configuration of the starting compound (cholesterol) is known, no attempts were made to determine it for (**7**) by the *X*-ray studies. The co-ordinates given in the supplementary material correspond to the absolute configuration. An interesting feature of the crystal internal arrangement is a hydrogen bond between the OH of one molecule and the C=O belonging to another molecule, the two being symmetry related by a screw axis. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ 6β-Methoxy-19-norcholest-5(10)-en-3β-yl acetate, a positional isomer of (**8**), was isolated as the major product in 56% yield.

¶ Attempts to trap the allylic cation (**6**) with nitrogen nucleophiles (N_3^-, MeCN) were unsuccessful.

‖ These conclusions may, seemingly, be in conflict with an earlier observation on the Tl^{III}-mediated cyclisation of (**12**) which was found readily to afford the hydroxytetrahydrofuran (**15**) with an endocyclic hydroxy group.[2] However, one can easily presume a mechanistic pathway involving an initial Markovnikov-type 4(O)^n-*exo-Trig* ring closure to (**13**) having an exocyclic C–Tl bond which, in fact, is in line with our findings.

We are confident that our novel fragmentation reaction will be of general use for a facile synthesis of 19-norsteroids of medicinal importance and that our observation on the scope of the thallium(III)-mediated cyclisation[11] could serve as a guide for planning syntheses of complex molecules.

We are grateful to the Swedish Natural Science Research Council for financial support. We thank Dr. D. Tanner for valuable discussions and Dr. V. Hanuš for mass spectra of (**7**).

Received, 2nd February 1990; Com. 0/00506A

References

1 J. P. Michael, P. C. Ting, and P. A. Bartlett, *J. Org. Chem.*, 1985, **50**, 2416 and references cited therein; J. P. Michael and M. M. Nkwelo, *Tetrahedron*, 1990, **48**, 2549.
2 H. M. C. Ferraz, T. J. Brocksom, A. C. Pinto, M. A. Abla, and D. H. T. Zocher, *Tetrahedron Lett.*, 1986, **27**, 811.
3 P. A. Bartlett, in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 411; A. McKillop and E. C. Taylor, in 'Comprehensive Organometallic Chemistry,' eds. G. Wilkinson, F. G. A. Stone, and E. W. Abel, Pergamon Press, Oxford, 1982, vol. 7, p. 465.
4 For notation, see P. Kočovský and I. Stieborová, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1969.
5 P. Kočovský, *J. Org. Chem.*, 1988, **53**, 5816.
6 P. Kočovský and M. Pour, *J. Org. Chem.*, 1990, **55**, in the press.
7 M. K. Begley, S. E. Mohamed, D. A. Whiting, F. D'Souza, and N. A. R. Hatam, *J. Chem. Soc., Perkin Trans. 1*, 1983, 883; T. Nakano, M. I. Hernández, J. M. Polachini, D. A. Peña, E. Corothie, A. Rojas, and A. T. McPhail, *ibid.*, 1986, 1727.
8 A. Schwartz and E. Glotter, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2470; Y. Yamada, S. Nakamura, K. Iguchi, and K. Hosaka, *Tetrahedron Lett.*, 1981, **22**, 1355; see, however, P. Bissek, G. Charles, and C. Berrier, *ibid.*, 1986, **27**, 4731.
9 D. T. Cromer and J. T. Waber, 'International Tables for *X*-Ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. IV, Table 2.2 A and 2.3.1.
10 For a discussion of competition between electronic (Markovnikov) and stereoelectronic effects in ring-closure reactions, see refs. 4, 6, and P. Kočovský, I. Starý, J. Zajíček, F. Tureček, and S. Vašíčková, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2297.
11 For the rules showing general limitations of cyclisation reactions, known as the Baldwin rules, see: J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734, 738; J. E. Baldwin and L. I. Kruse, *ibid.*, 1977, 233; J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Stilberman, *J. Org. Chem.*, 1977, **42**, 3846; J. E. Baldwin and M. J. Lusch, *Tetrahedron*, 1982, **38**, 2939.