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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).



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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 ($\Delta \epsilon + 12.5$; CH₃OH) classifies the arrangement of substituents on sulfur, including the lone pair, as R. Complementary chiroptical properties ($\Delta \epsilon - 8.8$, 238 nm; CH₃OH) 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, $12\rightarrow13$, proceeded satisfactorily (4h; 93%) with DIBAH in toluene at reflux temperature. An entirely analogous three-step deblocking scheme (9 \rightarrow 14 (88%), 14 \rightarrow 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 $(5\rightarrow 8/11, 1:3)$. 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) $7\rightarrow 6$ (93%), (2) $11\rightarrow 9$ (90%) (AcOH, NaBO₃-4H₂O, 22°C, 16h); (3) $7\rightarrow 12$ (87%) (NH₃, THF, Li, -55°C; NH₄Cl).

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.

- 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.
- (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.
- (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.
- Physical data for selected steroids are as follows. 2: mp 100-101°C (ethyl acetate/pentane); [α]_D -151.1° (c 0.51, CHCl₃). 4: mp 185-187°C (acetone/hexane); [α]_D -28.3° (c 0.51, CHCl₃). 5: mp 198-200°C (acetone/hexane); [α]_D -135.2° (c 0.51, CHCl₃). 6: amorphous; [α]_D 85.0° (c 0.45, CHCl₃). 7: amorphous; [α]_D -27.1° (c 0.52, CHCl₃). 8: amorphous; [α]_D -217.7° (c 0.53, CHCl₃). 9: mp 152-154°C (acetone/hexane); [α]_D +51.7° (c 0.51, CHCl₃). 11: mp 141-143°C (acetone/hexane); [α]_D +15.8° (c 0.51, CHCl₃). 10: mp 168-169°C (ether/pentane); [α]_D +51.7° (c 0.51, CHCl₃). 11: mp 141-143°C (acetone/hexane); [α]_D -18.8° (c 0.52, CHCl₃). 13: mp 178-180°C (acetone/hexane); [α]_D -18.8° (c 0.52, CHCl₃). 14: amorphous; [α]_D -107.0° (c 0.51, CHCl₃). 15: amorphous; [α]_D -116.3° (c 0.52, CH₃OH). All [α]_D-values were determined at 22°C.

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^{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.