# Stereo- and Regiocontrol of Electrophilic Additions to Cyclohexene Systems by Neighboring Groups. Competition of Electronic and Stereoelectronic Effects and Comparison of the Reactivity of Selected Electrophiles

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*Received November 15, 1989 (Revised Manuscript Received June 5, 1990)*

Neighboring group participation in the addition of $Br^+$, $I^+$, PhSeX, $Hg^{2+}$, $Tl^{3+}$, and $Pd^{2+}$ to a series of steroidal olefins **5–13** has been studied. The relative importance of the electronic (Markovnikov) and stereoelectronic effects has been assessed. In cases where these effects are in opposition, the neighboring group participation may suppress the stereoelectronic control and alter the regioselectivity of the addition in favor of a diequatorial product (**12** → **39–42**). Iodination reagents generated in different ways ($I_2$ + $Ag^+$, $Tl^+$, $Ce^{4+}$, $Cu^{2+}$, $Bi^{3+}$, or KI) can often cleanly differentiate between the di- and trisubstituted double bond. Silver(I)-mediated iodocyclizations are followed by subsequent solvolysis with an overall retention of configuration, employing a push–pull mechanism (**5** → **15** → **20**). Departing iodine atom in this stereospecific Koenigs–Knorr-type reaction must be exocyclic to the newly formed heterocycle and antiperiplanar to the participating C–O bond. Similarly, **5** can be converted to **20** on reaction with Tl(III) employing analogous 5(O)$^n$-*exo-trig* cyclization. In contrast, the organothallium intermediate **34**, arising from **9** by a 5(O)$^n$-*endo-trig* process, gives 19-norsteroid **37** as the product of a novel, stereoelectronically controlled fragmentation. An improved procedure for cyclooxypalladation–carbonylation has been developed (**5** → **19** → **24**).

Conversion of $sp^2$ to $sp^3$ carbon atoms employing electrophilic additions is a general and widely used method for building up vicinal chiral centers. Stereo- and regioselective introduction of hetero-substituents in this way serves as an essential strategic process for the construction of complex polyfunctional molecules.[1] Development of further tools for controlling the stereo- and regioselectivity of electrophilic additions is thus of eminent importance for organic synthesis.

Acyclic, nonsymmetrically substituted olefins generally obey the Markovnikov rule[2] and react with hypobromous acid and related electrophiles to give products with the nucleophile linked to the most electrophilic center, usually the more substituted carbon.[3] Additions that proceed via cyclic "onium" ions undergo stringent stereoelectronic control that becomes particularly apparent in cyclohexene systems[4] which produce preferentially 1,2-trans-diaxial adducts (Fürst–Plattner rule).[5]

Depending on the olefin structure, the electronic (Markovnikov) and stereoelectronic effects can either be consonant or dissonant.[6] Cholesteryl acetate (**1**) is a typical example of the latter case: Although the Markovnikov rule requires that e.g. hypobromous acid be added to form a bromohydrin by cleavage of the corresponding bromonium ion at the more substituted carbon (C-5), the reaction is entirely dominated by stereoelectronic effects that favor axial cleavage at the less substituted carbon (C-6), producing the diaxial bromohydrin **2** (Scheme I).[4a]

We have shown earlier[6,7] that judicious anchoring of a functional group near to the reaction center can dramatically affect the course of the HOBr addition. Thus, for instance, addition of HOBr to the hydroxy olefin **3** affords solely the diequatorial product **4** as the result of an exclusive Markovnikov-type cleavage of the corresponding 5α,6α-bromonium ion.[8]

In the last few years we have published numerous examples of similar effects of various neighboring groups in the addition of HOBr.[6–9] Here we report on the results obtained with other electrophiles and show that our earlier conclusions derived from the reactivity toward HOBr are

**Scheme I**

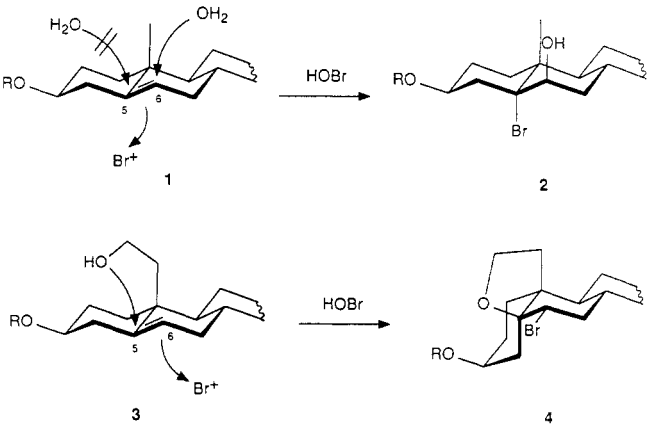
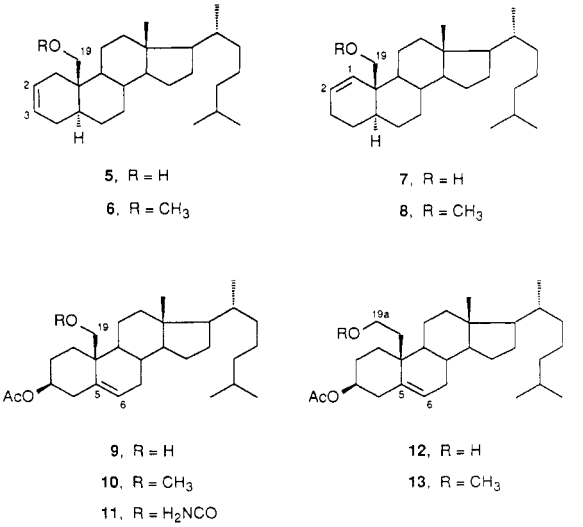



**Chart I**

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0022-3263/90/1955-5580$02.50/0 

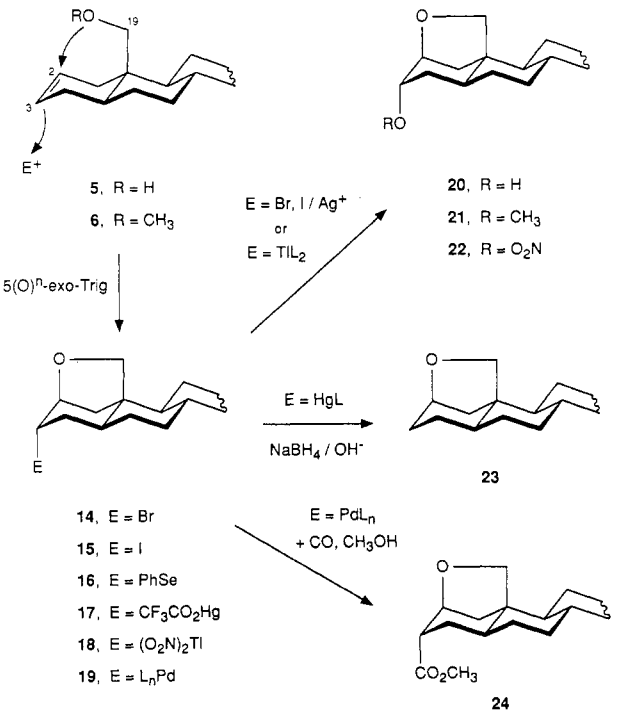
**Table I. Isolated Percentage Yields in Electrophilic Additions to 19- and 19a-Substituted Olefins (5–13)**

| entry | compd | reagents[a] | product (E) | % yield[b] | entry | compd | reagents[a] | product (E) | % yield[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5 | NBA | 14 (Br) | ≥95[c] | 25 | 7 | $Hg^{2+}$ | **27** → **23**[g] | 40 |
| 2 | 5 | $I_2/Tl^+$ | 15 (I) | ≥97 | 26 | 7 | $Pd^{2+}$/CO, $CH_3OH$, $Cu^{2+}$, $Cu^+$, LiCl | **29** + **24** ($CO_2CH_3$)[h] | 62 |
| 3 | 5 | $I_2/Ag^+$,$H_2O$ | 20 (OH) | 74 | | | | | |
| 4 | 5 | $I_2/Ag^+$, $CH_3OH$ | 21 ($CH_3O$) | 69 | 27 | 8 | NBA | 25 (Br) | 91 |
| 5 | 5 | $I_2/Ce^{4+}$ | 15 (I)[d] | 82 | 28 | 8 | $I_2/Tl^+$ | 26 (I) | 71 |
| 6 | 5 | $I_2/HIO_4$ | 20 (OH) | 39[e] | 29 | 8 | $I_2/Ag^+$, $H_2O$ | 26 (I) | 86 |
| 7 | 5 | $I_2$/KI | 15 (I) | 72 | 30 | 9 | NBA | 30 (Br) | ≥97[c] |
| 8 | 5 | $I_2/Cu^{2+}$ | 15 (I) | ≥96 | 31 | 9 | $I_2/Tl^+$ | 31 (I) | ≥96 |
| 9 | 5 | $I_2/Bi^{3+}$ | 15 (I) | ≥94 | 32 | 9 | $I_2/Ag^+$, $H_2O$ | 31 (I) | ≥99 |
| 10 | 5 | PhSeCl/$Tl^+$ | 16 (PhSe) | ≥98[f] | 33 | 9 | $I_2/Ce^{4+}$ | 31 (I) | ≥92 |
| 11 | 5 | $Hg^{2+}$ | **17** → **23**[g] | 81 | 34 | 9 | $I_2/HIO_4$ | 31 (I) | ≥93 |
| 12 | 5 | $Tl^{3+}$ | **20** + **22** (OR)[h] | 88 | 35 | 9 | $I_2/KIO_3$ | 31 (I) | 54[e] |
| 13 | 5 | $Pd^{2+}$/CO, $CH_3OH$, $Cu^{2+}$ | 24 ($CO_2CH_3$) | 29 | 36 | 9 | $I_2/Cu^{2+}$ | 31 (I) | 32[e] |
| | | | | | 37 | 9 | $I_2/Bi^{3+}$ | 31 (I) | 45[e] |
| 14 | 5 | $Pd^{2+}$/CO, $CH_3OH$, $Cu^{2+}$, LiCl | 24 ($CO_2CH_3$) | 63 | 38 | 9 | PhSeCl/$Tl^+$ | 32 (PhSe) | ≥96 |
| | | | | | 39 | 9 | $Hg^{2+}$ | **33** → **35** + **36**[g] | 45[l,m] |
| 15 | 5 | $Pd^{2+}$/CO, $CH_3OH$, $Cu^{2+}$, $Cu^+$, LiCl | 24 ($CO_2CH_3$) | 92 | 40 | 9 | $Tl^{3+}$ | 37 | 81 |
| | | | | | 41 | 10 | NBA | 30 (Br) | 57[i] |
| 16 | 6 | NBA | 14 (Br) | ≥96[i] | 42 | 10 | $I_2/Ag^+$, $H_2O$ | 31 (I) | 60 |
| 17 | 6 | $I_2/Tl^+$ | 15 (I) | 94 | 43 | 12 | NBA | 39 (Br) | ≥90[n] |
| 18 | 6 | $I_2/Ag^+$, $H_2O$ | 20 (OH) | 59 | 44 | 12 | $I_2/Ag^+$, $H_2O$ | 40 (I) | ≥93 |
| 19 | 6 | PhSeCl/$Tl^+$ | 16 (PhSe) | 89 | 45 | 12 | PhSeCl/$Tl^+$ | 41 (PhSe) | ≥97 |
| 20 | 7 | NBA | 25 (Br) | ≥91[j] | 46 | 12 | $Hg^{2+}$ | **42** → **43**[g] | ≥72 |
| 21 | 7 | $I_2/Tl^+$ | 26 (I) | ≥98 | 47 | 13 | NBA | 39 (Br) | 73[n] |
| 22 | 7 | $I_2/Ag^+$, $H_2O$ | 26 (I) | ≥97 | 48 | 13 | $I_2/Ag^+$, $H_2O$ | 40 (I) | 86 |
| 23 | 7 | $I_2/Cu^{2+}$ | 26 (I) | ≥93 | 49 | 11 | NBA | 44 (Br) | 89[o] |
| 24 | 7 | $I_2/Bi^{3+}$ | 26 (I) | ≥90 | 50 | 11 | $Ag^+/Ag^+$, $H_2O$ | 45 (I) | 84 |

[a] Reactions were carried out at room temperature over 5–15 min unless stated otherwise. [b] Isolated yields; ≥ denotes that no other products were detected. [c] Reference 9a. [d] About 60% conversion to **20** when the reaction was worked up after 24 h. [e] After 24 h. [f] Silver(I)-assisted reaction gave essentially the same result. [g] $NaBH_4/OH^-$ reduction. [h] **20** (47%), **22** (41%). [i] Reference 9b. [j] Reference 9d. [k] **29** (39%), **24** (23%). [l] **35** (27%), **36** (18%). [m] Reference 9g. [n] Reference 8. [o] Reference 6.

of a general character. In order to study the neighboring group effects we have employed a set of cholestene derivatives with the double bond located in 2,3-, 1,2-, or 5,6-position, respectively, and hydroxy, methoxy, or carbamoyloxy groups attached to C-19 or C-19a (**5–13**; Chart I).[10]

**Scheme II**




## Results

On reaction with HOBr (generated in situ from *N*-bromoacetamide and perchloric acid in aqueous dioxane) the 2,3-unsaturated alcohol **5** (Scheme II) readily affords the bromotetrahydrofuran **14** as the result of 5(O)$^n$-*exo-trig*

(1) For reviews, see: (a) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986; Vols. I and II. (b) Bartlett, P. A. In Olefin Cyclization Processes that form Carbon-Heteroatom Bonds. *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic: New York, 1984; Vol. 3, p 411. (c) Bartlett, P. A. *Tetrahedron* **1980**, *46*, 3. (d) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171. (e) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.

(2) Markovnikov, V. *Liebigs Ann. Chem.* **1870**, *153*, 256. For a discussion of modern interpretation, see: Isenberg, N.; Grdinic, M. *J. Chem. Educ.* **1969**, *46*, 601.

(3) De la Mare, P. B. D; Bolton, O. *Electrophilic Additions to Unsaturated Systems*; Elsevier: Amsterdam, 1982.

(4) (a) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, 1968. (b) For a discussion of "onium" vs "open" intermediates, see: Ruasse, M.-F. *Acc. Chem. Res.* **1990**, *23*, 87. Galland, B.; Evleth, E. M.; Ruasse, M.-F. *J. Chem. Soc., Chem. Commun.* **1990**, 898. (c) For recent evidence in favor of the existence of bromonium ions and their role in addition reactions, see: Slebocka-Tilk, H.; Ball, R. G.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 4504. Bellucci, G.; Bianchini, R.; Ambrosetti, R. *J. Am. Chem. Soc.* **1985**, *107*, 2464.

(5) Fürst, A.; Plattner, P. A. Abstract Papers, 12th International Congress on Pure and Applied Chemistry; New York, 1951; p 409. For a discussion, see: Eliel, E. L.; Allinger, N. L.; Angyal; S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience; New York, 1965, p 102.

(6) Kočovský, P.; Stieborová, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1969.

(7) Kočovský, P.; Starý, I.; Zajíček, J.; Tureček, F.; Vašíčková, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2297.

(8) Kočovský, P. *Collect. Czech. Chem. Commun.* **1983**, *48*, 3597 and 3606.

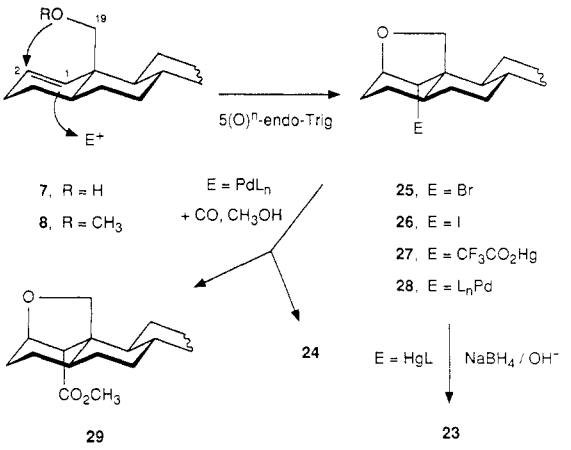
(9) (a) Kočovskyý, P.; Černý, V. *Collect. Czech. Chem. Commun.* **1978**, *43*, 327. (b) Kočovský, P.; Černý, V. *Ibid.* **1978**, *43*, 1924. (c) Kočovský, P.; Tureček, F. *Tetrahedron* **1983**, *39*, 3621. (d) Černý, V.; Kočovský, P. *Collect. Czech. Chem. Commun.* **1982**, *47*, 3062. (e) Kočovský, P.; Černý, V.; Synáčková, M. *Ibid.* **1979**, *44*, 1483. (f) Kočovský, P.; Tureček, F.; Černý, V. *Ibid.* **1982**, *47*, 117. See also: (g) Welzel, P.; Holtmeier, W.: Wessling, B. *Liebigs Ann. Chem.* **1978**, 1327.

(10) For the preparation of the model compounds, see: (a) For **5**, **6**, and **9**, ref 9a. (b) For **6** and **10**, ref 9b. (c) For **12** and **13**, ref 8. (d) For **7** and **8**, ref 9d. (e) For **11**, ref 6 and: Kočovský, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

cyclization (Table I, entry 1).[9a] Rather surprisingly, **5** was found to be inert to iodine in various solvents (dioxane, THF, DME, $CHCl_3$, and $CH_2Cl_2$). It turned out, however, that the iodocyclization can be facilitated by thallium(I).[11] Thus, when iodine was slowly added to a solution of **5** in the presence of a slight excess of thallium(I) trifluoroacetate (or perchlorate),[12] an almost instantaneous reaction could be observed which resulted in the formation of the iodotetrahydrofuran **15** as the single product (entry 2).

When thallium(I) was replaced by silver(I), again an instantaneous reaction occurred. However, in this instance the process did not stop at the stage of the iodotetrahydrofuran **15**. Instead, the intermediate **15** further reacted with $Ag^+$ to afford the hydroxy derivative **20** as the product of a stereospecific Koenigs–Knorr-type solvolysis (entry 3). In methanolic solution, formation of its methoxy congener **21** was observed (entry 4).[13] The mechanism was verified by the solvolysis of iodotetrahydrofuran **15** upon action of $Ag^+$ that furnished the same products **20** or **21**, respectively.[15,16] To obtain a good yield of **20** on the silver(I)-mediated iodination, 2 equiv of $Ag^+$ are required. When only 1 equiv was used, some of the hydroxy olefin **5** remained unreacted, and formation of both the iodotetrahydrofuran **15** and the hydroxy ether **20** could be detected in ca. 5:1 ratio. This indicates that the rate of solvolysis of **15** is comparable with the rate of its formation.[17] Other reagents including cerium(IV),[18] periodic acid, copper(II) chloride, bismuth(III) acetate,[19] and potassium iodide were also found to promote iodocyclization (entries 5–9), but in a less efficient way. The $I_2$/KI mixture gives a substantial amount of byproducts (entry 7). Methyl ether **6**, exhibits the same reactivity pattern as **5** (entries 16–18).

**Scheme III**




Phenylselenenylation of **5** with PhSeCl or PhSeBr afforded the expected cyclic product **16** which was, however, contaminated by a few percents of unidentified byproducts. It turned out that when the phenylselenenylation was carried out in the presence of $Tl^+$, the reaction of **5** was faster and afforded pure product (entry 10).[21] Under the same conditions, the unsaturated methoxy derivative **6** was also cyclized to **16** (entry 19).

Mercuration of **5** produced the intermediary organomercurial **17** (characterized in situ by $^1H$ NMR), which on reduction with alkaline borohydride furnished ether **23** (entry 11), whose structure was corroborated by an independent synthesis through a radical reduction of **14–16** with tri-*n*-butyl hydride.

While olefins are generally inert toward $Tl^+$, they often react with $Tl^{3+}$ yielding various products.[1b,1c,22] It was, therefore, desirable to include thallium(III) into our set

(11) For the method, see: (a) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Chem. Commun.* **1973**, 359; *J. Chem. Soc., Perkin Trans. 1* **1974**, 1858. (b) Cambie, R. C.; Gash, D. M.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1157 and references cited therein. See also: (c) Cambie, R. C.; Hayward, R. C.; Jurlina, J. L.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2608. (d) Grieco, P. A.; Ivanga, J.; Sham, H. L.; Sasaki, S.; Kim, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1044.

(12) Used either as commercially available substances or generated in situ from AcOTl or AcOAg and stoichiometric amounts of $CF_3CO_2H$ or $HClO_4$. No substantial difference in reactivity was observed.

(13) For the structure elucidation of **20** and **21**, see ref 14.

(14) Kočovský, P. *J. Org. Chem.* **1988**, *53*, 5816.

(15) As we have reported recently for bromotetrahydrofurans,[14] the solvolytic reaction employs a push–pull mechanism, crucially dependent on the participation of the neighboring oxygen.

(16) For further examples of the silver-mediated solvolysis of halogen atoms assisted by neighboring groups, see: (a) Dailey, C. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (b) Gonzales, A. G.; Bermejo, J.; Massanet, G. M.; Amaro, J. M. *Ann. Quim.* **1978**, *74*, 1443. (c) Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533. (d) Liu, H. J.; Browne, E. N. C.; Pednekar, P. R. *Can. J. Chem.* **1982**, *60*, 921. (e) De Bernado, S.; Tengi, J. P.; Sasso, G. J.; Wegele, M. *J. Org. Chem.* **1985**, *50*, 3457. (f) Knapp, S.; Levorse, A. T. *Tetrahedron Lett.* **1987**, *28*, 3213; *J. Org. Chem.* **1988**, *53*, 4006. (g) Broka, C. A.: Gertlis, J. F. *J. Org. Chem.* **1988**, *53*, 2144. (h) See also: Paquette, L. A.; Weber, J. C.; Kobayashi, T.; Miyahara, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8591. (i) Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986**, *27*, 291. (j) Kato, M.; Kageyama, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1305. (k) Zárraga, M.; Alvarez, E.; Ravelo, J. L.; Rodriguez, V.; Rodriguez, M. L.; Martin, J. D. *Tetrahedron Lett.* **1990**, *31*, 1633.

(17) *m*-Chloroperoxybenzoic acid (MCPBA) is also capable of oxidative extrusion of iodine followed by nucleophilic quenching.[20] Our iodotetrahydrofuran **15** was converted to hydroxy derivative **20** with retention of configuration by means of MCPBA in wet $CH_2Cl_2$ at room temperature overnight, while the bromo analogue **14** was inert. By contrast, both the iodotetrahydrofurans **26** and **31** gave mixtures of several products which were not further analyzed. For further examples of extrusion of halogen in higher oxidation state, see refs 20f–k and 40h. Finally, $(CF_3CO_2)_2Hg$ was found to convert **14** and **15** to **20** in a fast reaction, similarly to $CF_3CO_2Ag$.

(18) Cerium(IV) has recently been used to promote iodination of aromatic and heteroaromatic compounds: (a) Sugiyama, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2847. (b) Asakura, J.; Robins, M. J. *Tetrahedron Lett.* **1988**, *29*, 2855.

(19) Bismuth(III) acetate is another reagent that can promote the neighboring group assisted substitution in the "dry" or "wet" Prévost reaction: Campi, E. M.; Deacon, G. B.; Edwards, G. L.; Fitzroy, M. D.; Giunta, N.; Jackson, W. R.; Trainor, R. *J. Chem. Soc., Chem. Commun.* **1989**, 407. For a similar application of copper(II) acetate, see: Mangoni, L.; Adinolfi, M.; Barone, G.; Parrili, M. *Tetrahedron Lett.* **1973**, 4485.

(20) (a) Beeley, N. R. A.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1977**, 321. (b) Cambie, R. C.; Lindsay, R. C.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Chem. Commun.* **1978**, 919. (c) Cambie, R. C.; Chambers, D.; Lindsay, R. C.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 822. (d) Macdonald, T. L.; Narasimhan, N.; Burka, L. T. *J. Am. Chem. Soc.* **1980**, *102*, 7760. (e) Eaton, P. E.; Cunkle, G. T. *Tetrahedron Lett.* **1986**, *27*, 6055. (f) Hendrickson, J. B.; Singh, V. *Tetrahedron Lett.* **1983**, *24*, 431. (g) Shah, M.; Taschner, M. J.; Koser, G. F.; Rach, N. L. *Tetrahedron Lett.* **1986**, *27*, 5437. (h) Zefirov, N. S.; Zhdankin, U. V.; Makhon'kova, G. V.; Dan'kov, Yu. V.; Koz'min, A. S. *J. Org. Chem.* **1985**, *50*, 1827 and references cited therein. (j) Sicinski, R. R.; Szczepek, W. J. *Tetrahedron Lett.* **1987**, *28*, 5729. (k) Černý, V. *Collect. Czech. Chem. Commun.* **1989**, *54*, 2211.

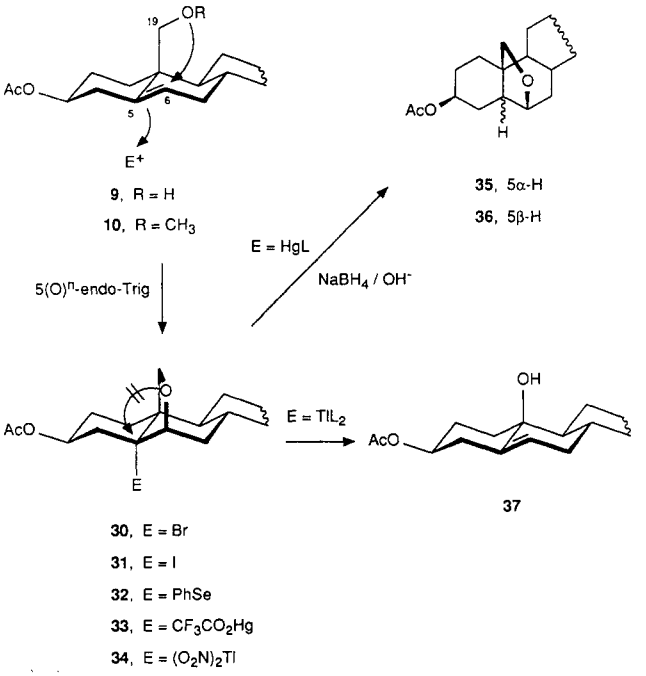
(21) Phenylselenenylylation using PhSeCl/$Ag^+$ is another established method: (a) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1974**, 100. (b) Reich, H. J. *J. Org. Chem.* **1974**, *39*, 428. (c) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429. (d) Clive, D. L. J.; Russel, C. G.; Chittattu, G.; Singh, A. *Tetrahedron* **1980**, *36*, 1399. (e) Murata, S.; Suzuki, T. *Chem. Lett.* **1987**, 849. (f) Murata, S.; Suzuki, T. *Tetrahedron Lett.* **1987**, *28*, 4415. For related examples, see: (g) Schmid, G. H., Garatt, D. G. *Tetrahedron Lett.* **1975**, 3991. (h) Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1173. (i) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75. (j) Francisco, C. G.; León, E. I.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1986**, *27*, 2513. (k) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Balducci, R. *J. Org. Chem.* **1990**, *55*, 429.

(22) (a) Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416 and references cited therein. (b) Michael, J. P.; Nkwelo, M. M. *Tetrahedron* **1990**, *46*, 2549. (c) Schwartz, A.; Glotter, E. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2470. (d) Faraz, H. M. C.; Brockson, T. J.; Pinto, A. C.; Abla, M. A.; Zocher, D. H. T. *Tetrahedron Lett.* **1986**, *27*, 811. (e) For review, see: McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. VII, Chapter 47.

of reagents. With **5**, a smooth cyclization was observed on treatment with thallium(III) nitrate, which gave rise to a mixture of the hydroxy ether **20** and its nitrate **22** (entry 12), presumably via a thallium intermediate **18**. Under the same conditions, the methyl ether **6** did not react and was quantitatively recovered.

Another reaction of our interest was oxypalladation followed by CO insertion[23] for this transformation obviously has the promise of a valuable expansion of the methodology of organic synthesis. As the reported yields are often low[23] and since relatively little is known of the intramolecular version that would involve trapping the transiently formed $\eta^2$-palladium complex by a hydroxy group,[24-26] we set out to explore its scope with our model compounds. We were particularly curious whether the $\eta^2$-complexes would behave similarly to their classical electrophilic counterparts such as bromonium or iodonium ions.[27] A catalytic amount (10 mol %) of $PdCl_2$ was added to the methanolic solution of **5** containing 3 equiv of $CuCl_2$ (to reoxidize Pd), and the mixture was stirred under an atmosphere of CO at room temperature (22 °C) for 48 h. About 30% conversion to the expected product **24** was then observed (entry 13). However, when the reaction was repeated in the presence of an excess of LiCl (4 equiv), the isolated yield of **24** climbed up to 63% (entry 14).[28,29a] Finally, when copper(I) chloride (3 equiv) was added to the latter mixture and the reaction was run in the same manner, almost a quantitative yield of **24** was achieved in 24 h (entry 15). This result suggests that both the $Cu^{2+}$ and $Cu^+$ are required in sufficient concentrations to keep up the cascade of the catalytic cycle[29b] involving **19** as an intermediate.

**Scheme IV**




Transmetalation of the mercury derivative **17** with $PdCl_2$ in methanol under the CO atmosphere was also attempted, but not more than 10% of the product (**24**) could be detected in the reaction mixture after 72 h. Obviously, direct cyclooxypalladation of **5** is superior to this method.[30] Methoxy derivative **6** was inert toward both the mercuration and cyclooxypalladation.

Both the 1,2-unsaturated alcohol **7** and its methyl ether **8** (Scheme III) are known to cyclize upon action of HOBr to the bromotetrahydrofuran **25** as the result of 5(O)$^n$-*endo-trig* participation (entries 20 and 27).[9d] As expected, iodination of **7** and **8** in the presence of $Tl^+$ gave analogous iodo derivative **26** (entries 21 and 28). In contrast to **5**, iodination mediated by $Ag^+$ (entries 22 and 29) stopped at the stage of iodotetrahydrofuran **26**, apparently because the solvolysis assisted by the ring oxygen would create a highly strained intermediate.[31] The same iodotetrahydrofuran **26** was also obtained in high yield on the copper(II) and bismuth(III)-mediated iodination (entries 23 and 24).

Mercuration of **7** was also found to follow the 5(O)$^n$-*endo-trig* pathway giving rise to the intermediate mercurial **27**. Although TLC analysis of the reaction mixture indicated a quantitative conversion of **7** to **27**, subsequent reduction (alkaline $NaBH_4$) afforded a substantial amount of the starting olefinic alcohol **7** (47%) together with the expected product **23** (40%, entry 25), identical with an authentic sample.

While no reaction of **7** with $Tl(NO_3)_3$ occurred at room temperature, formation of a complex mixture of polar products was observed at 50 °C in which only traces of the corresponding hydroxytetrahydrofuran could be detected.

(23) (a) James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810. (b) Hegedus, L. S.; Siralla-Hansen, K. *J. Am. Chem. Soc.* **1974**, *97*, 1184. (c) For review, see: Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.

(24) For the stereochemistry of the reaction of $\eta^2$-palladium complexes with heteroatom nucleophiles, see: (a) Åkermark, B.; Bäckvall, J.-E., Siiralla-Hansen, K.; Sjöberg, K.; Zetterberg, K. *Tetrahedron Lett.* **1974**, 1363. (b) Bäckvall, J.-E. *Tetrahedron Lett.* **1977**, 467. (c) Tsuji, J.; Yamakawa, T.; Mandi, T. *Tetrahedron Lett.* **1978**, 565. (d) Kurosawa, H.; Asaka, N. *Tetrahedron Lett.* **1979**, 255. (e) Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. (f) Stille, J. K.; Divakaruni, R. *J. Organomet. Chem.* **1979**, *169*, 239. (g) Change, T. C. T.; Foxman, B. M.; Rosenblum, M.; Stockman, C. *J. Am. Chem. Soc.* **1981**, *103*, 7361. (h) Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* **1984**, *106*, 5560. (i) Bäckvall, J.-E.; Heumann, A. *J. Am. Chem. Soc.* **1986**, *108*, 7107. (j) Arnek, R.; Zetterberg, K. *Organometallics* **1987**, *6*, 1230. For the quantum chemistry calculations, see: (k) Eisenstein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308. (l) Bäckvall, J.-E.; Björkman, E. J.; Petersson, L.; Siegbahn, P. *J. Am. Chem. Soc.* **1984**, *106*, 4369; **1985**, *107*, 7265. (m) Fujimoto, H.; Yamasaki, T. *J. Am. Chem. Soc.* **1986**, *108*, 578.

(25) For the intramolecular version, see: (a) Hayashi, T.; Hegedus, L. S. *J. Am. Chem. Soc.* **1977**, *99*, 7093. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. (c) Hegedus, L. S.; McKearing, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444 and references cited therein. (d) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. However, CO insertion was successful only in certain, most recently reported cases (ref 26).

(26) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583. (b) Semmelhack, M. F.; Zask, A. *Ibid.* **1983**, *105*, 2034. (c) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *Ibid.* **1982**, *104*, 5850. (d) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *Ibid.* **1988**, *110*, 3994 and references therein. (e) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731 and references therein. (f) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. For correction, see: *Ibid.* **1984**, *106*, 5388. (g) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*, 5803. (h) Hegedus, L. S.; Mullhern, T. A.; Asada, H. *J. Am. Chem. Soc.* **1986**, *108*, 6224. (i) For review, see: Hosokawa, T.; Murahashi, S. *Acc. Chem. Res.* **1990**, *23*, 49.

(27) For comparison of Pd(II)-catalyzed cyclization of an olefinic alcohol with cyclization promoted by iodine, see ref 26f.

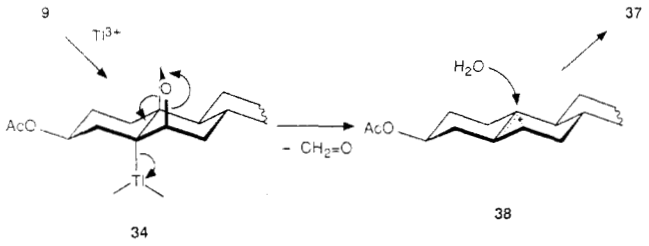
(28) Unreacted starting material (23%) was recovered.

(29) (a) The beneficial effect of LiCl on a palladium-catalyzed reaction is demonstrated here again. For other examples of the influence of LiCl, see, e.g.: Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335. (b) For application of CuCl as an oxidant in the regiocontrolled Wacker-type oxidation, see: Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474.

(30) Low yields have been obtained with other olefins: Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 335. By contrast, allenes seem to give much higher yields as the metal in the intermediate is linked to a vinylic carbon: Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1988**, *29*, 5505; **1987**, *28*, 1023. See also: Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett.* **1986**, *27*, 6009 and Walkup, R. D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112*, 1597.

(31) The iodotetrahydrofuran **26** turned out to be completely stable to the treatment with $CF_3CO_2Ag$ at room temperature over one week.

**Scheme V**



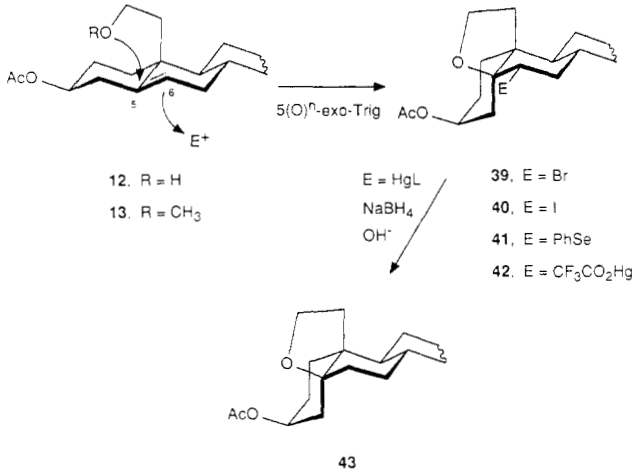
Palladation of **7** in methanol under an atmosphere of CO was carried out in the presence of CuCl, $CuCl_2$, and LiCl and afforded a mixture of the expected carboxymethyl tetrahydrofuran **29** and its isomer **24** (entry 26). The former compound is produced via the expected 5-(O)$^n$-*endo-trig* cyclization, whereas formation of the latter is indicative of a partial isomerization of **7** to **5**, presumably at the stage of $\eta^2$-complexes.

The 5,6-unsaturated alcohol **9** exhibits reactivity similar to that of **5** and **7** (Scheme IV). Addition of HOBr results in the formation of bromotetrahydrofuran **30** via the stereoelectronically controlled, anti-Markovnikov 5(O)$^n$-*endo-trig* cyclization (entry 30).[9a] The methyl ether **10** is less prone to the cyclization, producing only 57% of **30** on HOBr addition (entry 41).[9b] Iodination of **9** carried out in the presence of $Tl^+$, $Ag^+$, or other reagents, always stopped at the stage of iodotetrahydrofuran **31** (entries 31–35) since its subsequent solvolysis is impaired for the same reason as in **26**. Copper(II)- and bismuth(III)-assisted iodinations are much slower, giving 32% and 45% conversion to **31**, respectively, after 24 h at room temperature (entries 36 and 37). No reaction occurs with $I_2/KI$. In contrast to the smooth iodocyclization of **9** under a variety of conditions, the methyl ether **10** was inert toward $I_2/Cu^{2+}$ and $I_2/Bi^{3+}$, while a very slow reaction was observed with $I_2/Tl^+$ (ca. 10% conversion over 24 h). Silver(I)-mediated iodination of **10** (entry 42) was completed in 20 min which also contrasts with an instantaneous reaction of **9**.

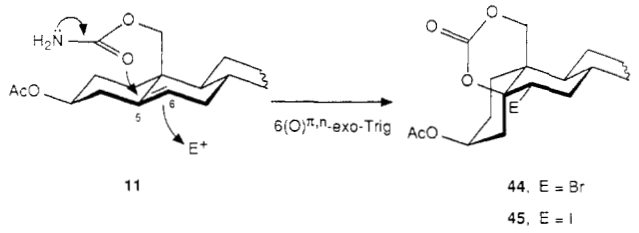
Thallium(I)-mediated phenylselenenylation of **9** afforded the cyclic ether **32** (entry 38), whereas the reaction run in the absence of $Tl^+$ gave the same compound contaminated by a small amount of byproducts. Mercuration of **9** by means of $(CF_3CO_2)_2Hg$ was described by Welzel et al.[9g] and was the first example of an anti-Markovnikov mercuration (entry 39).[9g] Methyl ether **10** was inert toward both phenylselenenylation and mercuration.

In contrast to **7**, the 5,6-unsaturated alcohol **9** reacted with $Tl(NO_3)_3$ instantaneously, producing essentially a single compound in an 81% isolated yield, identified as the 10$\beta$-hydroxy-10-norsteroid **37** by spectroscopic methods (entry 40).[32] This unique degradation can be rationalized as follows (Scheme V): the 5,6-double bond in **9** first undergoes an electrophilic attack by $Tl^{3+}$, followed by a stereoelectronically controlled anti-Markovnikov 5-(O)$^n$-*endo-trig* ring closure furnishing a diaxial organothallium intermediate **34**. Then, instead of the bridge-oxygen assisted solvolysis of the C–Tl bond, another competing pathway operates in which a molecule of formaldehyde is lost, leaving allylic cation **38**. The latter is then trapped by the solvent to afford the trans-annulated product **37**. This fragmentation is obviously boosted by a stereoelectronic effect, since all the bonds involved ($C_5$–Tl, $C_6$–O, and $C_{10}$–$C_{19}$) are perfectly aligned. Methyl

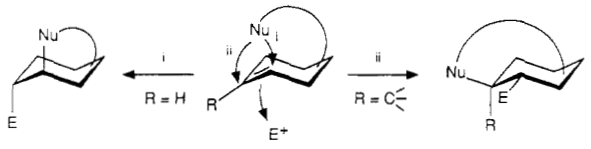
**Scheme VI**



**Scheme VII**



**Scheme VIII**



ether **10** and the corresponding acetate and aldehyde were inert under the same conditions.

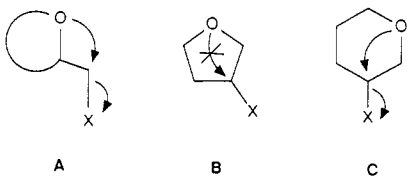
Unlike the hydroxy olefins **5** and **7**, both having a disubstituted double bond, the 5,6-unsaturated alcohol **9** (with a trisubstituted double bond) is inert toward palladation. Attempted transmetallation of the in situ generated organomercurial **33** with $PdCl_2$ in methanol under the CO atmosphere led to the starting olefinic alcohol **9** and partial decomposition.

With homologous alcohol **12** and its methyl ether **13** we have earlier observed reversion of the regioselectivity of HOBr addition in favor of the Markovnikov rule (Scheme VI).[8] These reactions resulted in the formation of a diequatorial product **39** rather than the diaxial one (entries 43 and 47). Now, we have found that iodination, phenylselenenylation, and mercuration follow the same pattern and afford the corresponding diequatorial products **40–42** (entries 44–46), respectively, in excellent yields. No solvolysis of iodo derivative **40** was observed in the presence of Ag(I).[33] The intermediate product of mercuration (**42**) was reduced with alkaline $NaBH_4$ to give **43**, identical with an authentic sample prepared by $Bu_3SnH$ reduction of **39**. In all these cases, competing axial cleavage of the corresponding reactive intermediates at C-6 was not observed. Hence, all the additions are entirely dominated by the electronic (Markovnikov) effects preferring thus the 5-(O)$^n$-*exo-trig* pathway.[34] Iodination of methyl ether **13**

(32) The structure of **37** was confirmed by a single-crystal X-ray analysis: Kočovský, P.; Langer, V.; Gogoll, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1026.

(33) The diequatorial disposition of the ether oxygen and iodine atom in **40** pervent the oxygen from participation and, therefore, the solvolysis does not occur.

**Chart II**



A B C

proceeded only in the presence of silver(I) (entry 48), while phenylselenenylation and mercuration did not occur. Palladation of both **12** and **13** as well as an attempted transmetalation of **42** were unsuccessful. Both **12** and **13** were inert to $Tl^{3+}$ at room temperature.

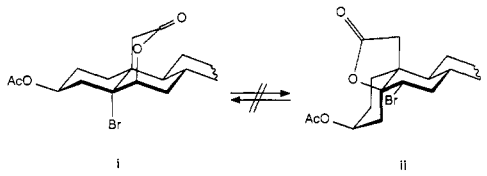
Acyloxy and carbamoyloxy groups in position 19 are also capable of the reversion of regiochemistry of the HOBr addition to the 5,6-double bond (Scheme VII, entry 49),[6,7] and this observation was used for the crucial step in our recent synthesis of strophanthidin.[35] Therefore, it was desirable to explore the reactivity of **11** toward other electrophiles. Attempts at phenylselenenylation, mercuration, and palladation failed,[36] but iodination boosted by $Tl^+$, $Ag^+$, or $Ce^{4+}$ ions gave fairly good yields of the expected diequatorial product **45**, as the result of electronically favored 6(O)$^{\pi,n}$-*exo-trig* cyclization (entry 50).[38] In contrast, no reaction could be observed with $I_2$/KI, $I_2$/$Cu^{2+}$, or $I_2$/$Bi^{3+}$. Carbamate **11** was also found to be inert toward $Tl^{3+}$.

## Discussion

The above results show that all the reagents we have tested share certain characteristic features, although some differences in the propensity to react with certain olefins were encountered. Disubstituted olefinic derivatives **5–8** prefer axial approach of the OH or $OCH_3$ groups to the double bond in agreement with the stereoelectronic requirements (path i in Scheme VIII), regardless whether the new ring is to be formed by an *exo-trig* (**5** and **6**) or *endo-trig* (**7** and **8**) mode. In contrast, trisubstituted olefins such as **11–13** react in a different manner, namely by the cleavage of the reactive intermediate at the most electrophilic site, which results in the formation of a diequatorial product (path ii in Scheme VIII) in an *exo-trig* fashion. However, when the spacer between the double bond and the participating group does not allow the closing up of at least a five-membered ring in this way, the axial cleavage will prevail again, as with **9** and **10**. This behavior is common for all the electrophilic reagents explored. In view of these results, the conclusions we have previously inferred for the hypobromous acid addition[6,7] can be generalized for a wide range of electrophiles as follows: electrophilic additions to cyclohexene systems are normally dominated by stereoelectronic effects favoring the formation of diaxial products. On the other hand, intervention of a judiciously incorporated neighboring group can reverse the regiochemistry.[41] This occurs, however, only when this pathway is boosted by an electronic (Markovnikov) effect, i.e. with cyclohexenes containing a nonsymmetrically substituted double bond that has an inherent tendency toward $S_N1$-like or a borderline mechanism in the nucleophilic step. It appears that while the electrophilic additions to cyclohexenes proceed predominantly via cyclic "onium" intermediates, the neighboring group intervention can result in the dominance of "open" species. This behavior parallels the known stabilization of the "open" intermediates by the aromatic ring in additions to styrenes.[4b]

Noteworthy are the differences in reactivity of the iodination reagents toward olefinic alcohols. It appears that $Ag^+$ and $Tl^+$ salts are the best promoters for iodination.[42]

(34) In view of a relatively easy equilibration of diaxial 5α,6β-dibromocholesteryl acetate to the 5β,6α-dibromide,[4a] one can argue that our diequatorial products arise by thermodynamic equilibration of the primarily formed diaxial isomers. However, we believe that this is not the case, since e.g. no equilibration of bromolactones i and ii was observed[9c] (see also ref 6). Thermodynamic control in phenylselenenylation has been shown to involve the kinetic formation of an adduct of PhSeX followed by slow substitution of the halogen atom by a neighboring group, presumably with PhSe-participation via an "onium" ion.[21d,37a] Finally, equilibration of organomercurials generally requires much longer time (several days) in polar solvents ($CH_3NO_3$).[37h]



i ii

(35) Kočovský, P.; Stieborová, I. *Tetrahedron Lett.* **1989**, *30*, 4295.

(36) (a) Neighboring groups in these compounds are probably not sufficiently reactive for trapping the possibly formed π-complexes with the reagents. Other substrates with carbamate, ureido, or amide groups, but with double bonds less than trisubstituted, frequently react both with PhSeCl and Hg(II).[37] The $^1H$ NMR spectrum of the reaction mixture of **11** with $(CF_3CO_2)_2Hg$ in $CDCl_3$ or $C_6D_6$ does not indicate formation of an organomercury product that would correspond to the cyclization. (b) For a discussion of nucleophilicity of various neighboring groups in electrophilic additions, see e.g. refs 6, 9a, and: Kurth, M. J.; Beard, R. L.; Olmstead, M.; MacMillan, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3712.

(37) (a) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *40*, 2120. (b) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018. (c) Toshimitsu, A.; Terao, K.; Uemura, S. *Tetrahedron Lett.* **1984**, *25*, 5917. (d) Betancor, C.; Leôn, E. I.; Prange, T.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Chem. Commun.* **1989**, 450. (e) Freire, R.; Leôn, E. I.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Chem. Commun.* **1989**, 452. (f) Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 4822. (g) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920. (h) Harding, K. E.; Marman, T. H. *J. Org. Chem.* **1984**, *49*, 2838.

(38) (a) Preferential participation of carbamate and amide groups by carbonyl oxygen, i.e. by an (O)$^{\pi,n}$-pathway, in this type of reactions is typical.[6,39] For nitrogen participation, i.e. for (N)$^n$- or (N)$^{\pi,n}$-cyclization, see refs 16f–h and 40. For ether oxygen (O)$^n$-participation, see refs 6 and 39g. (b) The carbamate derived from **5** (R = $H_2NCO$) afforded two products on reaction with $I_2$/$Tl^+$: cyclic iodotetrahydrofuran **15** (42%) arising by the 5(O)$^n$-*exo-trig* cyclization, and a more polar, unstable component (ca. 35%), which was tentatively assigned the structure of 3α-iodo-5α-cholestane-2β,19-diol 2,19-carbonate in analogy with the second product of HOBr addition.[6] The latter pathway corresponds to 7(O)$^{\pi,n}$-*exo-trig* participation. Phenylselenenylation carried out in the presence of $Tl^+$ gave **16** (33%) and several polar products which were not characterized.

(39) (a) Corey, E. J.; Fleet, W.; Kato, M. *Tetrahedron Lett.* **1973**, 3963. (b) Clive, D. L. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 397. (c) Hirama, M.; Uei, M. *Tetrahedron Lett.* **1982**, *23*, 5307. (d) Kozikowski, A. P.; Scripko, J. *Tetrahedron Lett.* **1983**, *24*, 2051. (e) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Org. Chem.* **1984**, *106*, 1079. (f) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 530. (g) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586. (h) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (i) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron* **1987**, *43*, 4377. (j) Kamiyama, K.; Urano, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1987**, *28*, 3123. (k) Takano, S.; Sato, S.; Goto, E.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1986**, 156. (l) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1527. (m) Fuji, K.; Node, M.; Naniwa, Y.; Kawabatta, T. *Tetrahedron Lett.* **1990**, *31*, 3175.

(40) (a) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330. (b) Aida, T.; Legault, R.; Dugat, D.; Durst, T. *Tetrahedron Lett.* **1979**, 4493. (c) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233. (d) Hirama, M.; Iwashita, M.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett.* **1984**, *25*, 4963. (e) Rajendra, G.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4471; *Tetrahedron Lett.* **1987**, *28*, 6257. (f) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491. (g) Kurth, M. J.; Bloom, S. H. *J. Org. Chem.* **1989**, *54*, 411 and references cited therein. (h) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365.

(41) The stereochemistry of the addition to cyclohexenes can also be altered by neighboring groups; see ref 7.

(42) For a discussion of the differences in mechanism of these reactions, see ref 11.

Iodinations mediated by $Ce^{4+}$ are slower (several minutes for **9**) and the mechanism is not clear. Reagents generated in situ by mixing iodine with $Bi^{3+}$ or $Cu^{2+}$ are even less reactive, particularly toward hydroxy olefins with trisubstituted double bonds (24 h or more). Finally, the $I_2$/KI mixture, often used for iodolactonizations, was found to be inert toward olefinic derivatives having a trisubstituted double bond.

Even more dramatic differences in reactivity were found with methoxy olefins. Again, those having a disubstituted double bond (**6** and **8**) react with NBA, $I_2$ (in the presence of $Ag^+$ or $Tl^+$), and PhSeCl. On the other hand, methoxy olefins containing a trisubstituted double bond (**10** and **13**) are inert to all the reagents except for NBA and $I_2/Ag^+$. These differences could obviously find application in the selective functionalization of complex molecules, as the neighboring group and/or the reagent can be tailored in order to discriminate between the di- and trisubstituted double bond. It is pertinent to note that this discrimination can be achieved regardless of the mode of the neighboring group participation (*exo-trig* or *endo-trig*). Furthermore, these findings demonstrate the critical importance of the nucleophilic step for the electrophilic addition to occur:[43] the methoxy group is apparently less efficient than hydroxyl which results in the lowered capability of assisting the addition. The behavior of the olefinic esters[6,7] and carbamate (**11**) further support this conclusion.

Phenylselenenylation carried out in the presence of thallium(I) salts parallels its known[21] silver(I)-mediated analogy, furnishing pure products. Whereas hydroxy olefins react readily irrespective of the degree of substitution on the double bond, methyl ethers and carbamates with a trisubstituted double bond are inert. This chemoselectivity is also of interest. According to the Clive mechanism[21d,37a] of cyclofunctionalization of unsaturated substrates with PhSeCl, the reagent first adds across the double bond to give a $\beta$-chloro selenide. The latter intermediate then reacts with an internal nucleophile, presumably via an episeleniranium ion. However, cholesterol, an olefin with trisubstituted double bond, fails to react with PhSeCl.[21c,44] In the case of its hydroxy congeners **9** and **12** the reaction is apparently facilitated by fast consumption of the intermediate in the final nucleophilic step, shifting thus the equilibrium to the product (**32** and **41**, respectively). Other internal nucleophiles (as in **10**, **11**, and **13**) are probably less prone to serve in the same way.

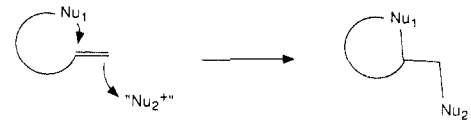
Mercuration proceeds readily with olefinic alcohols containing disubstituted double bonds and is somewhat slowed down for trisubstituted double bonds. The same control of regioselectivity by neighboring groups has been observed as with other electrophiles. Noteworthy is the 5(O)$^n$-*endo-trig* cyclization[45] of **7** and **9**, although the yields here were rather low due to the reversion to the starting compounds in the reduction step. No attempt to improve the yield[37h] has been made.

Structural effects that control the silver(I)-mediated Koenigs–Knorr-type solvolysis were largely discussed in our previous paper for bromides.[14] We were pleased to find the same effects operating with the iodides formed in situ on $I_2/Ag^+$ addition and with the organothallium intermediates. It appears that this stereospecific, anchimerically assisted reaction can occur readily with the intermediates arising from electrophilic *exo-trig* ring closure, regardless of the size of the ring initially formed (A in Chart II). By contrast, the solvolysis is highly disfavored for the heterocycles formed in a 5-*endo-trig* fashion, as the corresponding transition state would be too strained. The primary ring-closure product (B) is either stable enough to be isolated (X = I), or suffers a different consecutive reaction rather than a simple substitution (X = Tl). However, if a 6-membered heterocycle is being formed as the result of a 6-*endo-trig* cyclization (C), the following solvolysis is possible, at least for the thallium species.[22a] Tetrahydropyran thus appears to be the smallest ring allowing the anchimerically assisted endo-type solvolysis. All these facts clearly show that the anchimeric assistance by the ring heteroatom is of crucial importance for the stereospecific solvolysis to occur. In line with this concept is the readily occurring hydroxy cyclization of **5** on reaction with $Tl^{3+}$ to give **20**, the thallium(III)-mediated fragmentation **9** → **37**, and the reluctance of **7** to react with $Tl^{3+}$ under mild conditions.

Finally, the cyclooxypalladation/carbonylation of **7** which gave **29** shows that 5(O)$^n$-*endo-trig* cyclization is also possible for $\eta^2$-palladium complexes, together with the known[25,26] 5(O)$^n$-*exo-trig* (as, e.g., in **5**) and 6(O)$^n$-*exo-trig* processes.[46] However, the concomitant formation of the isomer **24** as a minor product indicates that this reaction course is less favored than its 5(O)$^n$-*exo-trig* counterpart. Compounds with trisubstituted double bonds were inert under the same conditions.[47]

The synthetic value of these transformations is visualized in Scheme IX. The overall process starting from an unsaturated alcohol and involving *exo-trig* cyclization can be formally considered as a one-pot electrophilic addition of a nucleophile ("$Nu_2^+$"), i.e. "$RO^+$" or "$^+CO_2R$". Other examples of similar methodology, known from the literature,[40h] involve "$N_3^+$" (ref 16f) and enol ethers (ref 16g) as "nucleophiles", while the addition is controlled by neighboring hydroxy, amino, and amido groups. $S_N2$ displacements of the auxiliary electrophile by e.g. $Ph_3P$ and stabilized C-nucleophiles have also been reported.[16f,48,49]

**Scheme IX**




(43) For further discussion, see refs 7, 41, and: (a) Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum: New York, 1976; Vol. 1. (b) Williams, D. L. H.; Bienvenue-Goetz, E.; Dubois, J. E. *J. Chem. Soc.* **1969**, 517. (c) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev.* **1971**, *40*, 272. (d) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 682. (e) Kočovský, P.; Starý, I.; Tureček, F.; Hannuš, V. *Collect. Czech. Chem. Commun.* **1983**, *48*, 2994.

(44) Ceccherelli, P.; Curini, M.; Macotullio, M. C.; Rosatti, O. *Tetrahedron Lett.* **1989**, *30*, 3175.

(45) For another example of 5(O)$^n$-*endo-trig* mercuration, see, e.g.: Salomon, R. G.; Roy, S.; Salomon, M. F. *Tetrahedron Lett.* **1988**, *29*, 769.

(46) For examples of 5(N)$^n$-*endo-trig* cyclopalladation, see e.g. ref 25d.

(47) Addition of $Et_3N$[26i] was also to no avail.

(48) The second "nucleophilic" species can also be attached to the original double bond by a radical reaction of an iododerivative[50] or an organomercurial,[51] or via a photoinduced displacement of PhSe group.[54]

(49) For further synthetically useful reactions of this kind, see ref 53.

(50) (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

(51) Danishefsky et al.[52] have demonstrated that the products of amidomercuration (Nu = NHCbz), when reduced with various borohydrides in an excess of acrylonitrile, afforded adducts to the $\beta$-carbon via a radical mechanism. This complements the intramolecular version of Heck reaction employed by Hegedus et al.[53] in the synthesis of indol alkaloids.

(52) Danishefsky, S.; Taniyama, E. *Tetrahedron Lett.* **1983**, *24*, 11 and 15.

(53) (a) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2583. (b) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 1982.

## Conclusions

The regio- and stereochemistry of electrophilic additions to highly discriminating cyclohexene systems can be controlled by neighboring groups. Stringent stereoelectronic effects (resulting normally in the formation of diaxial products) can be suppressed and the regiochemistry of the addition reversed by neighboring groups in those structures, in which the electronic (Markovnikov) effect favors this reaction course. Diequatorial adducts are then formed preferentially (Scheme VIII). This appears to be a general behavior for a wide range of electrophiles.[55]

Remarkable differences have been observed in the reactivity of iodination reagents generated in different ways ($I_2$ + $Ag^+$, $Tl^+$, $Ce^{4+}$, $Cu^{2+}$, $Bi^{3+}$, or KI). Since most of these reagents can cleanly differentiate between di- and trisubstituted double bonds (depending on the nature of the participating neighboring group), this cyclofunctionalization methodology could serve as a useful tool for the construction of complex molecules. Similar differentiation has been found for phenylselenenylation, mercuration, and cyclooxypalladation/carbonylation reactions.

Silver(I)-mediated iodocyclization is followed by solvolysis when the departing halogen is exocyclic to the newly formed heterocycle and antiperiplanar to the carbon–heteroatom bond (Chart II).[58] The same effects operate in the thallium(III)-mediated hydroxycyclization. When the ring is to be formed in a 5-*endo-trig* fashion, the reaction either does not occur or leads to a novel stereocontrolled fragmentation (Scheme V). We believe that our observations on the scope of this tandem transformation could serve as a guide for planning syntheses of complex molecules. In particular, the limits we have found for the thallium(III)-mediated hydroxy cyclization can make this capricious methodology more reliable. Moreover, we are confident that the one-carbon degradation (Scheme V) will be of general use for a facile synthesis of 19-norsteroids of medicinal importance.

An improved procedure for cyclooxypalladation/carbonylation has been developed.

## Experimental Section

**Materials and Equipment.** Melting points (uncorrected) were obtained on a Kofler block. Optical rotations were measured in $CHCl_3$ with an error of ±3°. The infrared spectra were obtained on a Perkin-Elmer 621 instrument in $CCl_4$. $^1H$ NMR spectra were measured on Varian XL-200 (200.058 MHz, FT mode) and Tesla BS 476 (60 MHz) instruments for $CDCl_3$ solutions at 25 °C. Chemical shifts are given in δ values (ppm) relative to the signal of tetramethylsilane (δ = 0.00). Apparent coupling constants were obtained from a first-order analysis. The mass spectra were measured on a JEOL D-100 double-focusing spectrometer (75 eV, 3 kV). The samples were introduced by using a direct inlet at lowest temperature enabling evaporation. Standard workup of an ethereal solution means washing with 5% HCl (aqueous), water, and 5% $KHCO_3$ (aqueous), drying with $Na_2SO_4$, and evaporation of the solvent in vacuo. Petroleum ether refers to the fraction boiling in the range 40–60 °C. The identity of samples prepared by different routes was checked by mixed melting point determination, TLC, and IR and NMR spectra. Yields are given in milligrams of isolated product showing one spot on a chromatographic plate and no trace of impurities detectable in the NMR spectrum.

**General Procedure for the Silver-Assisted Addition.** A solution of iodine (0.30 mmol) in 1,2-dimethoxyethane or dioxane (1 mL) was added to a solution of unsaturated derivative (0.25 mmol) in 1,2-dimethoxyethane or dioxane (5 mL) containing water or methanol (0.5 mL) and silver trifluoroacetate (0.30 or 0.60 mmol) at room temperature over 1 min. Immediate formation of yellowish silver iodide was observed. The mixture was stirred for another 5 min; the solid material was filtered off and washed with ether. The filtrate was washed with water, 5% $Na_2S_2O_3$ (aqueous), 5% $KHCO_3$ (aqueous), and water and dried with $Na_2SO_4$, and the solvent was evaporated in vacuo. The residue was dissolved in a benzene–ether mixture (5:1) and filtered through a pad of aluminum oxide, and the filtrate was evaporated to afford pure products. In cases when this procedure still did not give a pure product, the residue was chromatographed on two plates of silica gel (20 × 20 cm) with petroleum ether–ether–acetone (70:15:15) mixture as developer to obtain pure hydroxy derivatives. The isolated yields are given in Table I.

**General Procedure for the Thallium(I)-Assisted Addition.** A solution of iodine (0.30 mmol) or phenylselenenyl chloride (0.30 mmol) in 1,2-dimethoxyethane or dioxane (1 mL) was added to a solution of the unsaturated derivative (0.25 mmol) in 1,2-dimethoxyethane or dioxane (5 mL) containing thallium(I) trifluoroacetate (0.30 mmol) at room temperature over 1 min. The orange mixture was stirred for another 5 min, then diluted with ether and worked up as in the previous experiment.

**General Procedure for the Cerium(IV)-Assisted Iodination.** A solution of iodine (0.30 mmol) in 1,2-dimethoxyethane (1 mL) was added to a solution of unsaturated derivative (0.25 mmol) in 1,2-dimethoxyethane (5 mL) containing cerium(IV) ammonium nitrate (0.30 or 0.60 mmol) at room temperature over 1 min. The mixture was stirred at room temperature for 15 min (or overnight) and worked up as above.

**General Procedure for Mercuration.** A solution of mercury(II) trifluoroacetate (0.30 mmol) in 1,2-dimethoxyethane (2 mL) was added to a solution of olefinic substrate (0.25 mmol) in 1,2-dimethoxyethane (5 mL), and the mixture was set aside for 1 h at room temperature. Then a solution of sodium borohydride (30 mg) and sodium hydroxide (100 mg) in water (2 mL) was

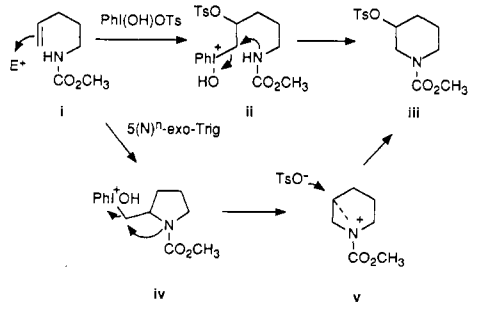
(54) Pandey, G.; Sekkar, B. B. V.; Bhalearo, U. T. *J. Am. Chem. Soc.* **1990**, *112*, 5650.

(55) This analysis applies for rigid systems which cannot attain other conformations by ring flipping. For "equatorial" opening in flexible systems resulting either from the reaction in another conformation or from equilibration, see, e.g. ref 21j and ref 56. Vicinal electron-withdrawing substituents and/or the nature of the reagent can also alter the regiochemistry.[57]

(56) (a) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1984**, *49*, 3951. (b) Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1983**, 1031. (c) Holmes, A. B.; Raithby, P. R.; Rosales, M. J.; Russell, K.; Stern, E. S.; Stubbs, M. E. *Tetrahedron Lett.* **1984**, *25*, 5705. (d) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5657. (e) Tanner, D.; Sellén, M.; Bäckvall, J.-E. *J. Org. Chem.* **1989**, *54*, 3374.

(57) Inghardt, T.; Frejd, T.; Magnusson, G. *J. Org. Chem.* **1988**, *53*, 4542.

(58) **Note added in proof**: Moriarty et al. (unpublished results cited in review 40h) have cyclized the olefinic carbamate i by treatment with [hydroxy(tosyloxy)iodo]benzene to the piperidine derivative iii. They have proposed a Markovnikov-type addition product ii as intermediate, which should readily cyclize to iii. In light of our and Bartlett's results[22a] we feel that another mechanism may better explain this reaction. The reagent would first react with concomitant 5(N)$^n$-*exo-trig* participation to give iv as an intermediate. The following expulsion of the exocyclic electrophile would lead to v, quenching of which in a Markovnikov fashion should also produce iii. In view of the stronger nucleophilicity of the carbamate nitrogen (compared to $TsO^-$) we feel that the cyclization i → iv in the first step is more likely than the simple addition i → ii. Further experiments will be needed to rule out one of these mechanisms. For related examples, see ref 59.




(59) (a) Dailey, C. D.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (b) Liu, H. L.; Browne, E. N. C.; Pendekar, P. R. *Can. J. Chem.* **1982**, *60*, 921. (c) Heathcock, C. H.; von Gerden, T. W.; Lebrilla, C. B.; Maier, W. F. *J. Org. Chem.* **1985**, *50*, 968. (d) Borka, C. A.; Gertlis, J. F. *J. Org. Chem.* **1988**, *53*, 214. (e) Thottathil, J. K.; Moniot, J. L. *Tetrahedron Lett.* **1986**, *27*, 151. (f) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.

added while stirring. The mixture was stirred for another 5 min, the solid material was filtered off and washed with ether, and the filtrate was worked up as usual. The residue was filtered through a pad of aluminum oxide or chromatographed as above. The isolated yields are given in Table I.

**General Procedure for Thallation.** A solution of thallium(III) nitrate trihydrate (0.30 mmol) in dioxane (2 mL) was added to a solution of olefinic substrate (0.25 mmol) in dioxane (5 mL); the mixture was stirred for 10 min at room temperature, diluted with ether, and worked up as usual. Purification of the product was carried out as in the first experiment.

**General Procedure for Cyclooxypalladation/Carbonylation.** To a solution of olefinic alcohol (0.40 mmol) in methanol (20 mL) were added copper(I) chloride (1.20 mmol), copper(II) chloride (1.20 mmol), lithium chloride (2.50 mmol), and palladium chloride (0.04 mmol), and the mixture was stirred at room temperature under an atmosphere of carbon monoxide (ca. 1.1 atm) for 24 h. After ca. 1 h, deposition of a thick yellowish solid was observed, which dissolved again in ca. 5 h. After completion of the reaction (as checked by TLC) the black solid of Pd(0) begun to form. The mixture was concentrated by evaporating in vacuo, diluted with ether, and filtered, and the filtrate was worked up as usual. The residue was chromatographed on two plates of silica as in the first experiment. The isolated yields are given in Table I.

**General Procedure for the $Bu_3SnH$ Reduction of Halides.** A solution of a halogen derivative (40 mg) in benzene (3 mL) was refluxed with a 1 M benzene solution of tributyltin hydride (0.3 mL) and a catalytic amount of 2,2'-azoisobutyronitrile for 1 h (for Br derivatives) or 15 min (for I derivatives). The mixture was diluted with ether, washed with 5% NaF (aqueous), and 5% $KHCO_3$ (aqueous), and dried with $Na_2SO_4$, and the solvent was evaporated. The residue was purified by filtration through a pad of aluminum oxide or chromatographed on silica as given in the first experiment.

**2β,19-Epoxy-3α-iodo-5α-cholestane (15)**: $[\alpha]_D$ +31° (*c* 3.4); $^1H$ NMR 0.60 (s, 3 H, 18-H), 3.73 (m, *W* = 15 Hz, 1 H, 3β-H), 3.77 (s, 2 H, collapsed AB system, 19-H), 4.32 (m, *W* = 11 Hz, 1 H, 2α-H).

Anal. Calcd for $C_{27}H_{45}IO$: C, 63.27; H, 8.85; I, 24.76. Found: C, 62.98; H, 9.01; I, 24.52.

**2β,19-Epoxy-3α-(phenylselenenyl)-5α-cholestane (16)**: mp 125–126 °C (aqueous acetone); $[\alpha]_D$ +80° (*c* 2.5); IR 693, 734 (arom.), 1018, 1024, 1030 (C–O–C), 1582, 2060, 3075 (arom.) $cm^{-1}$; $^1H$ NMR 0.61 (s, 3 H, 18-H), 3.52 (m, *W* = 12 Hz, 1 H, 3β-H), 3.65 and 3.85 (AB system, *J* = 9 Hz, 2 H, 19-H), 4.37 (dd, *J* = 6 and 4 Hz, 1 H, 2α-H), 7.25 (m, 2, H, arom.), 7.45 (m, 3 H, arom.).

Anal. Calcd for $C_{33}H_{50}OSe$: C, 73.17; H, 9.30. Found: C, 72.91; H, 9.59.

**2β,19-Epoxy-5α-cholestane (23)**: mp 92–93 °C (methanol); $[\alpha]_D$ +42° (*c* 1.5) [lit.[60] mp 90–92 °C; $[\alpha]_D$ +41°]; $^1H$ NMR (0.61 (s, 3 H, 18-H), 3.63 and 3.85 (AB system, *J* = 9 Hz, 2 H, 19-H), 4.23 (m, *W* = 17 Hz, 1 H, 2α-H).

**2β,19-Epoxy-3α-(methoxycarbonyl)-5α-cholestane (24)**: mp 101–103 °C; $[\alpha]_D$ +17° (*c* 1.5); $^1H$ NMR 0.70 (s, 3 H, 18-H), 2.36 (m, *W* = 16 Hz, 1 H, 2α-H), 3.66 (s 3 H, $CO_2CH_3$), 3.77 and 3.96 (AB system *J* = 11.5 Hz, 2 H, 19-H).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.16; H, 10.94.

**2β,19-Epoxy-1α-iodo-5α-cholestane (26)**: $[\alpha]_D$ −88° (*c* 3.2); $^1H$ NMR 0.60 (s, 3 H, 18-H), 3.73 (s, collapsed AB system, 2 H, 19-H), 4.28 (m, *W* = 18 Hz, 2 H, 1β-H and 2α-H).

Anal. Calcd for $C_{27}H_{45}IO$: C, 63.27; H, 8.85; I, 24.76. Found: C, 63.06; H, 9.03; I, 24.29.

**2β,19-Epoxy-1α-(methoxycarbonyl)-5α-cholestane (29)**: mp 114–116 °C; $[\alpha]_D$ +26° (*c* 2.6); $^1H$ NMR 0.69 (s, 3 H, 18-H), 3.66 (s, 3 H, $CO_2CH_3$), 3.78 and 3.94 (AB system, *J* = 12.0, 2 H, 19-H); IR 1156, 1737 $cm^{-1}$.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.09; H, 11.03.

**6β,19-Epoxy-5-iodo-5α-cholestan-3β-yl acetate (31)**: mp 133–134 °C (acetone–methanol–water); $[\alpha]_D$ −2° (*c* 2.8); $^1H$ NMR 0.70 (s, 3 H, 18-H), 2.02 (s, 3 H, $CH_3CO_2$), 3.59 and 3.95 (AB system, *J* = 8.5 Hz, 2 H, 19-H), 4.12 (d, *J* = 4 Hz, 1 H, 6α-H), 5.27 (m, *W* = 30 Hz, 1 H, 3α-H).

Anal. Calcd for $C_{29}H_{47}IO_3$: C, 61.04; H, 8.30; I, 22.24. Found: C, 59.87; H, 8.54; I, 21.93.

**6β,19-Epoxy-5-(phenylselenenyl)-5α-cholestan-3β-yl acetate (32)**: mp 167–168 °C (acetone–methanol–water); $[\alpha]_D$ −46° (*c* 2.5); $^1H$ NMR 0.72 (s, 3 H, 18-H), 1.95 (s, 3 H, $CH_3CO_2$), 3.77 and 3.98 (AB system, *J* = 8 Hz, 2 H, 19-H), 3.95 (d, *J* = 4 Hz, 1 H, 6α-H), 5.43 (m, *W* = 30 Hz, 1 H, 3α-H), 7.25 (m, 2 H, arom.), 7.62 (m, 3 H, arom.).

Anal. Calcd for $C_{35}H_{52}O_3Se$: C, 70.09; H, 8.74. Found: C, 69.73; H, 8.90.

**19-Norcholest-5-ene-3β,10β-diol 3-monoacetate (37)**: mp 146–147 °C (acetone–methanol–water); $[\alpha]_D$ −64° (*c* 1.9); $^1H$ NMR 0.68 (s, 3 H, 18-H), 2.04 (s, 3 H, $CH_3CO_2$), 4.65 (m, *W* = 31.5 Hz, 1 H, 3α-H), 5.56 (br d, *J* = 5.5 Hz, 1 H, 6-H); $^{13}C$ NMR 11.70 (q), 18.70 (q), 20.15 (t), 20.42 (q), 22.55 (q), 22.81 (q), 23.79 (t), 24.25 (t), 27.05 (t), 27.99 (d), 28.20 (t), 31.57 (t), 32.16 (d), 34.75 (t), 35.71 (d), 36.14 (t), 37.45 (t), 39.24 (t), 39.49 (t), 42.25 (s), 48.90 (d), 55.73 (d), 56.11 (d), 69.14 (s), 73.05 (d), 126.00 (d), 136.65 (s), and 170.61 (s); IR 1034, 1246 (C—O), 1735 (C=O), 3500, 3615 (OH) $cm^{-1}$; *m/z* (rel intensity, %) 430 (0.2, M), 370 (100, M − AcOH), 352 (52, M − AcOH − $H_2O$), 239 (8, $C_{18}H_{23}$), 197 (36, $C_{15}H_{17}$), 144 (27, $C_{11}H_{12}$).

Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.13; H, 10.58.

**6α-Iodo-5,19a-epoxy-19-homo-5β-cholestan-3β-yl acetate (40)**: $[\alpha]_D$ −5° (*c* 2.8); $^1H$ NMR 0.66 (s, 3 H, 18-H), 2.04 (s, 3 H, $CH_3CO_2$), 3.97 (m, *W* ≅ 30 Hz, 2 H, 19a-H), 4.51 (dd, *J* = 10.5 and 4 Hz, 1 H, 6β-H), 5.06 (m, *W*/2 = 10 Hz, 1 H, 3α-H).

Anal. Calcd for $C_{30}H_{49}IO_3$: C, 65.92; H, 9.04; I, 16.26. Found: C, 65.71; H, 9.25; I, 16.43.

**6α-(Phenylselenenyl)-5,19a-epoxy-19-homo-5β-cholestan-3β-yl acetate (41)**: $[\alpha]_D$ +36° (*c* 3.3); $^1H$ NMR 0.62 (s 3 H, 18-H), 2.05 (s, 3 H, $CH_3CO_2$), 3.26 (dd, *J* = 12 and 5 Hz, 1 H, 6β-H), 3.98 (m, *W* ≅ 30 Hz, 2 H, 19a-H), 5.12 (m, *W*/2 = 11 Hz, 1 H, 3α-H).

Anal. Calcd for $C_{36}H_{54}O_3Se$: C, 70.45; H, 8.87. Found: C, 70.12; H, 8.91.

**5,19β-Epoxy-19-homo-5β-cholestan-3β-yl acetate (43)**: $[\alpha]_D$ +15° (*c* 4.2); $^1H$ NMR 0.67 (s, 3 H, 18-H), 2.03 (s, 3 H, $CH_3CO_2$), 3.92 (m, *W* ≅ 25 Hz, 2 H, 19a-H), 4.97 (m, *W*/2 = 8 Hz, 1 H, 3α-H).

Anal. Calcd for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.26; H, 11.32.

**6α-Iodo-5β-cholestane-3β,5,19-triol 3-acetate 5,19-carbonate (45)**: mp 158–160 °C; $[\alpha]_D$ −8° (*c* 2.0); $^1H$ NMR 0.65 (s, 3 H, 18-H), 2.07 (s, 3 H, $CH_3CO_2$), 3.97 and 4.77 (AB system, *J* = 11 Hz, 2 H, 19-H), 4.63 (dd, *J* = 11 and 4 Hz, 1 H, 6β-H), 5.08 (m, *W*/2 = 8 Hz, 1 H, 3α-H).

Anal. Calcd for $C_{30}H_{47}IO_5$: C, 58.62; H, 7.70; I, 20.65. Found: C, 58.37; H, 7.91; I, 20.32.

**2β,19-Epoxy-5α-cholest-3-ene. (A) From 16**: To a solution of phenylselenenyl derivative **16** (62 mg) in dioxane (2 mL) was added a mixture of 30% hydrogen peroxide (0.02 mL), acetic acid (0.01 mL), and water (0.3 mL), and the resulting mixture was stirred at room temperature for 8 h. The mixture was then diluted with water and extracted with ether. The ethereal phase was washed with water, 5% $Na_2S_2O_3$ (aqueous), 5% $KHCO_3$ (aqueous), and water, and dried with $Na_2SO_4$, and the solvent was evaporated in vacuo. The residue was crystallized from an acetone–methanol–water mixture to afford 2β,19-epoxy-5α-cholest-3-ene (32 mg): mp 64–66 °C; $[\alpha]_D$ +10° (*c* 1.2); $^1H$ NMR 0.61 (s, 3 H, 18-H), 3.65 and 3.85 (AB system, *J* = 9 Hz, 2 H, 19-H), 4.32 (t, *J* = 5 Hz, 1 H, 2α-H), 5.35–6.00 (m, 2 H, 3-H and 4-H).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.29; H, 11.55. Found: C, 84.08; H, 11.76.

**(B) From 14**: A mixture of bromotetrahydrofuran **14** (80 mg) and diazabicycloundecene (120 μL) in xylene (3 mL) was refluxed for 10 days. The solvent was then evaporated in vacuo, the residue dissolved in ether, and the ethereal solution was worked up as usual. Crystallization of the crude produt from an acetone–methanol–water mixture furnished 2β,19-epoxy-5α-cholest-3-ene (46 mg): mp 64–66 °C.

**6β,19-Epoxycholest-4-en-3β-yl acetate**: To a solution of phenylselenenyl derivative **32** (50 mg) in dichloromethane (2 mL) was added 30% hydrogen peroxide (0.5 mL), and the mixture was stirred at room temperature for 12 h. Then the mixture was

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diluted with water and extracted with ether. The ethereal phase was washed with water, 5% $Na_2S_2O_3$ (aqueous), 5% $KHCO_3$ (aqueous), and water and dried with $Na_2SO_4$, and the solvent was evaporated in vacuo. The residue was dissolved in a petroleum ether–benzene mixture (2:1) and filtered through a pad of aluminum oxide. The filtrate was evaporated, and the product was crystallized from aqueous methanol to give 6β,19-epoxycholest-4-en-3β-yl acetate (24 mg): mp 57–59 °C; $[\alpha]_D$ −90° (c 1.5); $^1H$ NMR 0.72 (s, 3 H, 18-H), 2.02 (s, 3 H, $CH_3CO_2$), 3.37 and 4.12 (AB system, $J$ = 8 Hz, 2 H, 19-H), 4.48 (d, $J$ = 4 Hz, 1 H, 6α-H), 5.23 (m, $W/2$ = 8 Hz, 1 H, 3α-H), 5.57 (s, 1 H, 4-H).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.67; H, 10.49. Found: C, 78.90; H, 10.66.

**Acknowledgment.** We thank Dr. S. Vašíčková for measurement of IR spectra, Drs. J. Zajíček, M. Buděšínský, Mrs. J. Jelínková, and Mrs. M. Snopková for measurement of NMR spectra, and Drs. V. Hanuš and M. Smrčina for mass spectra.

# Reformatsky Reaction on α-Oxo Ketene Dithioacetals: Synthesis of Substituted and Fused Ethyl 2-Hydroxy-6-(methylthio)benzoates, 6-(Methylthio)pyran-2-ones, and 6-(Methylthio)-2(1*H*)-pyridone Derivatives

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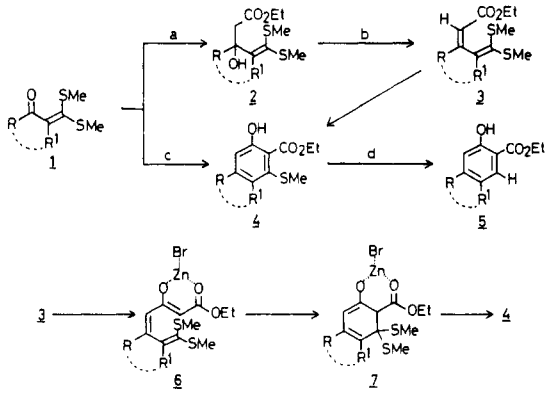
*Received October 6, 1989*

A novel cycloaromatization reaction leading to substituted and annelated ethyl 2-hydroxy-6-(methylthio)benzoates **4** by condensation of α-oxo ketene dithioacetals with an excess of Reformatsky reagent from ethyl bromoacetate through intermediate dienes **3** has been described. The reaction has also been extended for the synthesis of substituted ethyl 3-hydroxy-5-(methylthio)stilbenecarboxylates **9** by using cinnamoyl ketene dithioacetals **8**. A few of the benzoates **4** were desulfurized to the corresponding salicylate derivatives **5**. Reaction of acyclic oxo ketene dithioacetals with ethyl(bromozincio)acetate in the presence of cuprous iodide afforded 4- (or 4,5-) substituted 6-(methylthio)pyran-2-ones **15** in moderate to good yields. A probable mechanism for the formation of **15** is suggested. Cyclization of the acyclic dienes **3** or the carbinols **10** with ammonium acetate in refluxing acetic acid afforded the corresponding 4- (or 4,5-) substituted 6-(methylthio)-2(1*H*)-pyridones **22**.

The α-oxo ketene dithioacetals **1** have been extensively investigated as three-carbon units, which have been shown to undergo regio-, stereo-, and chemoselective C–C bond forming reactions.[1] As a part of our programmed studies, we have shown that these intermediates undergo exclusive 1,2-addition with methylmagnesium iodide while the higher alkyl and aryl Grignard reagents add sequentially in 1,4 and 1,2 fashion.[2] However, the allylmagnesium halide adds in an exclusive 1,2 fashion to yield the corresponding carbinol acetals, which undergo cycloaromatization in the presence of boron trifluoride etherate to afford the benzoannelated products in good yields.[3] Similarly, propargyl,[4] acetonitrile,[5] 2-picolyl,[6] and 5-methylisoxazolyl[7] anions were shown to undergo 1,2-addition followed by cycloaromatization in the presence of Lewis acids to afford a variety of aromatic and heteroaromatic compounds. However, the reaction of benzylmagnesium chloride with **1** was found to undergo sequential 1,4 and 1,2 addition to afford the corresponding carbinol acetals, which underwent similar Lewis acid assisted cycloaromatization involving aromatic ring π-participation to yield the corresponding naphthoannelated products.[8] These results have since been reviewed.[9] The lithioacetate and ethyl (bromozincio)acetate have also been reacted with **1** in a 1,2 manner to afford the hydroxy esters

**Scheme I**[a]




[a] (a) $BrZnCH_2CO_2Et$ (1.5 equiv)/$C_6H_6$/Δ; (b) $I_2/C_6H_6$/Δ; (c) $BrZnCH_2CO_2Et$(4 equiv)/$C_6H_6$/$Et_2O$/Δ; (d) Raney Ni/EtOH/Δ.

in high yields, which have been further converted either to the corresponding pyran-2-ones[10] or to the dienes **3** (Scheme I) under iodide ion catalyzed dehydration.[11] In our preliminary communication these dienes were further shown to react with (bromozincio)acetate to yield the corresponding substituted and annelated ethyl 2-hydroxy-6-(methylthio)benzoates **4** in good yields[12] (Scheme I). This two-step reaction involving intermediates **6** and **7** could be achieved in one pot in equally high yields by reacting **1** with an excess of ethyl (bromozincio)acetate. We now report a full account of these studies, including the scope and limitations. The intermediate dienes **3** and the carbinols **10** have also been utilized for the synthesis

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