Tetrahedron Letters Vol. 21, pp 2549 - 2552

0040-4039/80/0622-2549$02.00/0

STEREOSPECIFIC S-ASSISTED CATIONIC OLEFIN CYCLIZATION A SYNTHETIC APPLICATION TO THIASTEROID[1]

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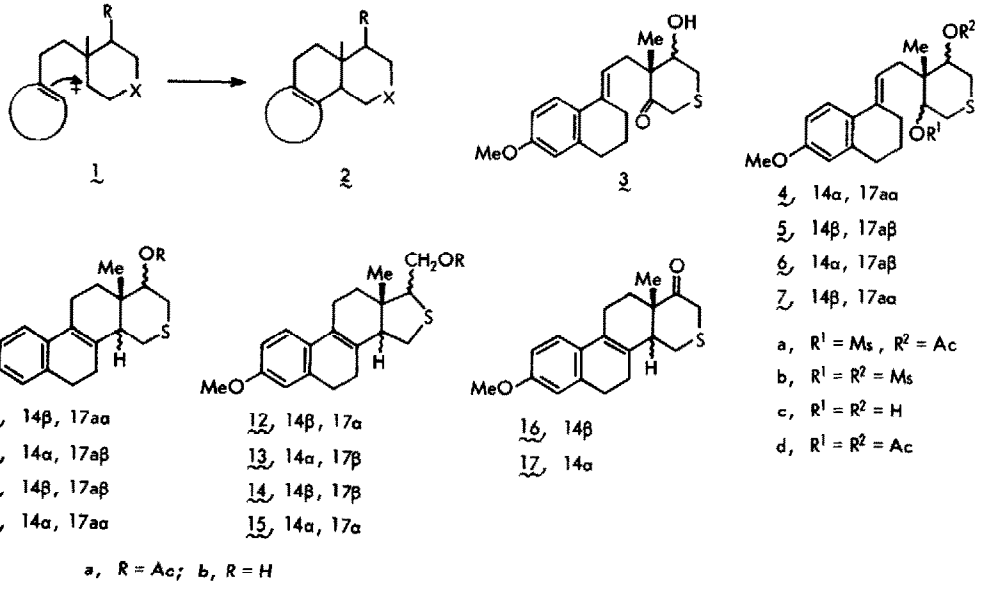
Summary: A new annelation method involving cationic olefin cyclization reaction via neighboring sulfur participation, which proceeds in an entirely stereospecific manner, is demonstrated on a thiasteroid synthesis.

Thus far, numerous examples of cationic olefin cyclization and its synthetic utility have been reported.[2] Little is known, however, about cyclization of the type 1→2 which involves intramolecular attack upon a secondary ring cation by an adjacent endocyclic double bond. Our recent interest has been directed toward the cyclization 1→2 (X = S) as a new annelation method. This was realized, based on the idea that a neighboring sulfur atom which is capable of participating in stabilization of an incipient carbocation would, if present, assist nucleophilic trapping of the ion by an internal double bond. Now we report herein our successful results with secosteroid diol derivatives 4-7, which are summarized in Table I.

The substrates[3,4] were readily prepared from the previously reported epimeric secoketols[5] 3 and stereochemically confirmed by their spectral data.

Initially, we observed that acetoxy mesylates 4a, 5a, 6a, and 7a on acetolysis (60-80°C) undergo facile cyclization with perfect stereospecificity to give exclusively tetracyclic products[6] 8a, 9a, 10a, and 11a (50~70%), respectively. The cyclization undoubtedly occurred with migration of the double bond to result in the six-membered ring formation. The existence of a tetrasubstituted styryl double bond in the product was clearly indicated by the characteristic UV absorptions coupled with disappearance of the vinylic hydrogen in the NMR signals. The stereochemical interrelations were clarified in the following manner. The corresponding alcohols,[6] obtained upon alkaline hydrolysis, were oxidized by the Oppenauer procedure or with Fetizon's reagent (Ag_2CO_3/Celite).[7] Thus, 8b and 10b both furnished the same cis-fused ketone 16, whereas 9b and 11b were converted into the trans-fused isomer 17. The C/D ring configuration was first deduced from the mass spectral data of both ketones on the basis of the findings of Wulfson et al.[8] It was ultimately established by X-ray crystallographic analysis[9] of 11a. This result revealed that the cyclization occurs with retention of configuration at the C-14 ring juncture. In a parallel study, we ascertained that the carbocyclic analog of 4a under the analogous solvolytic conditions affords no cyclized product.[10] We therefore believe that the facile cyclization proceeds via an episulfonium ion initially formed by intramolecular S_N2 displacement of the departing mesylate group, assuming an equatorial orientation, by the ring sulfur atom. Successive nucleophilic attack toward the cationic center by the internal double bond completes the ring closure with a double-inversion mode of substitution at



C-14. Contrary to expectation, the mesylate derivatives of ketols 3 gave no satisfactory results, presumably because of prior sensitivity of the carbonyl group to acid cyclization.

Similar acetolysis of dimesylates 4b, 5b, and 6b, which yielded again 8a, 9a, and 10a and 11a, respectively, was accompanied by solvolytic displacement of the additional mesylate to form the ring-contracted 12a, 13a, and 14a and 15a as by-products.[11] The formation of the latter products may be also rationalized by the intermediacy of episulfonium ions originating from incipient C-17a cations. Equilibration experiments(HCOOH, 100°C, 3 h)[12] confirmed that each pair of the corresponding alcohols obtained on saponification is indeed interconvertible. Unequivocal proof of the structure of 15a was obtained by X-ray analysis.[9,13]

Strikingly, analogous ring closure was realized in direct solvolysis of the corresponding diols and diacetates under slightly more vigorous conditions. The best results were obtained with diol 4c and diacetate 5d. When 4c was treated with acetic acid at 55-60°C for 2-3 h in the presence of methanesulfonic acid (MsOH), C/D-cis 8a was predominantly formed (72%). On the other hand, cyclization of 5d was effected during acetolysis at a higher reaction temperature (100°C), preferentially leading to C/D-trans 9a (70%). In both cases, the major products favorably separated as crystals immediately from the respective reaction mixtures, thereby minimizing the formation of the by-products. Formic acid, trifluoroacetic acid, and acetone-$HClO_4$ were less effective, while use of Lewis acids such as BF_3 and $SnCl_4$ proved abortive. As anticipated, solvolysis of the trans substrates 6 and 7 led to a somewhat complex mixture of products owing to two different directions for the initiation of cyclization compared to the cis materials.

This methodology appears widely applicable to the construction of sulfur-containing fused ring systems other than thiasteroids.

Table I. Solvolytic Cyclization of Secodiol Derivatives[a]

Substrate	Conditions	Products (Yield, %)[b]
4a	HOAc, 60°C, 1.5 h	8a (70.6)
4b	HOAc, 60°C, 3 h	8a (61.9), 12a (2.0)
4c	HOAc, MsOH,[d] 58°C, 2.5 h	8a (72.4), 12a (6.1)
4c	HCOOH, 60°C, 2 h[c]	8b (30.8), 12b (23.3)
4c	An-$HClO_4$,[e] 70°C, 3 h	8b (42.9), 12b (9.7)
4d	HOAc, MsOH,[d] 100°C, 5 h	8a (30.4), 12a (30.0)
5a	HOAc, 80°C, 0.5 h	9a (72.6)
5b	HOAc, 60°C, 3 h	9a (50.1),[h] 13a (1.8)[h]
5c	HCOOH, 60°C, 2 h[c]	9b (23.8), A+B (29.1)[g]
5c	An-$HClO_4$,[f] 70°C, 3 h	9b (22.1), A+B (43.7)[g]
5d	HOAc, MsOH,[d] 100°C, 3 h	9a (69.5), 13a (2.4)
6a	HOAc, 80°C, 3 h	10a (43.0)
6b	HOAc, 80°C, 3 h[c]	10b (6.2), 11b (8.8), 14b (2.8), 15b (2.6)
6c	HCOOH, 60°C, 3 h[c]	11b (21.1), 15b (12.3), A+B (10.0)[g]
6d	HOAc, MsOH,[d] 100°C, 14 h	10a (13.4), 11a (28.9), 15a (5.4)[h]
7a	HOAc, 80°C, 2 h	11a (49.9)[h]

[a] All the mesylates, prepared from the parent alcohols with Et_3N and MsCl in dichloromethane,[14] were used without purification for the solvolyses. [b] Isolated. [c] Followed by alkaline hydrolysis. [d] 1.2 Equiv. [e] 60% Aqueous acetone-35% aqueous $HClO_4$. [f] 80% Aqueous acetone-35% aqueous $HClO_4$. [g] A = 9,11-saturated 3; B = D ring-contracted A (presumed); also see ref. 15. [h] The NMR spectra indicated a slight contamination by the 9,11-unsaturated isomer.

Acknowledgement. We express our thanks to Dr. M. Shiro and Mr. H. Nakai for performing the X-ray crystallographic analyses.

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2. For a recent review, see W. S. Johnson, Angew. Chem. Int. Ed. Engl. 15, 9 (1976).
3. 4d: mp 150-151°C, NMR ($CDCl_3$) δ 1.02 (s, 3H, 13-Me), 4.90 (q, 2H, J = 4.5 and 9 Hz, 14-and 17a-H), 6.00 (t, 1H, J = 7 Hz, 11-H); UV λ_{max} (EtOH) 265 nm (ε 20000). 5d: mp 131.5-133.5°C, NMR ($CDCl_3$) δ 1.13 (s, 3H, 13-Me), 4.97 (q, 2H, J = 6 and 9 Hz, 14- and 17a-H), 5.85 (t, 1H, J = 8 Hz, 11-H); UV λ_{max} (EtOH) 265.5 nm (ε 20800). 6d: mp 115.5-117°C, NMR ($CDCl_3$) δ 1.08 (s, 3H, 13-Me), 5.06 (q, 1H, J = 3.5 and 5 Hz, 17a-H), 5.25 (t, 1H, J = 6 Hz, 14-H), 5.80 (t, 1H, J = 7 Hz, 11-H); UV λ_{max} (EtOH) 265.5 nm (ε

20300).

4. Satisfactory elemental analyses (by combustion and mass spectrometry) have been obtained for all new compounds described herein.
5. T. Terasawa and T. Okada, J. Chem. Soc., Perkin Trans. I, 576 (1978).
6. 8a: mp 211-212.5°C, NMR ($CDCl_3$) δ 1.00 (s, 3H, 13-Me), 4.99 (q, 1H, J = 10.5 and 4.5 Hz, 17a-H); UV λ_{max} (EtOH) 277 nm (ε 20300). 8b: mp 167.5-169°C, IR (dilute CCl_4) 3632 cm^{-1} (free OH). 9a: mp 180-181.5°C, NMR ($CDCl_3$) δ 0.91 (s, 3H, 13-Me), 4.89 (br q, 1H, J = 10 and 6.5 Hz, 17a-H); UV λ_{max} (EtOH) 276 nm (ε 18500). 9b: mp 145.5-147°C, IR (dilute CCl_4) 3632 cm^{-1} (free OH). 10a: mp 149-151°C, NMR ($CDCl_3$) δ 1.01 (s, 3H, 13-Me), 4.88 (br t, 1H, J = 5 Hz, 17a-H); UV λ_{max} (EtOH) 277 nm (ε 19300). 10b: mp 143-144°C, IR (dilute CCl_4) 3502 cm^{-1} (bonded OH). 11a: mp 159-161°C, NMR ($CDCl_3$) δ 0.95 (s, 3H, 13-Me), 4.78 (t, 1H, J = 3 Hz, 17a-H); UV λ_{max} (EtOH) 275 nm (ε 19100). 11b: mp 137-139°C, IR (dilute CCl_4) 3528 cm^{-1} (bonded OH).
7. M. Fetizon and M. Golfier, Compt. redn., 267, 900 (1968).
8. N. S. Wulfson, V. I. Zaretskii, V. L. Sadovskaya, S. N. Ananchenko, V. M. Rzheznikov, and I. V. Torgov, Tetrahedron 22, 1885 (1966). The intensity of the cyclic fragment peak (m/e 226), formed by the D ring cleavage, was about six times as large in the spectrum of 16 (14β) as in that of 17 (14α).
9. Details of the X-ray analyses will be described elsewhere.
10. The major product was 3-methoxy-8,14-seco-D-homoestra-1,3,5(10),8 or 9(11),14-pentaen-17aα-ol acetate, arised by dehydromesylation: syrup, NMR ($CDCl_3$) δ 1.08 (s, 3H, 13-Me), 2.04 (s, 3H, OAc), 3.75 (s, 3H, OMe), 4.88 (t, 1H, J = 6 Hz, 17a-H), 5.3-5.8 (m, 3H, olefinic H); UV λ_{max} (EtOH) 269 nm (ε 11700); IR ($CHCl_3$) 1725 cm^{-1}. 17a-Phenylurethan was obtained as crystals: mp 123-125°C, mass m/e 417 (M^+); IR ($CHCl_3$) 3443, 1728 cm^{-1}.
11. 12a: mp 99-101°C, NMR ($CDCl_3$) δ 1.11 (s, 3H, 13-Me), 3.9-4.6 (m, 2H, CH_2O); UV λ_{max} (EtOH) 277 nm (ε 16900). 13a: mp 103-105°C, NMR ($CDCl_3$) δ 0.88 (s, 3H, 13-Me), 3.9-4.6 (m, CH_2O); UV λ_{max} (EtOH) 276 nm (ε 14600). 14a: syrup, NMR ($CDCl_3$) δ 1.05 (s, 3H, 13-Me), 3.9-4.6 (m, 2H, CH_2O); UV λ_{max} (EtOH) 276 nm (ε 14100). 15a: mp 124-126°C, NMR ($CDCl_3$) δ 1.01 (s, 3H, 13-Me), 3.8-4.5 (m, 2H, CH_2O); UV λ_{max} (EtOH) 278 nm (ε 15700).
12. The equilibria ratio (as the formates) were found by HPLC of the alcohols obtained after hydrolysis as follows: 8b/12b = 1/1.5; 9b/13b = 3.1/1; 10b/14b = 1/1.1; 11b/15b = 2.3/1.
13. Based on these results, examination of molecular models suggests that either of the transition states leading to 14 and 15 will take a boat-like conformation for the six-membered D ring having the intermediate episulfonium ion.
14. R. K. Crossland and K. L. Servis, J. Org. Chem. 35, 3195 (1970).
15. Quite unexpectedly, solvolysis of 5c followed by hydrolysis resulted in poor yields of the anticipated cyclization product 9b with the newly formed two compounds which were identified as A and B. Substance A, presumably formed as a *result of a disproportionation* reaction, was identical (NMR, IR) to the material from catalytic hydrogenation of 3. On heating with formic acid, A was partially converted into B after hydrolysis.

(Received in Japan 5 April 1980)