Hypervalent Iodine in Organic Synthesis

ROBERT M. MORIARTY* and OM PRAKASH

University of Illinois at Chicago, Department of Chemistry, Chicago, Illinois 60607

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A conspicuous feature of modern synthetic organic chemistry is the impressive proliferation of new reagents. Recently, D. H. R. Barton made the point that 20 years ago a synthetic chemist could function perfectly adequately using perhaps twenty synthetic reactions.[1] The tremendous increase in the application of organometallics to synthetic methodology has changed, certainly for the better, that rather complacent situation. This Account deals with the synthetic use of a class of compounds recently termed "organometallic" reagents.[2] This is an apt description because many of the reaction pathways of hypervalent iodine are formally similar to those of organometallic chemistry.

Hypervalent or higher valent iodine compounds have a long history in organic chemistry. In fact 1986 marks the centenary of the discovery of (dichloroiodo)benzene (1) by Willgerodt.[3] In 1914 Willgerodt published a lengthy review summarizing the considerable amount of work done by him.[4] This may have been a case in science in which his review was so comprehensive that people concluded that all that was worth knowing was known. At any rate very little systematic work was done in this area with the exception of studies by F. M. Beringer in the period 1950–1970[5] and Neilands and co-workers in Russia during the same period.[6]

A key date in the development of this field is 1969 when J. I. Musher published a review titled "The Chemistry of Hypervalent Molecules" and, in fact, introduced the term "hypervalency".[7] Musher was concerned with the bonding in molecules such as $C_6H_5ICl_2$ (1) in which the Lewis–Langmuir theory of valence could not accommodate "expanded octet" molecules. The term hypervalency refers to "molecules or ions formed by elements in Group V–VIII (5–10)[37] of the periodic table in any valence state other than their lowest stable chemical valence of 3, 2, 1, or 0, respectively. We refer to these molecules as hypervalent since they involve donor atoms which exceed the number of valences by traditional theory and thus utilize more electron-pairs of bonding than provide stability in the Lewis-Langmuir theory."

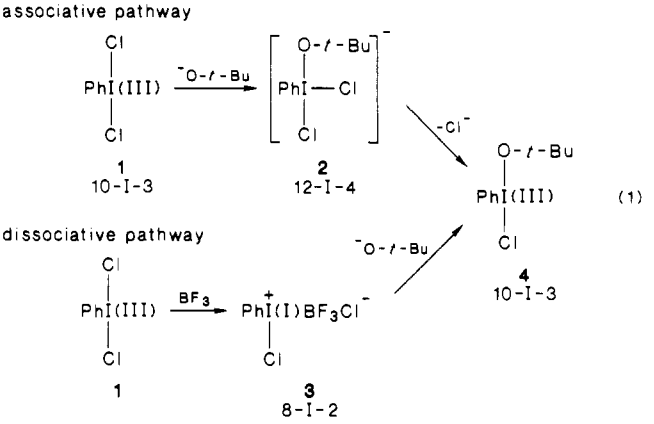
Thus C_6H_5IO, $C_6H_5IO_2$, CF_3IF_2, CF_3IF_4, $C_6H_5IF_6$, and $C_6H_5IC(CO_2Et)_2$ are examples of molecules containing hypervalent iodine according to the Musher definition. Bonding in a molecule such as $C_6H_5ICl_2$ (1) uses essentially pure p orbitals in the linear Cl–I–Cl system. This is a three-center four-electron bond with two electrons from the doubly occupied 5p orbital on iodine and one electron from the 3p orbital on each of the chlorine atoms. The phenyl ring is bound by a normal two-electron covalent bond. The result is a T-shaped molecule with elongated I–Cl apical bonds (0.22 Å longer than the same of the covalent radii).[8]

General Mechanistic Pathways

Two fundamental features of hypervalent iodine reactivity which form the basis for synthetic utility are the possibility of *ligand exchange occurring at iodine* with no change overall in the oxidation state of iodine and *ligand transfer with reductive elimination* of ArI. These processes may be illustrated as follows in the case of $C_6H_5ICl_2$ (1) in eq 1.

Ligand Exchange

Nucleophilic addition of $^-$O-*t*-Bu to 1 yields 2 which loses chloride anion to 4 the product of substitution.



Alternately, dissociation may occur to yield an iodonium

Robert M. Moriarty received his Ph.D. degree from Princeton University in 1959 and did postdoctoral work with R. Huisgen in 1960 and with E. J. Corey in 1961. His research interests are in synthetic and mechanistic organic chemistry.

Om Prakash received his Ph.D. degree from the University of Roorkee in 1976 and has been a postdoctoral co-worker at UIC since 1983. He was appointed to the post of lecturer (assistant professor) at Kurukshetra University, Kurukshetra, India in 1986. His research interests are in the areas of synthetic and physical organic chemistry.

(1) Barton, D. H. R. *Chem. Br.* **1973**, *9*, 149. I would not like to neglect to mention that we are very poor in synthetic methods in organic chemistry. Most of the synthetic work is done with organic reactions of the type which have been known for a long time. If you know 20 organic reactions you probably know most of the steps used in synthetic work, particularly in industry, but I am quite sure there must be hundreds of other organic reactions to be discovered. We have not in the past thought about these problems in the right way. When we have been faced with a problem of effecting a chemical synthesis, we have sought known methods. We have not paused to think why we do not invent a new method every time. If we adopt this philosophy we are going to be extremely busy till the end of the century (a) trying to equal the enzymes, and (b) thinking up new ways of synthesis.

(2) Martin, J. C. *Science* **1983**, *221*, 509. Also termed "nonmetalloorganic" compounds by Musher in ref 7.

(3) Willgerodt, C. *J. Prakt. Chem.* **1886**, *33*, 154.

(4) Willgerodt, C. *Die Organischen Verbindugen mit Mehrwertigen Jod*, Ferdinand Enke Verlag: Stuttgart, 1914.

(5) For a review see Koser, G. F. "Halonium Ions" In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Chapter 25.

(6) For a reivew, see: Koser, G. F. "Hypervalent Halogen Compounds" In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Chapter 18.

(7) Musher, J. I. *Angew. Chem., Int. Ed. Eng.* **1969**, *8*, 54.

(8) For a discussion of hypervalency in organoiodine(III) compounds see Moriarty, R. M., in *Tetrahedron Lett.*, in press.

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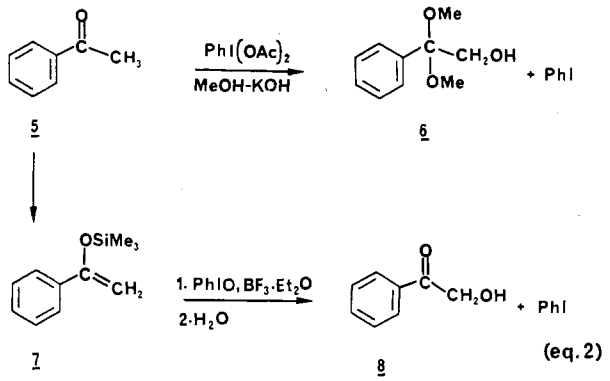
intermediate **3** which then may coordinate with $^-$O-*t*-Bu to yield **4**. The N–X–L nomenclature is used where *N* is the number of valence shell electrons formally assignable to the valence shell of the central atom, X, either as unshared pairs or electrons or electron pairs in σ bonds joining a number, *L*, or ligands to X.[9]

The exchange sequence **1** → **2** → **4** may be termed an associative pathway and bears some similarity to an S_N2 process. The detailed mechanism of the reaction is not known, but a 12-I-4 intermediate, $[C_6H_5I(Cl_2)O\text{-}t\text{-}Bu]^-$ (**2**) is likely. Reich et al.[10] have obtained evidence for the operation of this mechanism in the exchange reaction between aryllithium and aryl iodides, and recently a stable product, namely, $[C_6F_5I\text{–}F\text{–}IC_6F_5]^-\ S^+R_3$ has been isolated.[11] The pentacoordinate transition state of the carbon system in the S_N2 reaction has an analogy in the stable 12-I-4 intermediate occurring in the hypervalent iodine system.

Next we may consider two synthetic reactions which we found and which illustrate the operation of these two mechanisms, namely, α-hydroxy dimethyl acetal formation, **5** → **6**, and α-hydroxylation of ketones, **7** → **8** (*eq 2*)[12]. Reaction **5** → **6** occurs under basic conditions



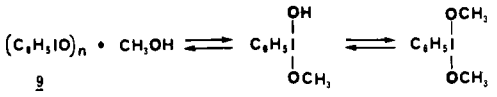
5 6 7 8 (eq. 2)

while **7** → **8** occurs under acidic conditions. It should be noted that completely different reaction pathways are followed.

The present Account will focus upon the synthesis of α-hydroxy dimethyl acetals under basic conditions. This choice excludes discussion of the considerable amount of work done by Koser using the Koser reagent, $C_6H_5I(OH)OTs$[13] as well as the valuable Dess–Martin reagent.[14]

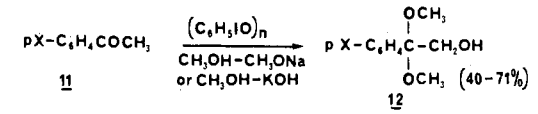
α-Hydroxy Dimethyl Acetal Formation in the Hypervalent Iodine Oxidation of Enolizable Ketones

The origin of this synthesis lies in our attempts to find a useful solvent system for iodosylbenzene oxidations. We learned by trial and error that iodosylbenzene was quite soluble in CH_3OH, and matters were further improved by addition of sodium methoxide. These facts are now understood on two bases: first, C_6H_5IO (**9**) is polymeric in the solid[15a,b], and secondly, iodosylbenzene reacts with CH_3OH by ligand transfer to yield $C_6H_5I(OCH_3)_2$ (**10**). (eq 3)



9 10 (eq. 3)

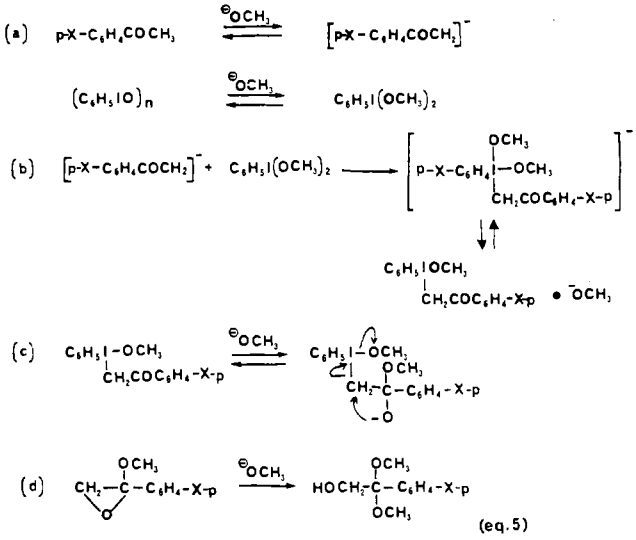
The requirement of CH_3OH as solvent and CH_3ONa as a nucleophile in the solubilization of $[C_6H_5IO]_n$ dictated the conditions in eq 4 in which we obtained high yields of α-hydroxy dimethyl acetals for a series of para-substituted acetophenones **11** → **12** (eq 4).[16]



11 12 (40–71%)

X = H, Me, OMe, 3,4-(OMe)$_2$, F, Cl, Br, I, NO$_2$ (eq. 4)

The mechanism which we proposed for this reaction (shown in equations 5a–d) has proven useful in subsequent work, and has survived new findings at least in its major features. The first step (a) is considered to be a base-catalyzed formation of an equilibrium concentration of the enolate anion; (b) the enolate anion exchange for a methoxyl ligand upon $C_6H_5I(OCH_3)_2$ which is formed in situ; (c) attack of $^-OCH_3$ upon the carbonyl group yields a tetrahedral intermediate, and the thus formed alkoxide anion (in step c) carries out an intramolecular reductive elimination of C_6H_5I. The reaction is completed (in step d) by attack of a second $^-OCH_3$.



(a) p-X-C$_6$H$_4$COCH$_3$ $\overset{\ominus OCH_3}{\rightleftharpoons}$ [p-X-C$_6$H$_4$COCH$_2$]$^-$

(C$_6$H$_5$IO)$_n$ $\overset{\ominus OCH_3}{\rightleftharpoons}$ C$_6$H$_5$I(OCH$_3$)$_2$

(b) [p-X-C$_6$H$_4$COCH$_2$]$^-$ + C$_6$H$_5$I(OCH$_3$)$_2$ → [p-X-C$_6$H$_4$I(OCH$_3$)CH$_2$COC$_6$H$_4$-X-p]$^-$

C$_6$H$_5$I(OCH$_3$)CH$_2$COC$_6$H$_4$-X-p + $^-$OCH$_3$

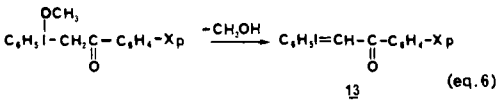
(c) C$_6$H$_5$I(OCH$_3$)CH$_2$COC$_6$H$_4$-X-p $\overset{\ominus OCH_3}{\rightleftharpoons}$ C$_6$H$_5$I$^-$OCH$_3$ CH$_2$C(OCH$_3$)C$_6$H$_4$-X-p O$^-$

(d) CH$_2$C(OCH$_3$)C$_6$H$_4$-X-p $\overset{\ominus OCH_3}{\rightarrow}$ HOCH$_2$C(OCH$_3$)$_2$C$_6$H$_4$-X-p

(eq. 5)

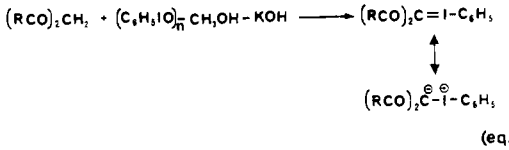
Exclusive attack at the benzylic position by $^-OCH_3$ in step d may be due to an S_N1 component in which some positive character exists at this position. The intermediate in step b has not been isolated, and no stable examples of this type of structure are known. It may be noted that loss of CH_3OH from this intermediate would yield an iodonium ylide (**13**) (eq 6). No examples of such monocarbonyl ylides are known, but

(9) Perozzi, E. F.; Michalak, R. S.; Figuly, G. D.; Stevenson, W. H., III; Dess, D. B.; Ross, M. R.; Martin, J. C. *J. Org. Chem.* **1981**, *46*, 1049.
(10) Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101.
(11) Farnham, W. B.; Calabrese, J. C. *Abstracts of Papers* 191st National Meeting of the American Chemical Society, New York, NY; American Chemical Society: Washington, DC, 1986; INOR 258.
(12) Moriarty, R. M.; Prakash, O.; Duncan, M. P. *Synthesis* **1985**, 943.
(13) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 2462, and references cited therein. Koser's Reagent, marketed by Aldrich (catalog no. 30, 103-5).
(14) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Dess-Martin periodinane, marketed by Aldrich (catalog no. 27462-3).
(15) (a) Bell, R.; Morgan, K. J. *J. Chem. Soc.* **1960**, 1209. (b) Siebert, H.; Handrich, M. J. *Z. Anorg. Allg. Chem.* **1976**, *426*, 173. (c) Schardt, B. C.; Hill, C-L. *Inorg. Chem.* **1983**, *22*, 1563.
(16) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283.



13 (eq. 6)

dicarbonyl examples formed from β-dicarbonyl compounds are well-known (eq 7).

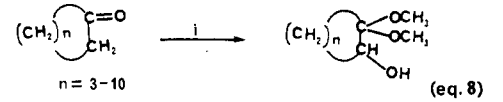


(eq. 7)

A requirement of the mechanism outlined in eq 5a–d is that the original carbonyl oxygen atom becomes the oxygen atom of the primary hydroxyl group. This point was established experimentally by using $C_6H_5CO^{18}CH_3$ and demonstrating that the label was incorporated into the hydroxyl group of the α-hydroxy dimethyl acetal.[17] Furthermore, the mechanism presented in eq 5a–d has stereochemical consequences. In step c an inversion of configuration must occur at the carbon at which the C–I(III) cleavage occurs. In step d trans diaxial ring opening of the epoxide ring results in an inversion of configuration at the carbon atom attacked by CH_3O^-. Both of these stereochemical points were fully confirmed in various cyclic systems which will be discussed below.

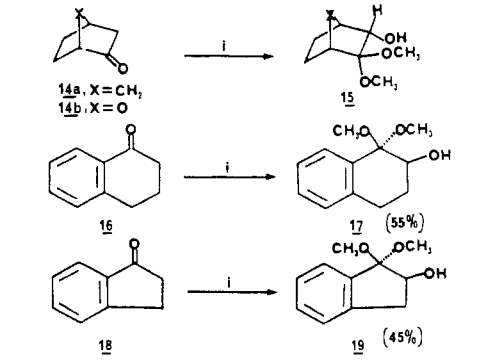
From an operational viewpoint, the overall synthetic reaction was simplified by using *o*-iodosylbenzoic acid in place of either iodosylbenzene or $C_6H_5I(OAc)_2$.[18] The reduction product, *o*-iodobenzoic acid, is soluble under the reaction conditions, and the α-hydroxy dimethyl acetal product is separated by extraction with methylene chloride.

Application of the hypervalent iodine oxidation, $C_6H_5I(OAc)_2$, CH_3OH–KOH, to a series of cyclic ketones as shown in eq 8 proceeded in excellent yields.



n = 3–10 (eq. 8)

Norbornanone (**14a**) yielded 2-*endo*-norbornanol-3-one 3-(dimethyl acetal) (**15a**).[18] Likewise 7-oxabicyclo[2.2.1]hept-2-one (**14b**) yields 7-oxabicyclo[2.2.1]-hept-2-one-3-*endo*-ol dimethyl acetal (**15b**).[19] 1-Tetralone (**16**) and 1-indanone (**18**) yielded the corresponding α-hydroxy dimethyl acetal products, **16** → **17** and **18** → **19**, respectively.[20]



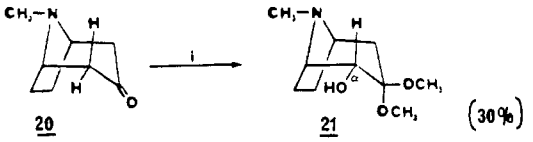
i = $C_6H_5(OAc)_2$, CH_3OH–KOH

(17) Hou, K. C. Ph.D. Thesis, University of Illinois at Chicago, Chicago, 1984.

(18) Moriarty, R. M.; Hou, K. C. *Tetrahedron Lett.* **1984**, *25*, 691.

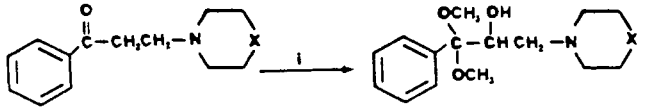
(19) Moriarty, R. M.; Prakash, I.; Penmasta, R., unpublished result, 1985.

Next we applied the reaction to molecules which contained other potentially oxidizable function groups such as secondary and tertiary amino, thioether, and olefinic.[21] For example, 3-tropanone (**20**) was converted to 2α-hydroxy-3-tropanone dimethyl acetal (**21**) in 30% yield.[21] The Mannich base derivatives **22**, **23**, and **24**



(30%)

yielded the α-hydroxy dimethyl acetals **25**, **26**, and **27**, respectively.[21,22]



22 = X = CH_2	**25** = X = CH_2	(50%)
23 = X = O	**26** = X = O	(60%)
24 = X = S	**27** = X = S	(65%)

The dimethyl acetal system is of course the precursor of the parent carbonyl system, and in this sense the overall synthetic reaction constitutes a synthesis of α-hydroxy ketones. In fact, the method is very useful for this purpose and compares very favorably with other synthetic methods for α-hydroxylation of carbonyl groups.[23] The dimethyl acetal system is of itself a potential value as a functionality for subsequent synthetic transformation because of the ease of carbonium ion formation, i.e., $R_2C(OCH_3)_2 \rightarrow R_2C^+–OCH_3 \rightarrow$ products. Thus, Mukaiyama-type $TiCl_4$-catalyzed aldol, Claisen, and Michael-type reactions could conceivably be used in conjunction with the dimethyl acetal.[24]

We have successfully employed this approach in the case of a steroidal example for the construction of the dihydroxyacetone side-chain starting from a C_{17}-acetyl precursor.[25] Hydroxylation (**28** → **29**) occurred at C_{21} without any interference at the C_3 secondary hydroxyl group of the C–C double bond.

Other examples of modification of the steroidal side chain using $C_6H_5I(OAc)_2$, CH_3OH, KOH have been reported.[26a,b] Next we turned our attention to α,β-unsaturated carbonyl systems such as chromone (**32**), flavone (**33**), chalcone (**34**), and flavanone (**35**) or *o*-

(20) Moriarty, R. M.; Prakash, O., unpublished results.

(21) Moriarty, R. M.; Prakash, O.; Karalis, P.; Prakash, I. *Tetrahedron Lett.* **1984**, *25*, 4745.

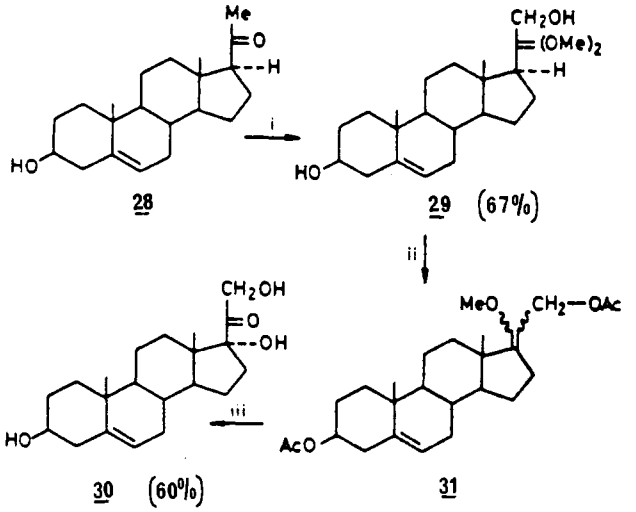
(22) Moriarty, R. M.; Prakash, O.; Thachet, C. T.; Musallam, H. A. *Heterocycles* **1985**, *23*, 633.

(23) (a) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578. (b) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (c) Rubottom, G. M.; Vazques, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (d) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427. (e) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (f) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607. (g) Franklin, A. D.; Vishwakarma, L. C.; Billmers, J. M. *J. Org. Chem.* **1984**, *49*, 3241.

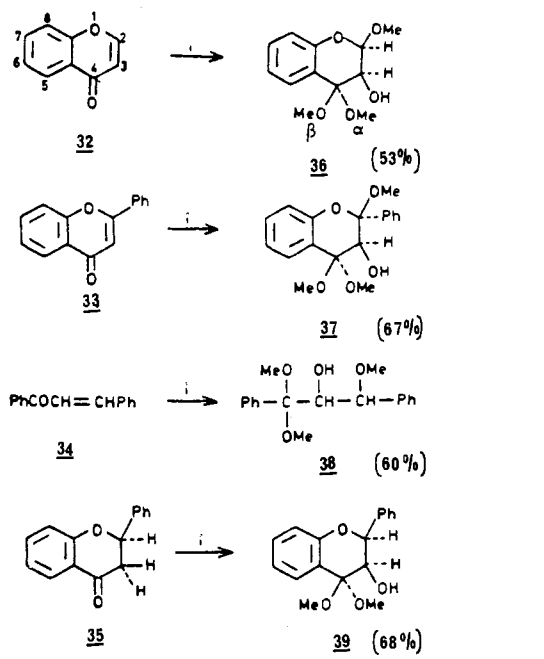
(24) For a review, see: Mukaiyama, T. *New Synthetic Methods*; Weinheim: New York, 1979; Vol. 6, p 247.

(25) Moriarty, R. M.; John, L. S.; Du, P. C. *J. Chem. Soc., Chem. Commun.* **1981**, 641.

(26) (a) Kamernitzky, A. V.; Turuta, A. M.; Fadeeva, T. M.; Istomina, Z. I. *Synthesis* **1985**, 326. (b) Turuta, A. M.; Kamernitzky, A. V.; Fadeeva, T. M.; Zhulin, A. Z. *Synthesis* **1985**, 1129.



(i) $(C_6H_5IO)_n$, KOH, MeOH;
(ii) Ac_2O, pyridine, then *p*-xylene, 138 °C;
(iii) *m*-$ClC_6H_4CO_3H$, 5 min, 0 °C

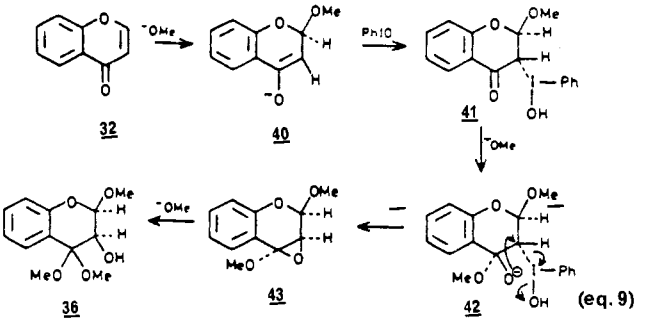


hydroxychalcone.[27] The assumption underlying the hypervalent iodine oxidation of these compounds using $C_6H_5I(OAc)_2$–KOH–MeOH was that requisite enolate system could be generated by Michael-type addition of methoxide anion to the α,β-unsaturated carbonyl group (**32** → **40**) (eq 9).

The α-hydroxy β-methoxy dimethyl acetal products **36**, **37**, **38**, and **39**, respectively, are formed regiospecifically as well as stereospecifically. The structure of **39** was determined by X-ray diffraction. Formation of the observed products may be understood in terms of the following mechanism (Scheme I). The stereochemistry in each case results from initial Michael addition of CH_3O^-, (**32** → **40**) followed by attack of the thus-formed enolate system upon $C_6H_5I(OCH_3)_2$ (**40** → **41**) which occurs in an anti manner because of steric interaction. Sequential addition of CH_3O^- to the carbonyl group (**41** → **42**) and intramolecular reductive elimination of C_6H_5I occurs with inversion of configuration (**42** → **43**). The reaction is completed by a second

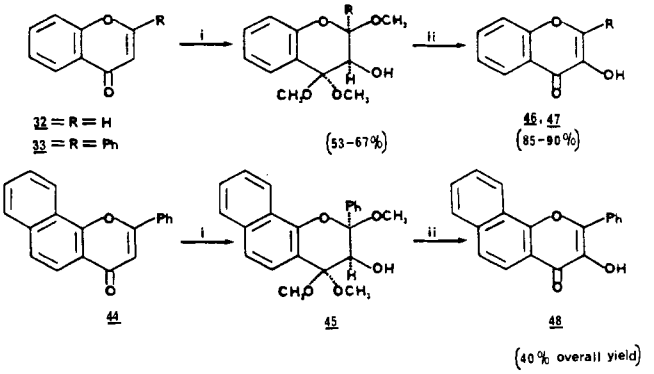
(27) Moriarty, R. M.; Prakash, O.; Freeman, W. A. *J. Chem. Soc., Chem. Commun.* **1984**, 927.

Scheme I



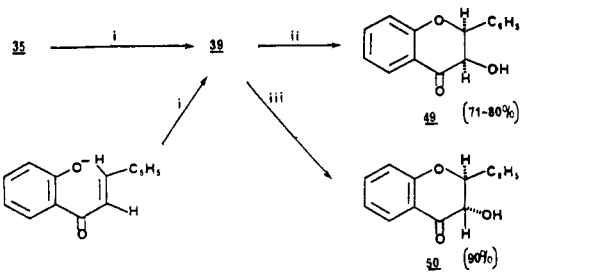
addition of CH_3O^- to the oxirane (**43** → **36**). Chalcone (**34**) presents an acyclic example of the above reaction. Flavanone (**35**) is considered to be equivalent to *o*-hydroxychalcone under the reaction conditions with the phenolic hydroxyl group playing an intramolecular nucleophilic role.[27]

The β-methoxy α-hydroxy dimethyl acetals derived from chromone (**32**), flavone (**33**) and α-naphthoflavanone (**44**), **36**, **37**, and **45**, respectively, were hydrolyzed by using acetone–HCl to yield the C_3-hydroxy products, **46**, **47**, and **48**, respectively.[28]



i, $C_6H_5I(OAc)_2$, KOH/MeOH;
ii, concentrated HCl/$(CH_3)_2CO$

Mild hydrolysis of acetal **39** formed by the oxidation of flavanone (**35**) or *o*-hydroxychalcone provides an excellent way of making *cis*-3-hydroxyflavanone (**49**). Under more vigorous hydrolytic conditions isomerization accompanies hydrolysis of **39** with the formation of *trans*-3-hydroxyflavanone (**50**).[29]



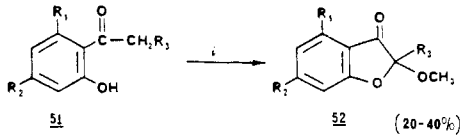
i, $C_6H_5I(OAc)_2$–KOH/MeOH;
ii, 3N HCl or dilute CH_3COOH;
iii, concentrated HCl/CH_3COCH_3

Steric Effects

Intramolecular Participation. In the general mechanism proposed for the oxidation of acetophenones with $C_6H_5I(OAc)_2$–CH_3OH–KOH (eq 5a–d), step c in-

(28) Moriarty, R. M.; Prakash, O.; Musallam, H. A. *J. Heterocycl. Chem.* **1985**, *22*, 583.
(29) Moriarty, R. M.; Prakash, O. *J. Org. Chem.* **1985**, *50*, 151.

volves intermolecular attack by $^-OCH_3$. In the case of *o*-hydroxyacetophenones, the *o*-hydroxy group acts analogously as an intramolecular nucleophile in the reductive cleavage of the C-I (III) bond. A series of substituted *o*-hydroxyacetophenones (**51a–d**) yielded the corresponding 2-methoxycoumaran-3-ones (**52a–d**).[30]

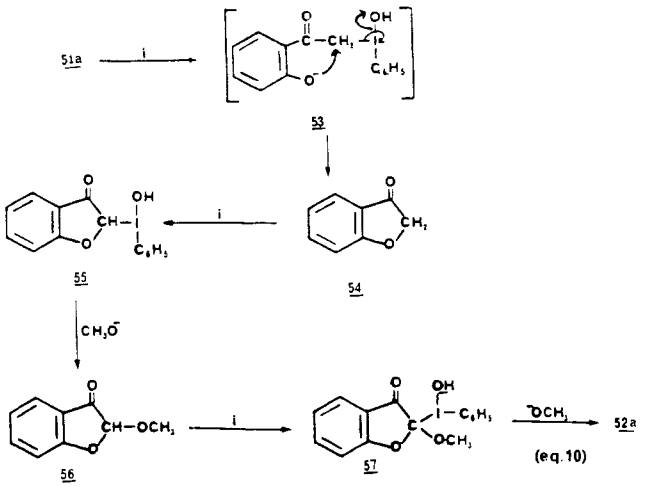


(a) $R_1 = R_2 = R_3 = H$
(b) $R_1 = R_2 = H$; $R_3 = Me$
(c) $R_1 = R_2 = Me$; $R_3 = H$
(d) $R_1 = R_2 = H$; $R_3 = CH_2Ph$

i = $C_6H_5I(OAc)_2$, KOH–MeOH

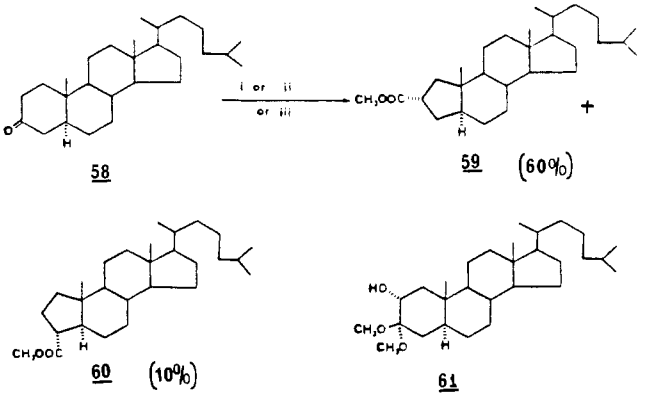
(a) $R_3 = OMe$
(b) $R_3 = Me$
(c) $R_3 = OMe$
(d) $R_3 = CH_2Ph$

The mechanism proposed for these transformations is presented in eq 10.



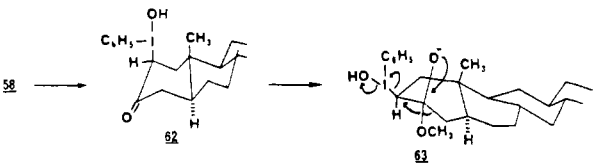
Favorskii-Type Ring Contraction. Reference to the general mechanism for the hyperiodination of acetophenones, eq 5a–d, imposes rather stringent steric demands which are not problematic in simple ketones such as acetophenones or cycloalkanones. However, in the case of more highly substituted systems alternate modes of decomposition of intermediate in eq 5a–d may occur. This is the observed course of events in the case of cholestanone (**58**) which yields 2α-carbomethoxy-A-norcholestane (**59**) in 60% yield and about 10% of 3α-carbomethoxy-A-norcholestanone (**60**) (Scheme II). None of the expected 2α-hydroxy-3,3-dimethoxycholestane (**61**) was observed.[31]

Scheme II[a]



[a] (i) $C_6H_5I(OAc)_2$–KOH/MeOH/THF; (ii) *o*-OIC_6H_4COOH–KOH/MeOH/THF; (iii) $C_6H_5IO_2$–KOH/MeOH/THF.

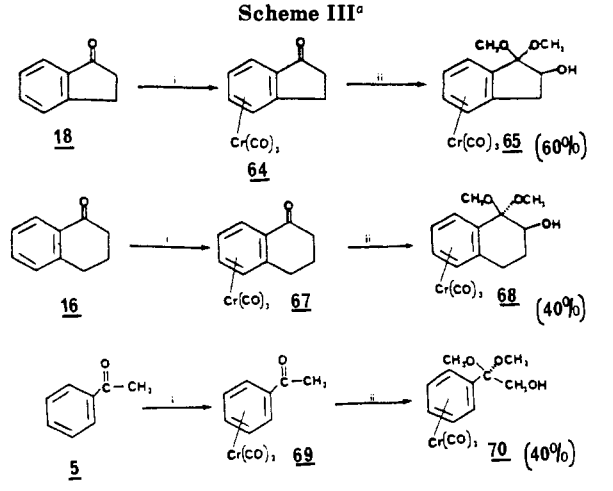
The formation of **59** (and not **61**) may be explained upon conformational and steric grounds. Initial C(2) axial hyperiodination (**58** → **62**) is considered to occur and this intermediate may convert torsionally to a twist-boat form (**62** → **63**). The C–I(III) is now stereoelectronically incorrect for intramolecular epoxide formation, but does have the correct stereoelectronic relationship with the C(3)–C(4) bond in the C(3) tetrahedral intermediate **63** for migration of the C(3)–C(4)



bond. This occurs with inversion of conversion of configuration at C(2) to yield the observed 2α-carbomethoxy-A-cholestane (**59**). The overall course of the reaction, ring contraction rather the α-hydroxy dimethyl acetal formation, is not unexpected based upon these stereoelectronic considerations.

The next problem we addressed was the control of stereochemistry. Toward this end we selected the two prochirotopic ketones, namely, 1-indanone (**18**) and 1-tetralone (**16**), which become chirotopic upon complexation with $Cr(CO)_3$ to yield (η^6-1-indanone)tricarbonylchromium(0) (**64**) and (η^6-1-tetralone)tricarbonylchromium(0) (**62**), respectively. Since the C(2) carbon atoms in **64** and **62** are prostereogenic, application of the hyperiodination reaction could yield a product in which the hydroxyl group is either syn or anti with respect to the $Cr(CO)_3$ tripod. In fact the only compounds obtained in the cases of **64** and **67** were **65** and **68**, respectively (Scheme III). This was established by an X-ray crystallographic study on **68**.[32]

Scheme III[a]



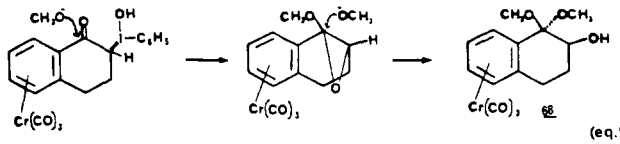
[a] i = $Cr(CO)_6$; ii = $PhI(OAc)_2$, KOH–MeOH.

(30) Moriarty, R. M.; Prakash, O.; Prakash, I.; Musallam, H. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1342.

(31) (a) Moriarty, R. M.; Prakash, I.; Musallam, H. A. *Tetrahedron Lett.* **1984**, *25*, 5867. (b) Daum, S. J. *Tetrahedron Lett.* **1984**, *25*, 4725.

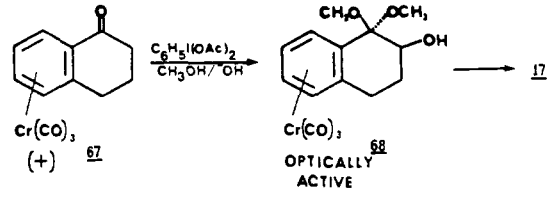
(32) Moriarty, R. M.; Engerer, S. C.; Prakash, O.; Prakash, I.; Gill, U. S.; Freeman, W. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1715.

This stereochemical result can be understood in terms of addition of C_6H_5IO anti to the $Cr(CO)_3$ group due to a simple steric effect. The stereochemistry of the C–I bond in the molecule determines the final stereochemical result, and this is shown in the following mechanism (eq 11).



(eq.11)

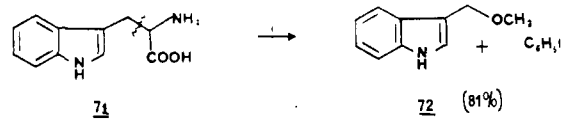
Since chirotopic **67** can be resolved, application of the hyperiodation reaction offers a way of making a pure enantiomer of 17 of known configuration after disengagement of the metal ligand (+)-67 → (–)-68 → 17.



It is also worth noting in these examples that the $Cr(CO)_3$ is stable to oxidation with hypervalent iodine.

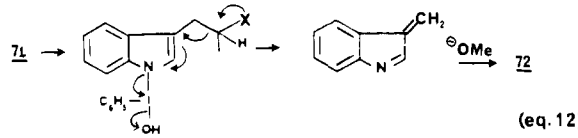
Oxidative Cleavage of Amino Acids and Peptides

We found a novel cleavage reaction of tryptophan (**71**) to 3-methoxymethylindole (**72**) under the standard basic conditions.[33]



(i) CH_3OH/KOH, $C_6H_5I(OAc)_2$

This process is a β-cleavage of the side chain and has not been observed, heretofore, in chemical systems; however, such a pathway has been invoked in biosynthetic schemes for the formation of gramine from tryptophan (**71**) as well as in the enzymic decarboxylation of 3-indoleacetic acid. The cleavage reaction, in the sense of **71** → **72**, was also observed to occur with DL-tryptophan methyl ester, *N*-methyl-L-tryptophan, DL-tryptophanamide, *N*-tryptamine, tryptaphol, DL-indolelactic acid, and indole-3-acetic acid in yields ranging from 52–81%. We proposed the following mechanism for this cleavage reaction which involves ligand exchange of the indole unit for HOAc followed by reductive elimination of C_6H_5I coupled with fragmentation (eq 12).

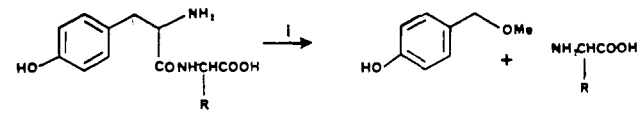


(eq.12)

X = NH_2, $NHCH_3$, OH, COOH

In this mechanism the $-NH_2$ or $-NHCH_3$ group plays the role of an electron donor center. Acylation of the primary amino group, i.e., *N*-acetyltryptophan failed to give the cleavage reaction. This suggested to us the possibility of using $C_6H_5I(OAc)_2$, KOH/CH_3OH for the specific cleavage of NH_2 terminal tryptophanyl peptide bonds. We were able to demonstrate this cleavage for L-tryptophyl-L-alanine, 68%, L-tryptophyl-L-phenylalanine, 60%, L-tryptophyl-L-leucine, 63%, L-tryptophyl-L-tryptophan, 65%.

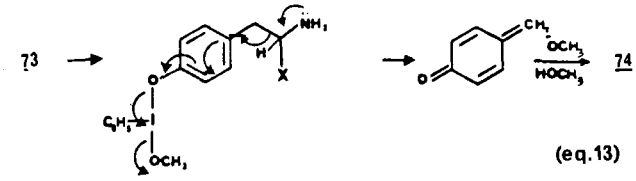
Cleavage of tyrosyl peptides (**73**) using $C_6H_5I(OAc)_2KOH–CH_3OH$ to yield *p*-(methoxymethyl)phenol (**74**) has been observed.[34]



73 **74** (52–71%)

R = H, CH_3, *p*-HO-C_6H_4, $(CH_3)_2CH$

The mechanism for this cleavage reaction is believed to be similar to the tryptophanyl case in that ligand exchange between the substituted phenol and $C_6H_5I(OAc)_2$ occurs. This triggers the fragmentation process with the primary amino group acting as an electron source (eq 13).



(eq.13)

X = CONHCHRCOOH

Again the necessity of the free amino group in the cleavage process, is demonstrated by the fact that L-alanyl-L-tyrosine does not undergo the reaction.

Conclusion

The essential lesson of this review is that introduction of hypervalent iodine into a molecule via addition of $ArI(III)X_2$ to the enolate produces a system set up for very selective nucleophilic substitution. As general as the reaction is, it may be viewed as a special example of the general phenomenon of the enhanced nucleofugacity of higher valent organo iodides (and organo bromides). Thus direct oxidation of R–I to RI(III) as well as conversion of ArI to Ar_2I^+ accomplish the same goal of allowing displacement reactions at R–I and ArI.

Our results to date indicate the essentially untapped synthetic utility of organo hypervalent iodine compounds. For example recently the interesting new class of I(V) ylides has been published.[35] Use of chiral I(III) reagents for asymmetric synthesis is an important area. Elaborating the similarities among Hg(II), Tl(III), Pb(IV), and I(III) as well as I(V), with respect to their synthetic capabilities, are areas of key interest.

Hypervalent iodine chemistry has been termed organononmetallic chemical.[2] Coupling of hypervalent iodine with group Va and VIa (15 and 16) elements leads to structures that are both organometallic and organo nonmetallic compounds. Group VIII (8–10)

(33) Moriarty, R. M.; Sultana, M. *J. Am. Chem. Soc.* **1985**, *107*, 4559.

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(36) Kutzelnigg, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 272.

(37) In this paper the periodic group notation in parentheses is in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is eliminated because of wide confusion. Groups IA and IIA become groups 1 and 2. The d-transition elements comprise groups 3 through 12, and the p-block elements comprise groups 13 through 18. (Note that the former Roman number designation is preserved in the last digit of the numbering: e.g., III → 3 and 13.)

organo ylides offer a challenging synthetic goal. Theoretical calculations on hypervalent iodine structures are possible and should yield important information about bonding.

I believe that in the future hypervalent iodine will assume a role in organic chemistry of comparable importance to boron, silicon, sulfur, selenium, and phosphorus.

We thank the Petroleum Research Fund PRF-14773-AC1 for support of this work.

Registry No. Iodine, 7553-56-2.

Hetero-Diels–Alder Reaction in Highly Functionalized Natural Product Synthesis†,[1]

RICHARD R. SCHMIDT

Fakultät Chemie, Universität Konstanz, D-7750 Konstanz, Federal Republic of Germany

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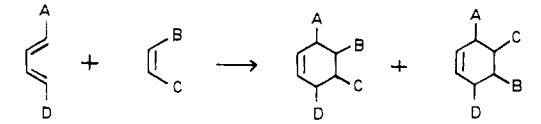
Functionally substituted dihydro- and tetrahydrofuran and -pyran structures play an important role as intermediates in syntheses of highly functionalized natural products. They are not only present in carbohydrates and related natural products, but they are also useful as chiral precursors in the synthesis of various classes of naturally occurring compounds.[2] The "chiron approach"[3] to such intermediates from carbohydrates is often lengthy and tedious because of multiple regiospecific and stereocontrolled functional group manipulations. Therefore de novo syntheses from achiral starting materials have become competitive or even superior.[4-9] Due to the nature of the target molecules a suitable method could be based on the Diels–Alder approach.[8,9]

The Diels–Alder reaction has become a powerful tool in natural product synthesis because it combines C–C bond formation with regio- and diastereoselectivity at several centers.[10] Due to supra–suprafacial reaction, polarity controlled orientation, and endo/exo selectivity of diene and dienophile, very often only one pair of enantiomers is obtained out of the maximum 32 possible isomers (Scheme I, the total number of possible isomers is reduced by each specificity by a factor of two). In addition, intramolecularity has been used extensively in support of this selectivity.[11] This selectivity can be explained in terms of frontier orbital overlap, which also differentiates the normal and inverse type Diels–Alder reaction and thus verifies the observed reactivity pattern of different diene/dienophile combinations.[12,13] Recently even enantioselectivity could be introduced successfully into the Diels–Alder reaction, leading to preferential or exclusive formation of one single stereoisomer.[14]

The incorporation of functional groups, especially electron-donating heterosubstituents, in the Diels–Alder adducts is most conveniently achieved by reactions with the corresponding electron-rich 1,3-dienes and dienophiles, respectively. The 1- and 2-monohetero- and the 1,3-diheterosubstituted 1,3-dienes have been extensively

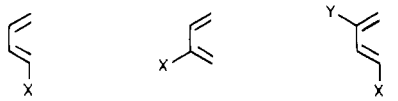
Scheme I



2^4 Stereoisomers 2^4 Stereoisomers

Nonspecific Cycloaddition	⟶	$2^1 \times 2^4 = 32$ Isomers
+ Supra-suprafacial Specificity	⟶	$2^1 \times 2^2 = 8$ Isomers
+ Regiospecificity	⟶	$2^0 \times 2^2 = 4$ Stereoisomers
+ Endo/exo-Specificity	⟶	$2^0 \times 2^1 = 2$ Stereoisomers (Racemate)
+ Enantiospecificity	⟶	$2^0 \times 2^0 = 1$ Stereoisomer

Scheme II[a]



X = OR	X = OR	X = OMe, Y = $OSiMe_3$
X = SR	X = SR	X,Y = NR_2
X = NR_2	X = NR_2	
X = N-COOR H		R = Alkyl, Acyl, $SiMe_3$

[a] References 4–7 and 10.

† This Account is dedicated to the memory of Wolfgang Abele, who contributed so much to this work.

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(2) Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, 1983.
(3) "Chiron Approach" is the transformation of easily available chiral templates into enantiomerically pure chiral synthons; see ref 2.
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Richard R. Schmidt received his Ph.D. from Stuttgart University working with Professor R. Gompper. After postdoctoral work with Professor Frank M. Huenneckens at Scripps Clinic, La Jolla (1965–1966), he became a Privat dozent at Stuttgart University 1969. In 1975 he was appointed professor of chemistry at Konstanz University. His current research interests are in glycoconjugate synthesis, cycloaddition reactions, and reactions with highly functionalized vinyllithium compounds for natural product syntheses.

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