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ORIGINS OF 1,2- AND 1,3-STEREOSELECTIVITY IN DICOBALTOCTACARBONYL ALKENE-ALKYNE CYCLIZATIONS FOR THE SYNTHESIS OF SUBSTITUTED BICYCLO[3.3.0]OCTENONES.

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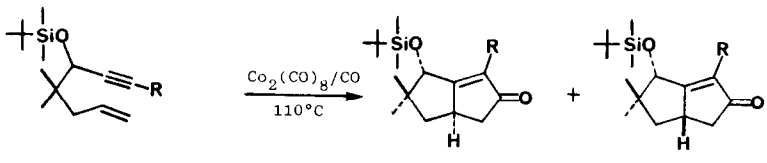
Summary: A working mechanistic hypothesis is proposed, which rationalizes the stereochemical outcome of the synthesis of substituted bicyclo[3.3.0]octenones, using dicobaltoctacarbonyl mediated alkene-alkyne cyclizations.

Both linear and angularly fused triquinanes have become increasingly popular synthetic targets in recent years, largely because they offer interesting opportunities to develop new methods and strategies for the synthesis of five-membered rings.[2] Recently, we have used the Pauson-Khand reaction[3] to synthesize the bicyclo[3.3.0]octenone 2 (R = Me), which was subsequently converted into an advanced precursor to the antitumor sesquiterpene coriolin. SCHEME 1.



1 2 3

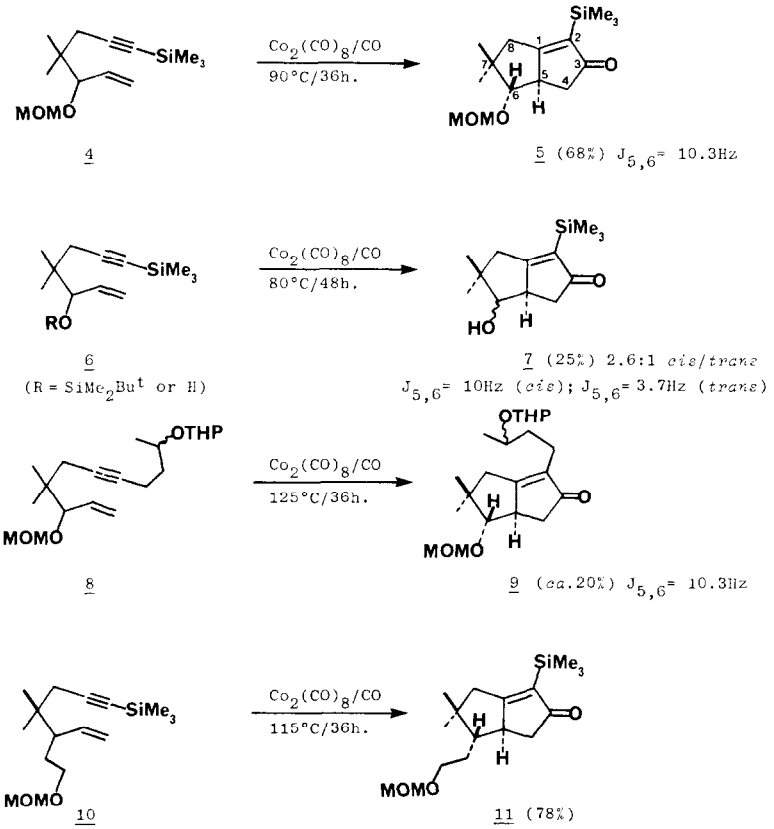
For R = $SiMe_3$, ratio of 2/3 is 26:1
For R = Me , ratio of 2/3 is 3:1

SCHEME 1

Clearly, the size of the group on the terminus of the acetylene has a controlling influence on the 1,3-stereoselectivity.

To investigate the potential for 1,2-stereoselectivity the substrates 4, 6, 8, and 10 were prepared by standard techniques, and subjected to the $Co_2(CO)_8$ enyne cyclization conditions (see representative example).[4] While the -$SiMe_2Bu^t$ secondary alcohol protecting group was stable in the propargyl system 1, for the allylic system 6 (R = $SiMe_2Bu^t$) we could isolate only desilylated material 7 in modest yield with poor stereoselectivity. Whereas, the corresponding MOM-ether derivative 4 gave the bicyclo[3.3.0]octenone 5

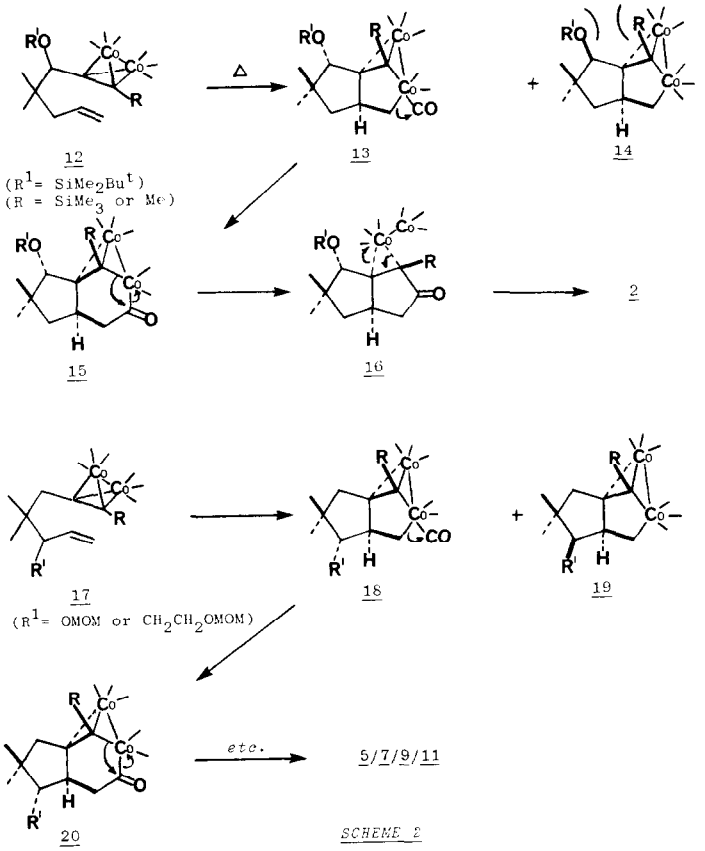
TABLE



(cis/trans refers to the relative stereochemistry of the C-6 oxygen substituent with respect to the C-5 hydrogen.)[5]

in good yield (68%, isolated, purified) as a single cis-stereoisomer. Similarly, the substrates 8 and 10 gave 9 and 11 respectively, with no evidence (360MHz NMR) for the trans-isomers. In a separate experiment it was established that 6 (R = H) also gave 7, and that the substrate 6 (R = $SiMe_2Bu^t$) was converted into 6 (R = H) prior to cyclization into 7.

The SCHEME 2 summarizes a working mechanistic hypothesis to explain the 1,3- and 1,2-stereoselectivity. The isolable complex 12 can form two cobalt metallocycles 13 and/or 14, upon alkene insertion into the internal C-Co bond. The newly formed five-membered ring Co-metallocycle is presumably cis-fused. The metallocycle 13 minimizes the steric interactions between R^1O- and R-; whereas, 14 has a severe 1,3-pseudo diaxial interaction on the endo-



SCHEME 2

face. Consequently, a large R-group (-SiMe$_3$) would be expected to favor 13. The metallocycle 13 can undergo CO-insertion to the acyl-Co complex 15, which is set up to migrate the C-Co bond to the adjacent electrophilic carbonyl group to give 16. Reductive elimination of the cobalt carbonyl residue in 16 establishes the cyclopentenone double bond.[6] *For the allylic substitutent case 17, the sterically favored metallocycle is 18 rather than 19, since this establishes* R^1 *cis- to the adjacent hydrogen atom rather than the five-membered ring Co-metallocycle. Also,* R^1 *is trans- to R, thus removing the 1,4-pseudo diaxial arrangement present in 19. This model also predicts that substituents at C-7 would not be expected to have much stereochemical bias, and this is the case.*[3]

In summary, it appears that the more-stable metallocycle 13/18 predicts the observed stereochemistry, which in these cases corresponds to the thermodynamically more stable product (substituent at C-6 or C-8 on the exo-face). It should be noted that the substrates 5, 9, and 11 have the correct relative stereochemistry for elaboration into more highly fused naturally occurring sesquiterpenes such as pentalenic acids and quadrone.[2] The dicobaltoctacarbonyl alkene-alkyne cyclization provides a tantalizingly direct route to these bicyclo[3.3.0]octenones from simple acyclic precursors, themselves available from isobutyrate-alkylation chemistry.[7,8]

References and Footnotes

1. *National Science Foundation Graduate Fellow 1983-1986.*
2. *L.A. Paquette, "Recent Synthetic Developments in Polyquinane Chemistry". Topics in Current Chemistry 119, Springer-Verlag, 1984.*
3. *C. Exon and P. Magnus, J. Am. Chem. Soc., 1983, 105, 2477 and references cited therein; P. Magnus, C. Exon, and P. Albaugh-Robertson, Tetrahedron, In Press; I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, and M. I. Foreman, J. Chem. Soc., Perkin Trans. 1, 1973, 977; M. J. Knudsen, and N. E. Shore, J. Org. Chem., 1984, 49, 5025; N. E. Shore, and M. C. Croudace, Ibid., 1981, 46, 5436; D. C. Billington, and D. Willison, Tetrahedron Letters, 1984, 4041.*
4. *$Co_2(CO)_8$ (1.10g 1.1eq) was added to dry heptane (5ml) in a resealable tube, which had been purged with CO for 2h. The enyne 4 (0.765g) was added, and the mixture stirred at 20°C for 2h, in order to form the $Co_2(CO)_6$-complex. The tube was sealed and heated at 90°C for 36h, cooled, evaporated in vacuo, and the residue dissolved in acetone-water (9:1). Ceric ammonium nitrate (ca. 11g) was slowly added to the above mixture until CO_2 evolution ceased (destruction of Co- complexes), and the aqueous solution extracted with petrol (3 x 20ml). The washed (brine) extract was dried ($MgSO_4$), evaporated, and the residue chromatographed over silica gel eluting with 30% ether/petrol to give 5 (0.57g 68%). IR (thin film) 1690cm^{-1}.*
5. *H. Seto, T. Sasaki, H. Yonehara, and J. Uzawa, Tetrahedron Letters, 1978, 924.*
6. *The number of CO ligands attached to the Co atoms in the depicted intermediates is not known, but CO can freely dissociate to give more reactive ligand unsaturated species.*
7. *The full details of the synthesis of the acyclic precursors to the bicyclo[3.3.0]octenones, along with transformations of 5, 9, and 11 into triquinanes will be reported in due course.*
8. *The NSF is gratefully thanked for their support of this research.*

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