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A VINYL SULFONE/VINYL SULFOXIDE BASED ROUTE TO C(6)-C(7) METHYLENE-BRIDGED DERIVATIVES OF ESTRADIOL

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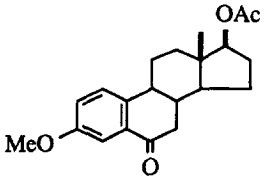
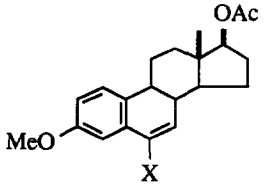
Summary. Acceptor substituted 3-methoxyestra-1,3,5(10),6-tetraene derivatives **3**, **4**, and **5** have been prepared and exploited in a synthesis of the title compounds **13** and **15** by key Michael-type addition reactions involving dimethylsulfoxonium methylide. α-Cyclopropanation was only slightly favored on the sulfone analogue **3** but strongly so on the (R)-sulfoxide **4**. On the contrary, the (S)-sulfoxide **5** displayed a weak preference for β-face attack.

A recent report from these laboratories has outlined the conversion of ketone **1** into vinyl sulfone **3** in conjunction with the utilization of this Michael acceptor to generate C(7) α-alkylated derivatives of estradiol.[2] It was shown that alkynyllithium reagents afford α-substituted products in good yield under excellent stereochemical control, while ordinary alkyllithium species either discriminate poorly between the two π-faces or add with reversed selectivity. Regrettably, other carbon-centered nucleophiles share unfavorable stereoselection characteristics in the latter sense. To overcome such shortcomings, we have also explored a lower oxidation state at sulfur, which introduces an additional stereogenic center in close proximity to the reaction site. This communication highlights the synthetic potential of sulfoxides **4** and **5** in a stereocontrolled approach to C(6)-C(7) cyclopropane annulated estradiol derivatives. These targets merit consideration because the 6α,7α-bridged analogue structurally resembles 7α-methylestradiol, a steroid known for remarkable biological properties.[3]

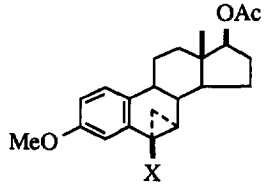
Dissolved in a three-component mixture (C_2H_5OH/THF/H_2O, 20:5:1), vinyl sulfide **2**[2] underwent smooth oxidation in the presence of magnesium monoperoxyphthalate (MMPP) at ambient temperature.[4] Since little substrate control over the stereochemical outcome at sulfur materialized in this reaction, **4** and **5** could be isolated in 48% and 39% yield, respectively, following chromatographic separation on silica gel (hexane/ethyl acetate, 1:1).



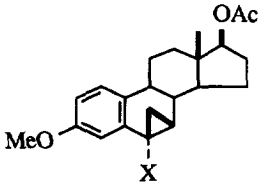
1



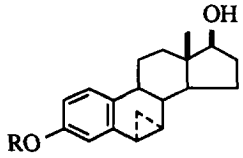
2 X= SPh
3 X= SO_2Ph
4 X= (R)-SOPh
5 X= (S)-SOPh



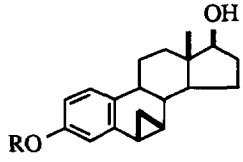
6 X= SO_2Ph
7 X= (R)-SOPh
8 X= (S)-SOPh



9 X= SO_2Ph
10 X= (R)-SOPh
11 X= (S)-SOPh



12 R= Me
13 R= H



14 R= Me
15 R= H

The configurational issue associated with the trivalent heteroatom in sulfoxides **4** and **5** was resolved by CD spectroscopy. For the polar isomer **4**, a positive primary band Cotton effect near 245 nm ($\Delta\epsilon$ +12.5; CH_3OH) classifies the arrangement of substituents on sulfur, including the lone pair, as R. Complementary chiroptical properties ($\Delta\epsilon$ -8.8, 238 nm; CH_3OH) point to the opposite configuration for the faster eluting derivative **5**.[5]

The stage was thus set to investigate sulfur ylide-mediated three-membered ring annulations on substrates **3**, **4**, and **5**.[6] Although vinyl sulfone **3** was subject to almost quantitative Michael-type methylenation (DMSO, NaH, $(CH_3)_3SOI$, 22°C),[7] the product ratio (**6/9**, 1.1:1), as determined after chromatographic separation on silica gel (cyclohexane/acetone, 3:2, gradient elution), fully matched earlier disenchanting observations.[2] Both adducts were separately transformed into the title compounds by standard procedures. Reductive removal of the phenyl sulfonyl group from **6** with magnesium turnings in methanol occurred with concomitant saponification of the acetate protecting group at C(17) and furnished methyl ether **12** in 90% yield. The remaining demethylation, **12**→**13**, proceeded satisfactorily (4h; 93%) with DIBAH in toluene at reflux temperature. An entirely analogous three-step deblocking scheme (**9**→**14** (88%), **14**→**15** (89%)) was relied upon in the β-bridged series.

Our companion study at the sulfoxide level displayed high cyclopropanation efficiency (35-40°C, 4h; combined yield 90%) as well as excellent stereocontrol, since **4** delivered pentacycles **7** and **10** in a ratio of 12:1 (dichloromethane/acetone, 9:1). For the epimeric sulfoxide **5**, stereoselectivity was less pronounced but reversed (**5**→**8/11**, 1:3). While three-membered ring orientation on sulfone scaffolds **6** and **9** was deduced by NMR experiments, including NOE measurements, structural assignments for sulfinyl derivatives **7**, **8**, **10**, and **11** are based on chemical correlations. Pertinent details concerning two oxidations and a single desulfurization performed on major products serve to illustrate this endeavor: (1) **7**→**6** (93%), (2) **11**→**9** (90%) (AcOH, $NaBO_3$-$4H_2O$, 22°C, 16h); (3) **7**→**12** (87%) (NH_3, THF, Li, -55°C; NH_4Cl).

Interestingly, our findings are in agreement with a model put forth to rationalize the stereochemical course of various conjugate additions to α,β-unsaturated sulfoxides.[8] According to this theoretical tool, vinyl sulfoxides adopt a reactive conformation in which the sulfur-oxygen linkage and the carbon-carbon double bond eclipse, thus rendering the region above/below the olefinic π-plane either sterically or electronically biased by virtue of the third substituent and the lone pair on the adjacent sulfur atom. A non-chelating nucleophile should therefore approach the double bond contrasterically on a trajectory anti to the area of high electron density defined by the lone pair.

In conclusion, this work has established **4** as a valuable new intermediate for the stereocontrolled synthesis of C(7) α-substituted estradiol analogues.[9]

References and Notes

1. Postdoctoral Fellow, 1993.
2. Künzer, H.; Thiel, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1994**, *35*, 1691.
3. Peters, R. H.; Crowe, D. F.; Avery, M. A.; Chong, W. K. M.; Tanabe, M. *J. Med. Chem.* **1989**, *32*, 2306.
4. Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.
5. Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 1958.
6. (a) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72. (b) Hamdouchi, C. *Tetrahedron Lett.* **1992**, *33*, 1701. (c) Bäckvall, J.-E.; Löfström, C.; Juntunen, S. K.; Mattson, M. *Tetrahedron Lett.* **1993**, *34*, 2007. (d) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717.
7. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867.
8. (a) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399. (b) Koizumi, T.; Arai, Y.; Takayama, H. *Tetrahedron Lett.* **1987**, *28*, 3689. (c) Kahn, S. D.; Dobbs, K. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 4602. (d) Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089. (e) Fujita, M.; Ishida, M.; Manako, K.; Sato, K.; Ogura, K. *Tetrahedron Lett.* **1993**, *34*, 645.
9. Physical data for selected steroids are as follows. **2**: mp 100-101°C (ethyl acetate/pentane); $[\alpha]_D$ -151.1° (c 0.51, $CHCl_3$). **4**: mp 185-187°C (acetone/hexane); $[\alpha]_D$ -28.3° (c 0.51, $CHCl_3$). **5**: mp 198-200°C (acetone/hexane); $[\alpha]_D$ -135.2° (c 0.51, $CHCl_3$). **6**: amorphous; $[\alpha]_D$ - 85.0° (c 0.45, $CHCl_3$). **7**: amorphous; $[\alpha]_D$ -27.1° (c 0.52, $CHCl_3$). **8**: amorphous; $[\alpha]_D$ -217.7° (c 0.53, $CHCl_3$). **9**: mp 152-154°C (acetone/hexane); $[\alpha]_D$ +23.2° (c 0.51, $CHCl_3$). **10**: mp 168-169°C (ether/pentane); $[\alpha]_D$ +51.7° (c 0.51, $CHCl_3$). **11**: mp 141-143°C (acetone/hexane); $[\alpha]_D$ +15.8° (c 0.51, $CHCl_3$). **12**: amorphous; $[\alpha]_D$ -8.8° (c 0.52, $CHCl_3$). **13**: mp 178-180°C (acetone/hexane); $[\alpha]_D$ -18.8° (c 0.52, CH_3OH). **14**: amorphous; $[\alpha]_D$ -107.0° (c 0.51, $CHCl_3$). **15**: amorphous; $[\alpha]_D$ -116.3° (c 0.52, CH_3OH). All $[\alpha]_D$-values were determined at 22°C.

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