Table I. Absolute Rate Constants for the Reactions of Methylidynes with Alkenes

alkene	$10^{-9}k$, M^{-1} s^{-1} CH	CF	CCl	CBr
C_2H_4	69 ± 6[a] 130 ± 50[b]	0.04 ± 0.01	0.16 ± 0.01 0.13 ± 0.01[c]	0.52 ± 0.02
C_3H_6		0.3 ± 0.1	1.0 ± 0.1	3.0 ± 0.3
1-C_4H_8		0.4 ± 0.1	1.7 ± 0.2	3.5 ± 0.3
trans-2-butene		1.1 ± 0.2	2.6 ± 0.2	7.4 ± 0.8
2-methyl-2-propene		1.1 ± 0.3	3.5 ± 0.3	8.0 ± 1.0
2-methyl-2-butene			8.0 ± 1.0	17 ± 2
2,3-dimethyl-2-butene			14 ± 3	23 ± 6
cyclohexene			3.1 ± 0.2	
1,3-cyclohexadiene			1.4 ± 0.2	
1,4-cyclohexadiene			3.7 ± 0.2	

[a] Reference 3. [b] Reference 4. [c] Reference 5; 25 ± 3 °C; errors are standard deviation; *cyclo*alkenes ~100-120 measurements; others, ~220-480 measurements.

1-0) transition at 223.79, 223.88, and 224.18 nm for CF; the Q_1 band of the ($\tilde{A}^2\Delta$(b)-$\tilde{X}^2\Pi$(a), 0-0) transition at 277.87 nm for CCl; and the Q_1 band of the ($\tilde{A}^2\Delta$(a)-$\tilde{X}^2\Pi$(a)) transition at 301.34 nm for CBr.

The absolute rate constants obtained for the reaction of CF with five alkenes, of CCl with ten alkenes, and of CBr with seven alkenes along with the only rate constant reported in the literature for the reaction of methylidyne with an alkene, namely ethylene, are presented in Table I.

As seen from the data, CF reacts with alkenes, as do the other two halomethylidynes studied before. By far the most reactive species of the four methylidynes studied quantitatively to date is CH; it reacts about 3 orders of magnitude faster than the halomethylidynes. For the halomethylidynes the order of reactivity is CF < CCl < CBr and the ratio of rate constants is ≈1:3-4:9-13 throughout the series. All three halomethylidynes exhibit a distinct electrophilic character as manifested by the increase in reactivity with increasing alkyl substitution on the alkenic carbon. In the case of CCl this increase is nearly 2 orders of magnitude in going from ethylene to tetramethylethylene. The reactivity of CCl with *trans*-2-butene, cyclohexene, and 1,4-cyclohexadiene is nearly identical and is in the order expected. The low value of the rate constant for 1,3-cyclohexadiene is in agreement with the electrophilicity of carbynes and rules out a radical-like reactivity for them.

The observed trend in the relative reactivities of the three halomethylidynes can be interpreted in terms of the relative amount of p_π-p_π overlap between the halogen and carbon. The values of the C-X bond dissociation energies, 131, 81, and 75 kcal/mol, and bond lengths, 1.27, 1.65, and 1.82 Å for CF, CCl, and CBr, respectively, reflect this p_π-p_π overlap, which increases when the size of the halogen p_π orbital approaches the size of the carbon p_π orbital. Hence, the strongest partial triple bond, and consequently the lowest reactivity, will be encountered with CF and the weakest triple-bond character and highest reactivity with CBr. This interpretation of π-bond strength and its effect on chemical reactivity is also in agreement with spectroscopic observations. The spectroscopic transition $^2\Delta \leftarrow {}^2\Pi$ in halomethylidynes is due to promotion of an electron from the $x\sigma$ orbital to the $v\pi$ orbital. The energy of this transition increases in the order CBr < CCl < CF and reflects increasing orbital energy separation. If the $v\pi$ orbital, which is antibonding in halomethylidynes, increases in energy, then the orthogonal bonding $w\pi$ orbital must decrease in energy. Therefore the increasing transition energy reflects stronger π bonding.

By analogy with CCO_2Et the primary product of the reaction $CX(\tilde{X}^2\Pi)$ + alkene is postulated to be a vibrationally excited cyclopropyl radical, C-C-C-X, which may undergo further unimolecular reactions. Ab initio molecular orbital calculations on the CH + C_2H_4 system predict that the reaction proceeds along a non-least-motion symmetry-allowed path and features a zero activation energy.[6] This is in agreement with the high experimental rate constant, ~10^{11} M^{-1} s^{-1}. The cycloaddition reactions of halomethylidynes probably follow a similar non-least-motion reaction path and are predicted to feature progressively increasing but small activation energies in the order CBr < CCl < CF.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for continuing financial support.

Registry No. CF, 3889-75-6; CCl, 3889-76-7; CBr, 3889-77-8; C_2H_4, 74-85-1; C_3H_6, 115-07-1; 1-C_4H_8, 106-98-9; *trans*-2-butene, 624-64-6; 2-methyl-2-propene, 115-11-7; 2-methyl-2-butene, 513-35-9; 2,3-dimethyl-2-butene, 563-79-1; cyclohexene, 110-83-8; 1,3-cyclohexadiene, 592-57-4; 1,4-cyclohexadiene, 628-41-1.

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Direct Total Synthesis of Traditional Sterols by Tricyclization of Polyunsaturated Cyclohexene Oxides

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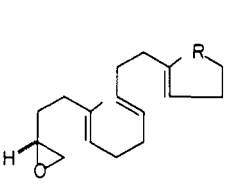
This laboratory recently recorded[1] the detection of (±)-allopregnanolone (4,5α-dihydro-**2a**) as a product resulting from the



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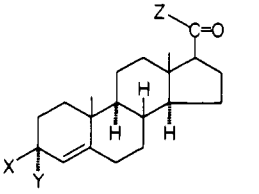

2

a X = OH; Y = H; Z = CH_3
b X, Y = O; Z = CH_3
c X, Y = O; Z = OH

nonenzymic cyclization of an acarbocyclic monosubstituted 1,2-oxide (**1**), a reaction of distinct theoretical interest. Now, by appropriate structural modification of the starting material, we have developed an approach of more practical import, in which polycyclization of the 1,2-oxide type **3**[2] yields, directly and efficiently, substances such as (±)-3β,5β-dihydroxypregnan-20-one

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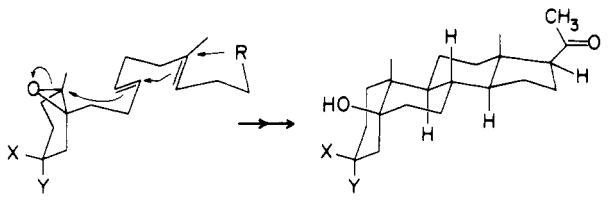
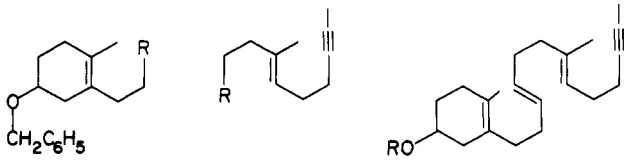


3 **4**

a X = OH; Y = H; R = C≡C-CH_3 **a** X = OAc; Y = H
b X, Y = O; R = C≡C-CH_3 **b** X, Y = $(OCH_2)_2$
c X, Y = $(OCH_2)_2$; R = C≡C-CH_3 **c** X = OH, Y = H
d X = OAc; Y = H; **d** X, Y = O
R = CH(COOMe)$COCH_3$

3-acetate (**4a**) or the 3-ethylene ketal of (±)-5β-hydroxy-pregnane-3,20-dione (**4b**), proceeding by way of the overall process **3** → **4**. The above transformations constitute the first examples of traditional sterol formation by nonenzymic polycyclization of epoxides and the first cases of *direct* genesis of typical bona fide nonaromatic sterols by any polycyclization route.[3] Moreover, the best yield of isolated, pure, single nonaromatic sterol in this new version is the highest so far reported for any overall nonenzymic polycyclization process, including ensuing molecular adjustments. In addition to providing in one step a specifically substituted, naturally occurring tetracyclic system with as many as eight asymmetric centers, this synthetic exercise includes a different approach to the construction of polyenes suitable for cyclization, use of a terminator new to the sterol area, and several novel reduction procedures of possible general interest.

Access to the trienyne oxide **3a** was provided through bilinear paths converging on a Schlosser–Wittig reaction between ylide **5d** and trans-aldehyde **6a** (prepared according to routes I and II,



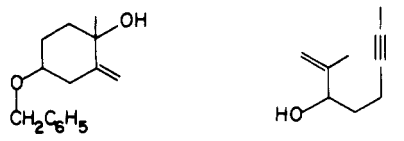
5 **6** **7**

a R = CHO **a** R = CHO **a** R = $CH_2C_6H_5$
b R = CH_2OH **b** R = CH=$P(C_6H_5)_3$ **b** R = H
c R = $CH_2P(C_6H_5)_3^+$
d R = CH=$P(C_6H_5)_3$

I: **8**[4] $\xrightarrow{a}$ **5a** $\xrightarrow{b}$ **5b** $\xrightarrow{c}$ **5c** $\xrightarrow{d}$ **5d**

II: **9**[5] $\xrightarrow{a'}$ **6a**

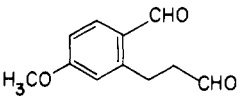
with (a) refluxing *n*-$C_4H_9OCH{=}CH_2$, $Hg(OAc)_2$ cat (62%); (a')



8 **9**

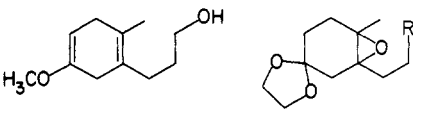
45%; (b) $LiAlH_4$; Et_2O; 0 °C (92%); (c) TsCl, pyridine, 0 °C; LiBr, refluxing acetone; $(C_6H_5)_3P$, refluxing C_6H_6 (92% overall); (d) C_6H_5Li, ether/THF, room temperature) in ether/THF at −78 to −30 °C, generating *trans,trans*-trienyne **7a** (52%). Although Na or Li in liquid NH_3 failed to produce **7b**, the desired selectivity was realized through Ca/NH_3 reduction. Regio- and stereoselective epoxidation of **7b** was managed through the $Mo(CO)_6$-catalyzed action of *t*-C_4H_9OOH (refluxing benzene),[6] giving **3a**.

Although it was possible to bring to hand ketal **3c** by reaction of epoxy ketone **3b** with ethylene glycol, the procedure was capricious and of no practical value. Instead, a previously described[2] route to aldehyde **12b** was improved through (1) direct "one pot" reduction of (unstable) dialdehyde **10** to **11** (20 equiv of Li in



10

refluxing NH_3, 54%) and (2) Moffatt oxidation (CH_3SOCH_3, $(COCl)_2$; Et_3N; 27%) of **12a** to **12b**. Interaction of **12b** with **6b**



11 **12**

a R = CH_2OH
b R = CHO

(secured from **6a** by the same procedure used for the **5a** → **5d** conversion), as described for that of **5d** and **6a**, yielded (50%) the trans,trans-epoxy ketal **3c**.

In the cyclization studies,[7] a large number of variables, including acid catalyst (e.g., $SnCl_4$, $BF_3{\cdot}Et_2O$, H_3PO_4, CH_3CO_2H, CF_3CO_2H), solvent (C_6H_6, $C_6H_5CH_3$, CH_2Cl_2, $CHCl_3$, *n*-pentane), and temperature were assayed. The best results were realized by using, with oxide **3c**, $SnCl_4$, $C_6H_5CH_3$, and ethylene carbonate at 0 °C → room temperature for 24 h then aqueous K_2CO_3, which conditions led to a 44% overall yield of pure isolated (HPLC) (±)-progesterone **2b**[8] (52% of both 17-α and -β isomers) (mp 182.5–184 °C) after hydrolysis and dehydration (TsOH, CH_3COCH_3/H_2O) of the crude, intermediary diketone monoketal **4b**. An overall yield of 19% of **2b** resulted when the 3-acetate of epoxide **3a** was cyclized under similar, but still optimal, conditions to **4a**[8] (mp 156–158 °C) followed by generation (NH_3, MeOH) of keto diol **4c**, oxidation (CrO_3/C_6H_5N, CH_2Cl_2) to the unstable diketone **4d**, and dehydration ($POCl_3$, refluxing C_6H_5N). In preliminary experiments, the enol acetate of β-keto ester **3d**[9] was converted[10] under similar conditions to cyclization product, which after treatment with KOH in MeOH followed by A-ring oxidation and dehydration, as already described, gave rise to (±)-4-androsten-3-one 17β-carboxylic acid (**2c**)[8] in a yield similar to that of **2b** from **3a** acetate at a comparable stage of development, indicating that the β-keto ester unit is also useful as a terminator in polyolefin cyclization routes to sterols.

Acknowledgment. We are grateful to NIH for grant (GM10421) support and to NSF for provision of an XL-100-FT NMR spectrometer (GP28142).

Supplementary Material Available: NMR as well as certain IR and mass spectra corroborated structures assigned to all intermediates (2 pages). Ordering information is given on any current masthead page.

(3) However, for the biogenetic-type synthesis of the triterpenoid lanosterol system from polyunsaturated 1,2-oxides, see: (a) van Tamelen, E. E.; Murphy, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 7204. (b) van Tamelen, E. E.; Anderson, R. J. *Ibid.* **1972**, *94*, 8225.

(4) Obtained by a modification of the method of the following: van Tamelen, E. E.; Loughhead, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 869.

(5) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274.

(6) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(7) For cases of ring formation through participation of acetylene bonds in solvolytic processes, see: (a) Peterson, P. E.; Kamat, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 4521. (b) E.g.: Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *Ibid.* **1971**, *93*, 4332.

(8) Identified by chromatographic as well as IR, NMR, and mass spectral comparison with an authentic specimen.

(9) Synthesized by Dr. E. Leopold, whose contributions will be reported elsewhere.

(10) For the first reported generation of cyclohexane rings by acid-catalyzed cyclization of unsaturated β-keto esters, see: Skeean, R. W.; Trammel, G. L.; White, J. D. *Tetrahedron Lett.* **1976**, 525.