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A CARBENOID ROUTE TO C(1)-C(11) BRIDGED STEROIDS

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Summary. The exocyclic olefin **3** enters into stereoselective cyclopropanations with dihalocarbenes on the steroid β-face to afford the protected spiro[2.5]octane analogues **4** and **5**. These intermediates are transformed into novel, highly strained steroid derivatives, like **9**, by utilizing an intramolecular cyclopropylidene insertion reaction en route to pentacyclic, C(1)-C(11) ethano-bridged steroids **13-20**.

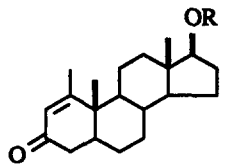
The incorporation of short carbon bridges spanning characteristic positions of the steroid backbone continues to be a popular stratagem in the search for new, biologically active steroid hormone analogues.[1] In continuation of our work on anabolic steroids[2] and steroidal aromatase inhibitors,[3] we have developed a novel protocol for bridging positions C(1) and C(11) by a two-carbon unit, which will be described in this communication.[4] The most salient feature in this useful synthetic scheme is represented by a stereoselective intermolecular addition of dihalocarbenes to an exocyclic steroidal double bond at C(1), followed by an intramolecular cyclopropylidene insertion reaction into the equatorial C(11)-H(11α) bond, to furnish a hexacyclic key intermediate containing a highly strained bicyclo[3.1.0]hexane substructure. In subsequent steps, C(1)-C(11) ethano-bridged analogues are obtained from this precursor by regioselective cleavage of the central, most-strained cyclopropyl C-C bond.

17β-Acetyloxy-1-methyl-5α-androst-1-en-3-one (**1**) served as convenient starting material. Ketalization of this enone with excess ethylene glycol and trimethyl orthoformate in refluxing methylene chloride, containing a catalytic amount of *p*-TsOH, proceeded with concomitant migration of the double bond into the exocyclic position, **1**→**3**.[5] It was imperative to run this ketalization-deconjugation reaction in the presence of an acetyloxy group at C(17), since the unprotected steroid **2** was subject to side reactions under these otherwise favorable conditions.

From an inspection of Dreiding molecular models, accessibility of the exocyclic double bond was predicted to be highest at the β-face. In fact, catalytic hydrogenation (THF, EtOH, Pd/C, H_2, 22°C; 91%) of the olefin in question, followed by deketalization (THF, aqueous H_2SO_4, 22°C, 6 h; 93%), stereoselectively afforded 17β-acetyloxy-1α-methyl-5α-androstan-3-one, identical in all respects to an authentic sample.[6]

Not unexpectedly, cyclopropanation of **3** with dichlorocarbene, generated at room temperature under phase-transfer[7] conditions in a well-stirred mixture of chloroform and 50% aqueous sodium hydroxide solution in the presence of a catalytic amount of benzyltriethylammonium chloride during 24 h, produced a single diastereoisomer, **4**, which was isolated in 52% yield after chromatography on silica gel. The corresponding dibromo derivative **5** was prepared by adding a solution of bromoform in cyclohexane to a stirred suspension of **3** and *t*-BuOK in the same solvent at 10°C over a period of 2.5 h.[8] After additional stirring of the heterogeneous mixture for 2.5 h, aqueous work-up and chromatographic separation from a large amount of starting material gave the ketal **5** in 19% yield. In both cases, the acetate functionality had survived

the basic reaction conditions. Acid-promoted removal (MeOH, THF, H_2O, oxalic acid, 70°C, 12 h) of the ketal protecting groups at C(3) delivered **6** and **7** in 95% and 89% yield, respectively, following chromatographic purification on silica gel. NMR spectral data for compounds **6** and **7** confirmed our expectation as to the stereochemical outcome in the dihalocarbene addition step. The assignment of the AB-subspectrum (300 MHz, $CDCl_3$) for the geminal three-membered ring protons (H_A: δ 1.71 ppm (1/2 ABq, J= 8.0, 1.8 Hz, 1 H); H_B: δ 1.51 ppm (1/2 ABq, J= 8.0 Hz, 1 H)) of the dibromo derivative, for example, is based on their dissimilar steric environment. Moreover, a long-range coupling between the downfield resonance H_A and



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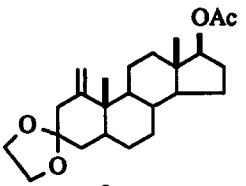
2 R=H



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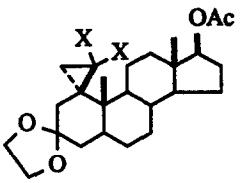

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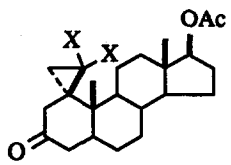
5 X=Br



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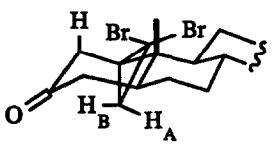
7 X=Br



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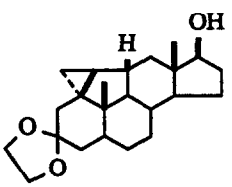

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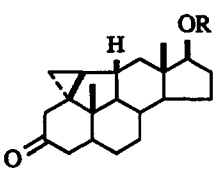

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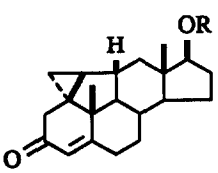

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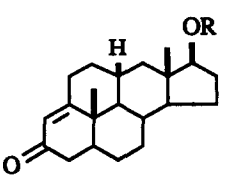
12 R=H



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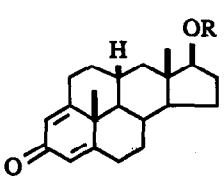
14 R=Ac



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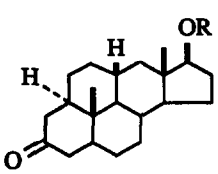
16 R=H



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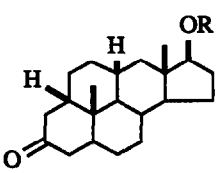
18 R=H



19 R=Ac
20 R=H

H(2β) is compatible only with the β-dibromo isomer **7**, which displays the adequate W-type alignment of bonds.

Our synthetic plan now called for an intramolecular insertion reaction of the cyclopropylidene species derived from either **4** or **5** into the equatorial C(11)-H(11α) bond. This transformation had to prevail over possible competing pathways[9] like dimerization, cyclopropylidene-allene rearrangement, intermolecular insertion into a C-H bond of a solvent molecule, or intramolecular insertion into a different steroidal C-H bond in the proximity of the three-membered ring.

Gratifyingly, exposure of the dibromo ketal **5** in toluene solution under an atmosphere of argon to the action of excess ethereal methyllithium at 0°C for 3 h afforded **8** as the sole reaction product in 86% yield after aqueous work-up and chromatography on silica gel. When the dichloro compound **4** was subjected to similar reaction conditions (toluene, MeLi-Et_2O, 22°C, 20 h), the insertion product **8** could be isolated in 80% yield. Subsequent cleavage (THF, MeOH, 8% aqueous H_2SO_4, 22°C, 4 h) of the ketal protecting group then produced the parent hexacyclic steroid **9** in 73% yield following chromatography on silica gel. The structure of this key intermediate was secured by extensive spectroscopic measurements. Although the first hints in support of structure **9** were provided by combustion analysis, HRMS data, and the presence of upfield resonances in both the ^1H and ^{13}C NMR spectra, recourse had to be taken to two-dimensional ^1H-^1H and ^1H-^{13}C correlation experiments, in order to assign relevant resonances unambiguously. The methine cyclopropyl proton (300 MHz, CD_2Cl_2) was not clearly resolved, but was part of a ten-proton multiplet at δ 1.60-1.26 ppm. The corresponding *cis* methylene proton on the three-membered ring formed a doublet of doublets (δ 0.02 ppm (dd, J= 7.9, 6.2 Hz, 1 H)) overlapping with the resonance of H(9) (δ 0.06 ppm (t, J= 12.1 Hz, 1 H)), while the remaining secondary cyclopropyl proton was located at δ 0.99-0.97 ppm. The stereochemistry at C(11) was deduced from the coupling pattern of the well-resolved methylene protons at C(12), (H(12β): δ 1.81 ppm (dd, J= 11.6, 4.0 Hz, 1 H); H(12α): δ 0.82 ppm (t, J= 11.6 Hz, 1 H)). The observed splitting for H(12α) requires the vicinal proton at C(11) to occupy the axial β-position. A similar conclusion evolves from the splitting pattern of H(9).

The stage was now set for the exploration of viable routes to biologically interesting derivatives of **9**. Temporary protection (pyridine, Ac_2O, 22°C, 17 h; 94%) of the hydroxyl group at C(17) marked the first step in the synthesis of the testosterone derivative **12**, via acetate **11**. Introduction of the requisite double bond was effected by an established procedure (*t*-BuOH, SeO_2, AcOH, 90°C, 28 h; 21%).[10] Saponification (MeOH, KOH, 22°C, 4 h) of **11** then gave the alcohol **12** in quantitative yield. Rupture of the central cyclopropyl C-C bond took place upon treatment of **9** with 70% aqueous perchloric acid in CH_2Cl_2 for 3.5 h at 22°C.[11] The bridged enone derivative **13**, obtained in 50% yield after chromatography on silica gel, was subsequently acetylated (pyridine, Ac_2O, 22°C, 20 h; 94%) as a prelude to the introduction of an additional double bond into ring A, **14**→**15**, utilizing the dehydrogenation procedure (toluene, $(PhSe)_2$, $PhIO_2$, 90°C, 3 h; 40%) of Barton and co-workers.[12] Once again, the parent steroid **16** was obtained upon saponification in quantitative yield. Stereoselective access to a pair of C(1) epimeric, C(1)-C(11) ethano-bridged androstane derivatives was gained by exploiting catalytic hydrogenation as the key transformation. The enone **14** was reduced smoothly under a blanket of hydrogen in methanol over Pd-$CaCO_3$ at 22°C to furnish **17** in 94% yield. On the other hand, direct reductive cleavage (AcOH, PtO_2, H_2, atmospheric pressure, 22°C) of the three-membered ring in **10** led to a product, in which reduction of the 3-oxo functionality had occurred concurrently.[13] The crude product was therefore oxidized by pyridinium dichromate in DMF[14] at 22°C to afford the desired ketone **19** after chromatography in 35% overall yield for the two steps. The parent alcohols **18** and **20** were

finally prepared by saponification in almost quantitative yield.[15] Poorly dispersed ^{1}H NMR spectra of compounds **15-18** reflect their local symmetry and allow for a ready discrimination between epimers **17/18** and **19/20**, respectively.

References and Notes

1. (a) Bull, J. R.; Thomson, R. I. *J. Chem. Soc., Chem. Commun.* **1986**, 451. (b) Ottow, E.; Neef, G.; Wiechert, R. *Angew. Chem.* **1989**, *101*, 776; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 773.
2. Neumann, F.; Wiechert, R. *Arzneim.-Forsch. (Drug Res.)* **1965**, *15*, 1168.
3. (a) Henderson, D.; Habenicht, U.-F.; Nishino, Y.; Kerb, U.; El Etreby, M. F. *J. Steroid Biochem.* **1986**, *25*, 867. (b) Künzer, H.; Sauer, G.; Wiechert, R. *Tetrahedron* **1989**, *45*, 6409.
4. For alternative procedures to C(1)-C(11) bridged steroids, consult: (a) Tanabe, M.; Chamberlin, J. W.; Nishiura, P. Y. *Tetrahedron Lett.* **1961**, 601. (b) Pitt, C. G.; Rector, D. H.; White, D. H.; Wani, M. C.; McPhail, A.T.; Onan K. D. *J. Chem. Soc. Perkin Trans. I* **1977**, 1144. (c) Wieland, P.; Kalvoda, J. *Tetrahedron Lett.* **1983**, *24*, 5603. (d) Tolf, B.-R.; Crowe, D. F.; Johansson, J. G.; Peters, R. H.; Tanabe, M. *Tetrahedron Lett.* **1984**, *25*, 4855. (e) Napolitano, E.; Fiaschi, R.; Hanson, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1330.
5. Wiechert, R.; Kerb, U.; Schulze, P.-E. *Naturwissenschaften* **1964**, *51*, 86.
6. Wiechert, R. Z. *Naturforschg.* **1964**, *19b*, 944.
7. Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; Verlag Chemie: Weinheim, 1980.
8. Paquette, L. A.; Browne, A. R.; Chamot, E.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 643.
9. (a) Kirmse, W. *Carbene Chemistry*; Academic Press: New York, 1964. On several occasions, steroidal dihalocarbene adducts have been successfully converted into more elaborate derivatives. Consult: (b) Birch, A. J.; Subba Rao, G. S. R. *J. Chem. Soc. (C)* **1967**, 2509. (c) Galantay; E.; Paolella, N.; Barcza, S.; Coombs, R. V.; Weber, H. P. *J. Am. Chem. Soc.* **1970**, *92*, 5771. (d) Rosen, P.; Karasiewicz, R. *J. Org. Chem.* **1973**, *38*, 289. (e) Dammann, R.; Braun, M.; Seebach, D. *Helv. Chim. Acta* **1976**, *59*, 2821. (f) Yates, P.; Winnik, F. M. *Can. J. Chem.* **1985**, *63*, 2501. (g) Ekhato, I. V.; Robinson, C. H. *J. Org. Chem.* **1989**, *54*, 1327.
10. Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS, Inc.: Philadelphia, PA, 1984; Chapter 3.
11. Birch, A. J.; Brown, J. M.; Subba Rao, G. S. R. *J. Chem. Soc.* **1964**, 3309.
12. Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc. Perkin Trans. I* **1982**, 1947.
13. Attah-Poku, S. K.; Alward, S. J.; Fallis, A. G. *Tetrahedron Lett.* **1983**, *24*, 681.
14. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
15. Physical data for representative steroids are as follows. **6**: mp 130-131°C (acetone-(*i*-Pr)$_2$O), $[\alpha]_D^{22}$ +27.2° (c 0.25); **9**: mp 150-151°C ((*i*-Pr)$_2$O), $[\alpha]_D^{22}$ +25.9° (c 0.51); **10**: mp 145-146 °C ((*i*-Pr)$_2$O), $[\alpha]_D^{22}$ +23.8° (c 0.51); **11**: mp 213-214°C ((*i*-Pr)$_2$O), $[\alpha]_D^{22}$ +70.1° (c 0.26); **13**: mp 177-179 °C ((*i*-Pr)$_2$O), $[\alpha]_D^{22}$ -103.4° (c 0.50); **15**: mp 220-221°C ((*i*-Pr)$_2$O), $[\alpha]_D^{22}$ +8.6° (c 0.26); **17**: mp 140-142°C ((*i*-Pr)$_2$O), $[\alpha]_D^{22}$ -8.7° (c 0.51); **19**: mp 115-116°C ((*i*-Pr)$_2$O), $[\alpha]_D^{22}$ +139.7° (c 0.49). All $[\alpha]_D^{22}$-values were determined with $CHCl_3$ solutions.

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