transition moments but show no systematic relation to the charge-transfer energies, suggesting that the ligand polarization contributions to the hypersensitive intensities are predominant. Charge-transfer bands are prominent in the spectra of lanthanide and transition-metal complexes, and the relative inefficacy of the charge-transfer contributions in the f–f absorption process and their putative role for d–d transition probabilities are problems for future investigation.

It is a pleasure to thank all of my co-workers, cited in references 21–26, on the ligand polarization projects. Our investigations are supported by the U.K. Science Research Council.

Organic Syntheses via the Polybromo Ketone–Iron Carbonyl Reaction

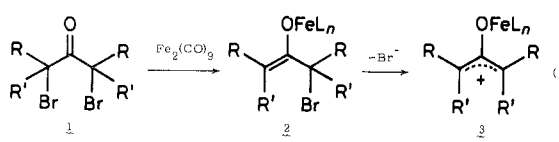
RYOJI NOYORI

Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

Received May 24, 1978

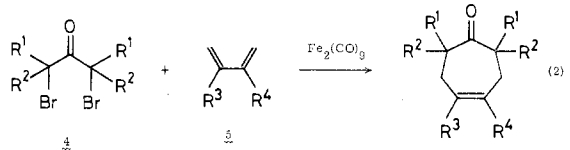
The chemistry of transition-metal carbonyls has a long history dating from the discovery by Mond in 1890 of the first metal carbonyls. These complexes have been used widely as both synthetic reagents in laboratories and catalysts of certain industrial processes, and development of significant synthetic methods via such complexes is still continuing.[1] This Account describes a new synthetic methodology using iron carbonyls which has been developed in our laboratories. Here, iron carbonyls, perhaps the most economical metal carbonyls, serve as efficient stoichiometric reducing agents.[2] These reagents are essentially neutral, and a variety of functional groups including carbonyl, ester, amide, cyano, ether linkage, etc., are tolerated under the reaction conditions.

Because there exist no general ways for preparing carbocyclic frameworks by use of bifunctional three-carbon building blocks, this work was started in hopes of generating a reactive three-carbon unit that is capable of undergoing cycloaddition across various unsaturated compounds. First, we employed a system combining α,α'-dibromo ketones and iron carbonyls, and this choice worked well.[3-5] Both mononuclear $Fe(CO)_5$ and dinuclear $Fe_2(CO)_9$ may be used, but the latter complex has stronger reducing ability. The reactive intermediates generated were found to be the enolate **2** and the oxyallyl species **3** as shown in eq 1.



Evidence for the generation of the cationic 2-oxyallyl species **3** from **1** as the product-determining intermediate was provided by nucleophilic trapping and several skeletal rearrangements.[3,4] Certain oxyallyl species suffer deprotonation, particularly in basic media such as THF or DMF, yielding α,β-unsaturated ketones. In a nonbasic or weakly nucleophilic environment, the allylic cation **3** reacts with a variety of carbon nucleophiles. It is worthwhile to point out that the presence of the central oxygen group in **3** allows the allyl cation to act as both a uni- and a bifunctional electrophile.

The 3 + 4 → 7 Cyclocoupling Reaction between Polybromo Ketones and 1,3-Dienes. Trapping of the oxyallyliron(II) species with 1,3-dienes produces seven-membered ketones directly. Thus, the reaction of the dibromo ketone **4** and an open-chain 1,3-diene, **5**, with the aid of $Fe_2(CO)_9$ in benzene at 60–70 °C gave the corresponding 4-cycloheptenone **6** in moderate to high yield (eq 2).[7,8] Both secondary (R^1 = alkyl; R^2 =



Ryoji Noyori was born in Japan in 1938. He joined the faculty at Kyoto University as an instructor, after obtaining his bachelor's and master's degrees there, and continued on to the Ph.D. at Kyoto with Hitosi Nozaki. In 1968, he moved to Nagoya University, where he is a Professor. He spent a postdoctoral year at Harvard University with E. J. Corey. His research interests are in the development of new methodologies in organic chemistry and their application to organic synthesis.

(1) Reviews: "Organic Synthesis via Metal Carbonyl", Vol. 1 and 2, I. Wender and P. Pino, Ed., Interscience, New York, N.Y., 1968 and 1977; R. F. Heck, "Organotransition Metal Chemistry", Academic Press, New York, N.Y., 1974; J. Tsuji, "Organic Synthesis by Means of Transition Metal Complexes", Springer-Verlag, Berlin and New York, 1975; J. Falbe, "Carbon Monoxide in Organic Synthesis", Springer-Verlag, Berlin and New York, 1970; M. F. Semmelhack, *Org. React.*, **19**, 115 (1972); R. Baker, *Chem. Rev.*, **73**, 487 (1973); C. W. Bird, "Transition Metal Intermediates in Organic Synthesis", Academic Press, New York, N.Y., 1967; M. Ryang, *Organometal. Chem. Rev., Sect. A*, **5**, 67 (1970); M. Ryang and M. Tsutsumi, *Synthesis*, 55 (1971); R. Noyori, "Transition Metal Organometallics in Organic Synthesis", Vol. 1, H. Alper, Ed., Academic Press, New York, N.Y., 1976, Chapter 2.

(2) Recent accounts on synthetic utility of iron carbonyl complexes: R. Pettit, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, **17**, 227 (1973); M. Rosenblum, *Acc. Chem. Res.*, **7**, 122 (1974); J. P. Collman, *ibid.*, **8**, 342 (1975); E. Weisberger and P. Laszlo, *ibid.*, **9**, 209 (1976); A. J. Birch and I. D. Jenkins, "Transition Metal Organometallics in Organic Synthesis", Vol. 1, H. Alper, Ed., Academic Press, New York, N.Y., 1976, Chapter 1.

(3) R. Noyori, Y. Hayakawa, M. Funakura, H. Takaya, S. Murai, R. Kobayashi, and S. Tsutsumi, *J. Am. Chem. Soc.*, **94**, 7202 (1972).

(4) R. Noyori, Y. Hayakawa, H. Takaya, S. Murai, R. Kobayashi, and N. Sonoda, *J. Am. Chem. Soc.*, **100**, 1759 (1978).

(5) Some of the reactions described herein have been achieved by dehalogenation agents other than iron carbonyls.[4] Particularly use of Zn/Cu couple and NaI has been extensively studied by Cookson and Hoffmann.[6]

(6) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **12**, 819 (1973).

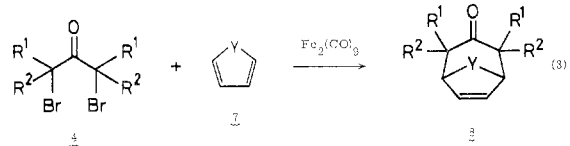
(7) R. Noyori, S. Makino, and H. Takaya, *J. Am. Chem. Soc.*, **93**, 1272 (1971).

(8) H. Takaya, S. Makino, Y. Hayakawa, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1765 (1978).

0001-4842/79/0112-0061$01.00/0

H) and tertiary dibromo ketones ($R^1 = R^2$ = alkyl) may be equally employed. As in the Diels–Alder reaction, dienes with a high equilibrium concentration of the s-cis conformer serve as efficient receptors of the bifunctional three-carbon intermediate. It should be noted that the use of diene–iron carbonyl complexes in place of the free dienes and $Fe_2(CO)_9$ results in a remarkable increase in yield of the cycloadducts. For instance, the $Fe_2(CO)_9$-promoted reaction of **4** ($R^1 = R^2 = CH_3$) and butadiene gave **6** ($R^1 = R^2 = CH_3$; $R^3 = R^4 = H$) in only 33% yield, while the reaction using 1,3-butadiene–$Fe(CO)_3$ gave the same adduct in 90% yield.

The ease with which the reaction of eq 3 occurs



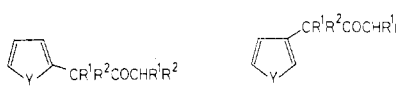
(3)

4 **7** **8**

R^1 = alkyl; R^2 = alkyl or H;
Y = CH_2, O, $NCOCH_3$, $NCOOCH_3$, etc.

depends on the nature of Y in the cyclic diene substrate **7**. The reaction of the dibromide **4** and cyclopentadiene or furan as an s-cis diene afforded bicyclic ketones (**8**, Y = CH_2 or O) in generally good yields (>80%).[5,8,9] The reaction of dibromocycloalkanones and furan gave tricyclic ketones (**9**) along with adducts of type **10**.

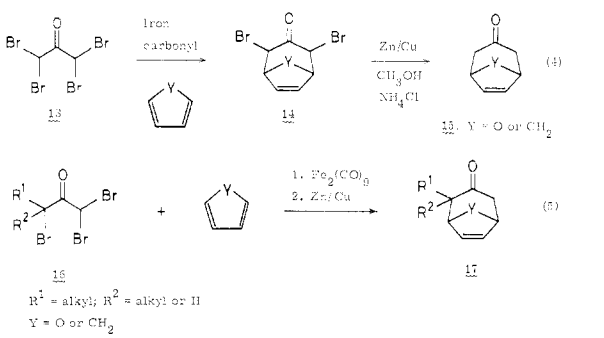
9, n = 3, 4, 5, and 6 **10**, n = 3, 4, 5, and 6



11, Y = NCH_3 or S **12**, Y = NCH_3 or S

Pyrrole derivatives having an electron-withdrawing group at the nitrogen atom gave 3 + 4 cyclocoupling adducts (**8**, Y = $NCOCH_3$, $NCOOCH_3$, etc.),[8,10] whereas *N*-methylpyrrole produced the electrophilic substitution products **11** and **12**. Thiophene also gave a mixture of the substitution products.

Unlike ordinary dibromo ketones having alkyl groups, α,α'-dibromoacetone could not be used as a source of the reactive three-carbon species. Fortunately, however, this problem could be solved by using $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone (**13**) as outlined in eq 4.[8,11] Thus, reaction of **13** and $Fe_2(CO)_9$ in furan gave the adduct **14** (Y = O) in 63% yield, and upon brief treatment with Zn/Cu couple in methanol, **14** was converted quantitatively to the desired ketone **15** (Y = O). Similarly, the $Fe(CO)_5$-aided reaction of **13** and cyclopentadiene followed by the Zn/Cu couple reduction led to the bicyclic ketone **15** (Y = CH_2).[12] Thus, **13** has proved to be synthetically equivalent to dibromoacetone in the 3 + 4 cycloaddition. This modified procedure was widely applicable, and the coupling reaction of eq 5 could be achieved by using the methyl alkyl ketone tribromide **16**.



(4)

13 **14** **15**, Y = O or CH_2

(5)

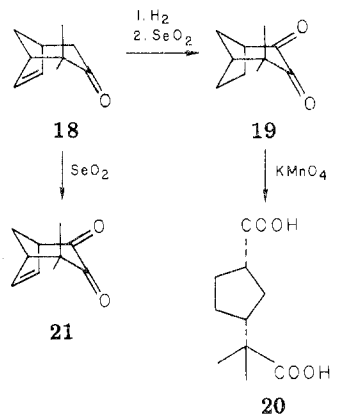
16 **17**

R^1 = alkyl; R^2 = alkyl or H
Y = O or CH_2

Regioselectivity of the 3 + 4 reaction has been discussed in terms of frontier molecular orbital theory.[13,14]

Synthetic Application of the 3 + 4 Reaction

The bicyclic ketone **18** can be prepared in high yield by the iron carbonyl promoted cyclocoupling reaction of methyl isopropyl ketone tribromide and cyclopentadiene followed by Zn/Cu couple reduction. Catalytic hydrogenation of **18** and subsequent selenium dioxide oxidation led to carbocamphenilone **19**[15] (eq 6).



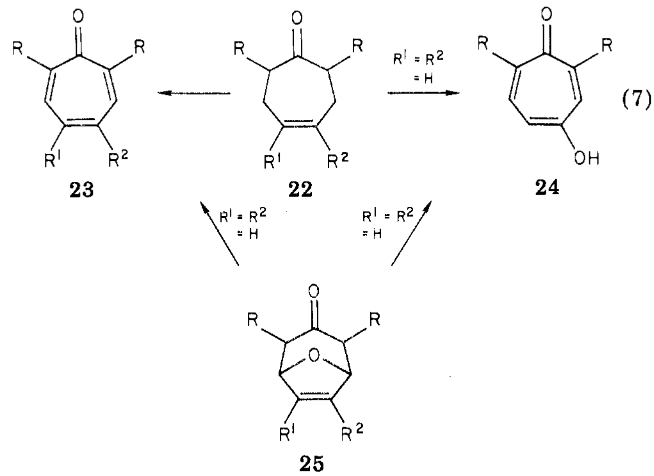
(6)

18 **19** **21** **20**

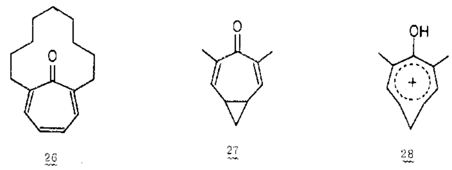
Camphenic acid (**20**) could be obtained by potassium permanganate oxidation. Treatment of the unsaturated ketone **18** with selenium dioxide afforded the 6,7-dehydro derivative of **19** (**21**), which exhibits characteristic spectral properties arising from strong homoconjugation between the olefinic and carbonyl moieties.

The 3 + 4 cycloadducts derived from secondary dibromo ketones and open-chain 1,3-dienes[7,8] appear to serve as versatile intermediates for troponoid synthesis.[7,16] The cycloheptenones of type **22** accommodated the newly formed double bond at the C-4–C-5 position and were easily transformed to the alkylated tropones **23** through a simple bromination (pyrrolidone hydrotribromide)–dehydrobromination (LiCl in DMF) procedure (eq 7). The overall yield was 45–85%. The γ-tropolone derivatives (**24**) were obtained in 45–55% yields by bromination of **22** with an excess of pyridine hydrobromide perbromide, dehydrobromination, and acid hydrolysis of the resulting 4-bromotropones (**23**,

(9) R. Noyori, Y. Baba, S. Makino, and H. Takaya, *Tetrahedron Lett.*, 1741 (1973).
(10) R. Noyori, S. Makino, Y. Baba, and Y. Hayakawa, *Tetrahedron Lett.*, 1049 (1974).
(11) R. Noyori, S. Makino, T. Okita, and Y. Hayakawa, *J. Org. Chem.*, **40**, 806 (1975).
(12) For a modified procedure, see S. A. Monti and J. M. Harless, *J. Am. Chem. Soc.*, **99**, 2690 (1977).
(13) R. Noyori, F. Shimizu, K. Fukuta, H. Takaya, and Y. Hayakawa, *J. Am. Chem. Soc.*, **99**, 5196 (1977).
(14) R. Noyori, *Ann. N.Y. Acad. Sci.*, **295**, 225 (1977).
(15) R. Noyori, T. Souchi, and Y. Hayakawa, *J. Org. Chem.*, **40**, 2681 (1975).
(16) H. Takaya, Y. Hayakawa, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1778 (1978).

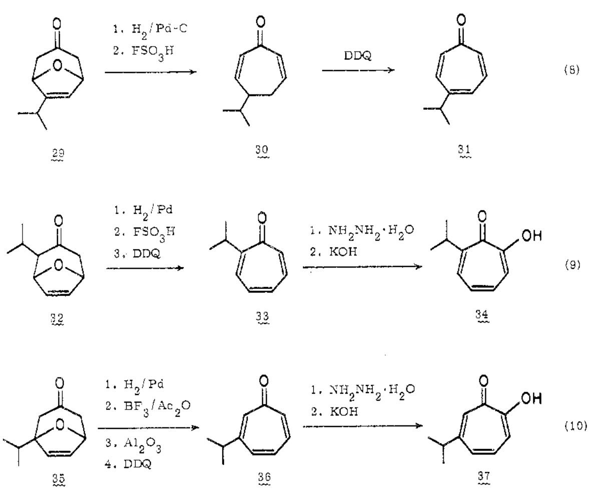


R^1 = Br; R^2 = H). In addition, the furan adducts of type **25** were also converted to the troponoids **23** and **24** by catalytic hydrogenation, acid-catalyzed carbon–oxygen bond cleavage, and aromatization.[16,17] Thus, the 2,7-bridged tropone **26** was obtained from the ketone **25** (R–R = $(CH_2)_9$; R^1 = R^2 = H).



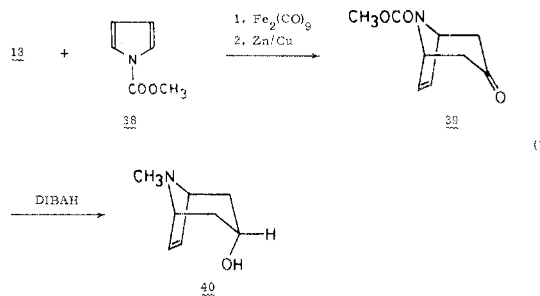
Cyclopropanation of **22** (R = CH_3; R^1 = R^2 = H) with diazomethane and a Cu(II) chelate catalyst[18] followed by bromination (Br_2) and dehydrobromination (LiBr–Li_2CO_3) led to the 4,5-homotropone **27**, a molecule having a stable *cis*-divinylcyclopropane structure.[16,19,20] This compound in concentrated H_2SO_4 exists as a hydroxyhomotropylium ion, **28**.

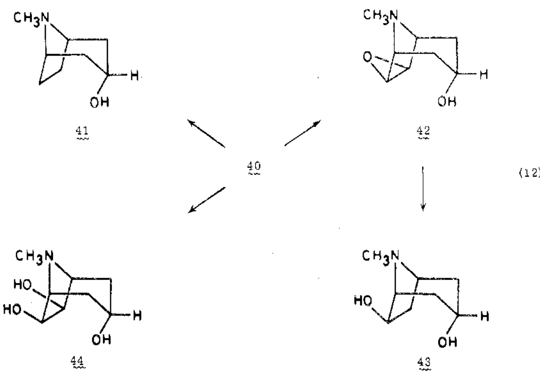
The successful use of tetrabromoacetone and tribromo derivatives of other methyl alkyl ketones as starting materials has opened a new route to various naturally occurring troponoid compounds (eq 8–10).[8,11]



Thus the bicyclic adduct **29**, obtained from tetrabromoacetone and 3-isopropylfuran, was hydrogenated and then treated with fluorosulfuric acid, giving the cross-conjugated dienone **30**. Subsequent dehydrogenation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone afforded nezukone (**31**).[16,21] In a similar fashion, 2-isopropyltropone (**33**) was obtained from the 3 + 4 adduct **32**. Its hydroxylation by the standard method produced α-thujaplicin (**34**).[11,16] β-Thujaplicin (hinokitiol, **37**) was prepared via a similar sequence involving **35** and **36** as the key intermediates.

The iron carbonyl promoted reaction of polybromo ketones and pyrrole derivatives leads directly to the tropane skeleton.[10,22,23] The cyclocoupling reaction of tetrabromoacetone (**13**) and *N*-carbomethoxypyrrole (**38**), followed by Zn/Cu couple treatment, afforded the azabicyclic ketone **39** in ~60% yield (eq 11). Reduction of **39** with diisobutylaluminum hydride at low temperature produced 6,7-dehydrotropine (**40**) having an α-hydroxyl group in high yield. This reducing agent thus can effect the desired stereoselective reduction of the carbonyl moiety[24] while leaving the carbon–carbon bond intact. As shown in eq 12, compound **40** is



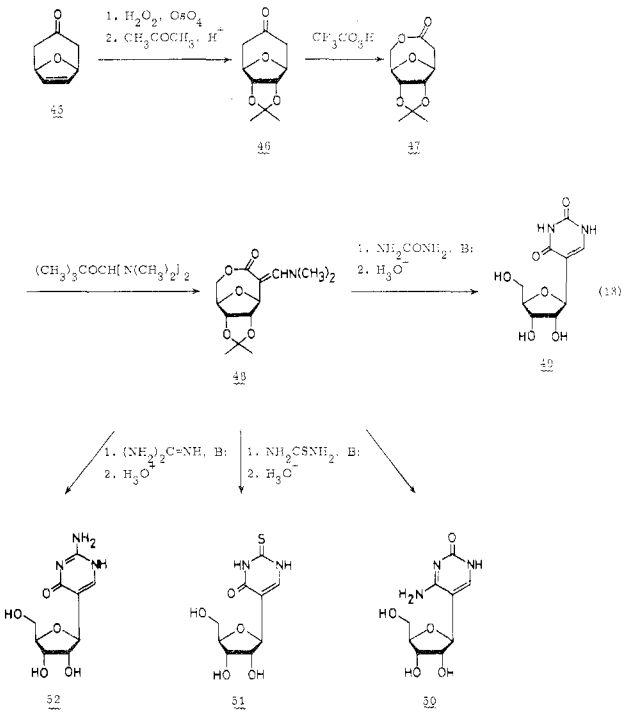


convertible through appropriate modification of the double bond to most naturally occurring tropane derivatives such as tropine (**41**), scopine (**42**), tropanediol (**43**), teloidine (**44**), etc. Since the 3 + 4 cyclocoupling reaction is applicable to a wide variety of α,α'-dibromo ketones and pyrrole derivatives,[16] this approach could be used in the synthesis of unnatural analogues as well. Thus, the present method marks the realization of a new, general synthesis of the alkaloid family.

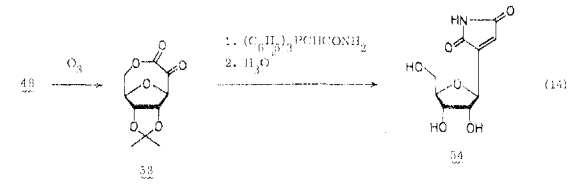
The ready availability of the oxabicyclic ketone **45** from tetrabromoacetone (**13**) and furan has provided an efficient entry to the *C*-nucleoside family,[25] a class

(17) R. Noyori, S. Makino, and H. Takaya, *Tetrahedron Lett.*, 1745 (1973).
(18) H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, *Tetrahedron*, **24**, 3655 (1968).
(19) R. Noyori, Y. Hayakawa, S. Makino, and H. Takaya, *Chem. Lett.*, 3 (1973).
(20) For the first synthesis of this skeleton, see O. L. Chapman and R. A. Fugiel, *J. Am. Chem. Soc.*, **91**, 215 (1969).
(21) Y. Hayakawa, M. Sakai, and R. Noyori, *Chem. Lett.*, 509 (1974).
(22) R. Noyori, Y. Baba, and Y. Hayakawa, *J. Am. Chem. Soc.*, **96**, 3336 (1974).
(23) Y. Hayakawa, Y. Baba, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, 100, 1786 (1978).
(24) Y. Hayakawa and R. Noyori, *Bull. Chem. Soc. Jpn.*, **47**, 2617 (1974).
(25) R. Noyori, T. Sato, and Y. Hayakawa, *J. Am. Chem. Soc.*, **100**, 2561 (1978).

of compounds that possess important antibiotic properties as well as potent anticancer and antiviral activities (eq 13).[26] First, the unsaturated ketone **45** was converted with perfect stereoselectivity to the acetonide **46** having α stereochemistry (65%). Baeyer–Villiger oxidation with peroxytrifluoroacetic acid afforded the lactone **47** in 92% yield (eq 13). The key



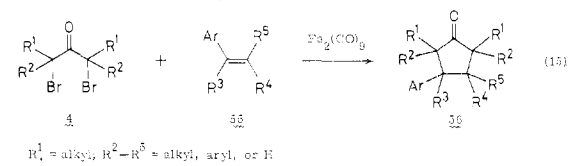
compound **47** thus obtained has an adequate *C*-β-glycoside structure and serves as a precursor of various natural and unnatural *C*-nucleosides. Its optical resolution to a form having proper absolute configuration was accomplished through hydrolysis, resolution via the cinchonidine salt, and relactonization. Reaction of the lactone **47** with bis(dimethylamino)-*tert*-butoxymethane gave **48** (64%), a common intermediate for the synthesis of pyrimidine *C*-nucleosides. Thus, condensation of **48** with urea in ethanolic sodium ethoxide, followed by removal of the glycol protective group, afforded pseudouridine (**49**; 60%). In addition, pseudouridine acetonide can be converted to pseudocytidine (**50**) through a stereocontrolled, standard method.[27] The base-catalyzed cyclization of **48** with thiourea and subsequent acid hydrolysis produced 2-thiopseudouridine (**51**; 60%). In a similar fashion, exposure of **48** to guanidine under basic conditions followed by removal of the protective group gave pseudoisocytidine (**52**), a chemotherapeutically active synthetic *C*-nucleoside,[28] in 70% yield. Furthermore, ozonolysis of **48**, followed by the Wittig reaction of the resulting keto lactone **53** with $(C_6H_5)_3PCHCONH_2$ and treatment with 50% trifluoroacetic acid, gave rise to showdomycin (**54**) in 32% yield (eq 14). The keto lactone **53** was also derived from **47** via aldol condensation with furfural followed by ozonolysis.[29]



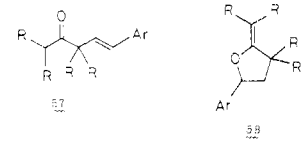
Most of the synthetic approaches presented so far are based on introduction of a heterocyclic nucleus into the C-1 position of the ribose skeleton.[26] Because such methods do not allow strict control of stereochemistry, they give a mixture of α and β epimers. In the present approach, on the other hand, the use of the rigid bicyclic system results in efficient stereochemical control throughout the overall transformation that consists of assembly of the ribose moiety and elaboration of the heterocyclic nuclei having β configuration at the anomeric center.

The 3 + 2 → 5 Cyclocoupling Reaction between α,α'-Dibromo Ketones and Olefinic Substrates. The cycloaddition of allylic moieties and olefinic substrates seems a promising method for construction of cyclopentane structures. Indeed, reaction of the 2-oxyallyl species (**3**) and certain olefins gives rise to five-membered ketones. Since concerted cycloaddition of an allyl cation and an olefin is classified as an orbital-symmetry forbidden process, this reaction is considered to proceed in a stepwise fashion. Regioselectivity was found to be controlled by the stability of the zwitterionic intermediates.[13,14]

The $Fe_2(CO)_9$ aided reaction of dibromo ketones (**4**) and aromatic olefins (**55**) in benzene at 50–60 °C gave the corresponding 3-arylcyclopentanones (**56**) in fair to good yields (eq 15).[30,31] As byproducts, open-chain 1:1



adducts of type **57** were formed via electrophilic olefinic



substitution of oxyallyls. In certain cases, 2-alkylidenetetrahydrofurans (**58**) were obtained as well. In order to achieve smooth reaction, placement of a carbocation-stabilizing group at the arylated olefinic carbon or in the aromatic ring is favorable. In general, reaction of tertiary dibromo ketones (**4**, $R^1 = R^2$ = alkyl) goes rather sluggishly compared with secondary dibromo ketones (**4**, R^1 = alkyl; R^2 = H). Tetrabromoacetone (**13**) could not be used under standard conditions. An experiment using **59** and *cis*-β-deuteriostyrene (**60**) demonstrated that the 3 + 2 reaction, giving **61**, proceeds in a stereospecific fashion, whereas

(26) Reviews: R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, pp 354–404; G. D. Daves, Jr., and C. C. Cheng, *Prog. Med. Chem.*, **13**, 30 (1976); S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biol.*, **33**, 111 (1976).

(27) A. M. Michelson and W. E. Cohn, *Biochemistry*, 1, 490 (1962).

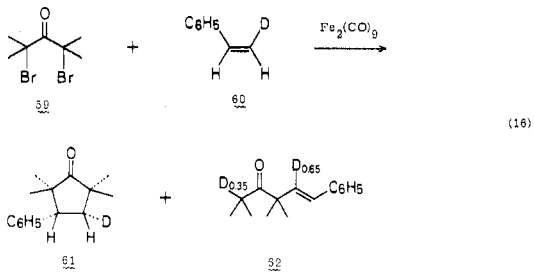
(28) J. H. Burchenal, K. Ciovacco, K. Kalaher, T. O'Toole, R. Kiefner, M. D. Dowling, C. K. Chu, K. A. Watanabe, I. Wempen, and J. J. Fox, *Cancer Res.*, **36**, 1520 (1976).

(29) T. Sato, R. Ito, Y. Hayakawa, and R. Noyori, *Tetrahedron Lett.*, 1829 (1978).

(30) R. Noyori, K. Yokoyama, and Y. Hayakawa, *J. Am. Chem. Soc.*, **95**, 2722 (1973).

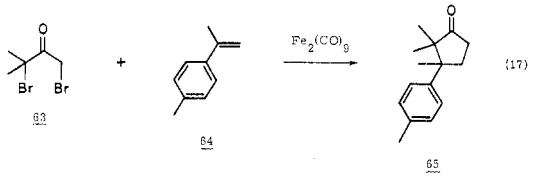
(31) Y. Hayakawa, K. Yokoyama, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1791 (1978).

the substitutive addition, giving **62**, goes in a nonstereospecific manner[32] (eq 16).



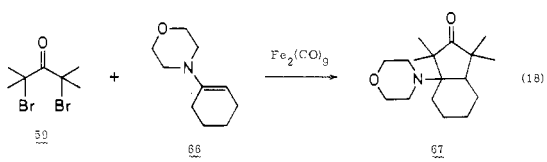
(16)

The regioselective 3 + 2 reaction was applied to the single-step synthesis of a cuparene-type terpene. Thus, the reaction of the dibromo ketone **63** and olefin **64** with the aid of $Fe_2(CO)_9$ gave directly α-cuparenone (**65**; eq 17).[33]



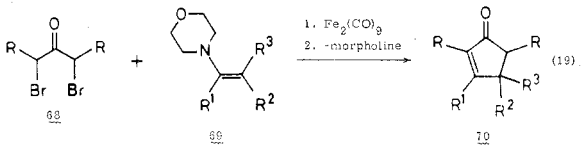
(17)

Reaction of $Fe_2(CO)_9$ and dibromo ketone **59** in the presence of the enamine **66** (benzene, 30 °C) afforded the morpholinocyclopentanone **67** in 87% yield (eq 18).



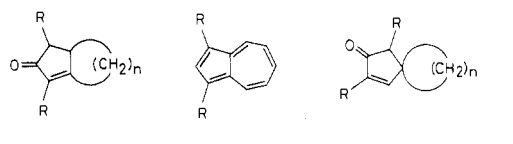
(18)

The adducts derived from secondary dibromo ketones (**68**) and enamines of type **69** can eliminate morpholine easily, and this reaction provides a new, single-pot procedure for the preparation of cyclopentenones (**70**) (eq 19). The 3 + 2 cyclocoupling proceeds in high yield



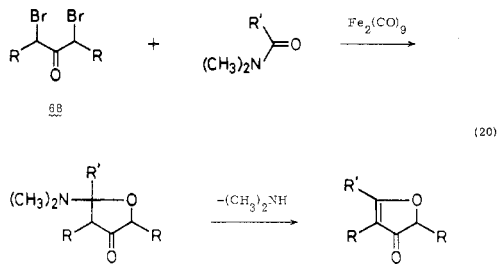
(19)

and has wide applicability.[34-36] A variety of bicyclo[*n*.3.0]alkenones (**71**) were prepared using the annelation of cyclic ketone enamines. Bicyclic ketones, 7/5-fused, are potential intermediates for the synthesis of azulenes (**72**). Another example is direct spiro annelation: in general, the reaction of **68** and enamines obtained from cycloalkanecarboxaldehydes and morpholine gave spiro[4.*n*]alkenones (**73**) in good yields. However, the advantages of the 3 + 2 reaction may be offset to some extent by the incapability of preparing α-unsubstituted cyclopentenones.



The 3 + 2 reaction using simple alkenes such as isobutylene as the substrate proceeds with difficulty. In certain cases, ene-type reaction of the oxyallyl intermediate becomes the major reaction pathway.[37]

The Hetero 3 + 2 Cyclocoupling Reaction between α,α'-Dibromo Ketones and *N,N*-Dimethylcarboxamides. Reduction of secondary dibromo ketones (**68**) with $Fe_2(CO)_9$ in DMF at 20–25 °C gave labile products of type **74** (R′ = H) which readily eliminated dimethylamine, affording 3(2*H*)-furanone derivatives (**75**) in fair to high yields (eq 20).[5,38,39] The

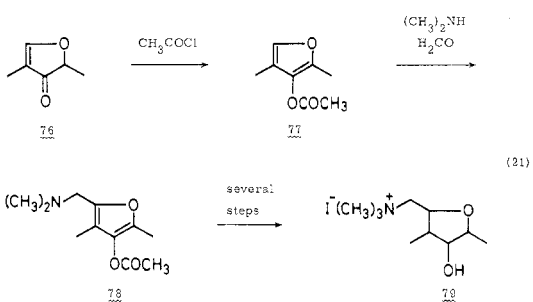


(20)

R = alkyl; R′ = H, alkyl, or aryl

overall transformation can be viewed as the construction of a carbon–oxygen bridge between α and α' positions of the parent dialkyl ketones. In place of DMF, *N,N*-dimethylacetamide or *N,N*-dimethylbenzamide may be used as the receptor. In addition, *N*-methylpyrrolidone, a lactam, may be employed as well. This reaction is classified as a hetero 3 + 2 → 5 reaction and is interpreted as a stepwise cycloaddition of a reactive 2-oxyallyliron(II) species across the carbon–oxygen double bond of carboxamides.

3(2*H*)-Furanones thus prepared are structurally related to muscarine alkaloids. In fact, 4-methylmuscarine iodide (**79**) could be obtained from the furanone **76** as outlined in eq 21. Here, the Mannich



(21)

reaction was used for the introduction of a dimethylaminomethyl group to the furan ring (**77** → **78**).

Conclusion

The discovery of the iron carbonyl promoted 3 + 2 and 3 + 4 annulations has enabled us to make a wide range of organic frameworks which are of theoretical

(32) Y. Hayakawa, K. Yokoyama, and R. Noyori, *Tetrahedron Lett.*, 4347 (1976).
(33) Y. Hayakawa, F. Shimizu, and R. Noyori, *Tetrahedron Lett.*, 993 (1978).
(34) R. Noyori, K. Yokoyama, S. Makino, and Y. Hayakawa, *J. Am. Chem. Soc.*, **94**, 1772 (1972).
(35) Y. Hayakawa, K. Yokoyama, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1799 (1978).
(36) For the detailed procedure, see R. Noyori, K. Yokoyama, and Y. Hayakawa, *Org. Syn.*, in press.
(37) R. Noyori, F. Shimizu, and Y. Hayakawa, *Tetrahedron Lett.*, 2091 (1978).
(38) R. Noyori, Y. Hayakawa, S. Makino, N. Hayakawa, and H. Takaya, *J. Am. Chem. Soc.*, **95**, 4103 (1973).
(39) Y. Hayakawa, H. Takaya, S. Makino, N. Hayakawa, and R. Noyori, *Bull. Chem. Soc. Jpn.*, **50**, 1990 (1977).

or practical importance. The examples described above may sufficiently display the general utility of this method but may still constitute only a part of bountiful harvest which will ultimately be yielded.[40]

This Account is based on the sustained intellectual and experimental efforts of my co-workers at Nagoya University: Y. Hayakawa, H. Takaya, S. Makino, K. Yokoyama, M. Sakai, R. Ito, T. Sato, F. Shimizu, K. Fukuta, T. Souchi, N. Hayakawa, Y. Baba, M. Funakura, and T. Okita. The mechanistic study has been done in collaboration with my colleagues of Osaka University: Professors S. Tsutsumi and N. Sonoda, Dr. S. Murai, and Mr. R. Kobayashi. This work was supported financially by the Ministry of Education of the Japanese Government, the Matsunaga Science Foundation, the Takeda Science Foundation, the Foundation for the Promotion of Research on Medicinal Resources, the Nitoh Research Grant, and the Asahi Science Research Grant.

(40) Recently synthesis of nonactic acid using the 3 + 4 reaction in the key step was reported: M. J. Arco, M. H. Trammell, and J. D. White, *J. Org. Chem.*, **41**, 2075 (1976).

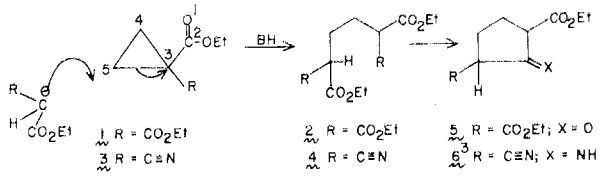
Electrophilic Cyclopropanes in Organic Synthesis

SAMUEL DANISHEFSKY

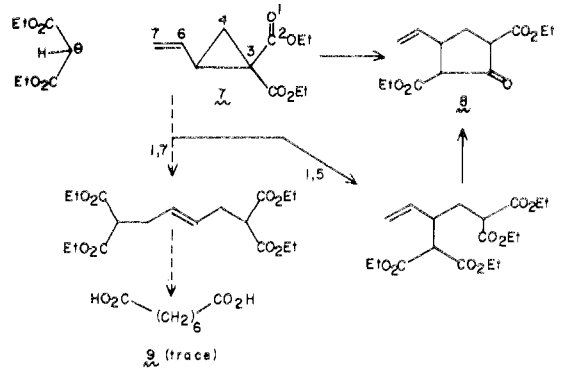
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received February 9, 1978

The formulation of the homologous (or 1,5) version of the classical Michael reaction is due to Bone and Perkin.[1] The reaction of cyclopropane **1** with diethyl malonate in the presence of sodium ethoxide gave tetraester **2** in "ca. 50% yield". Best and Thorpe[2] found



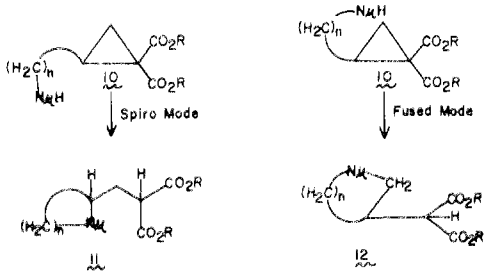
that the reaction of **3** and ethyl cyanoacetate in the presence of sodium ethoxide affords **6**[3] via cyclization (and decarbethoxylation) and **4**. Linstead and coworkers[4] studied ring-opening processes of the vinyl analogue **7**. The major product of its reaction with



diethyl malonate was shown to be **8**.[4] Minor competition from the vinylogously related 1,7-mode of opening was inferred by the eventual isolation of trace amounts of suberic acid (**9**) upon suitable treatment of the "tetraester" portion of the reaction mixture. Also, Linstead demonstrated that the original Bone and Perkin tetraester **2** suffers cyclization–decarbethoxylation to afford **5**.

Our own involvement in this area can be described along the following lines. Twelve years ago Robert Cavanaugh began a study of the homologous Michael reaction.[5] His purpose was to gain more information on the range of nucleophiles[6] which might be employed and to clarify the issue of 1,5- vs. 1,7-additions[7] in the opening of activated vinylcyclopropanes. George Rovnyak[7,8] determined that 1,5-addition occurs with clean inversion of configuration[9] and examined the effect of alkyl substitution on the direction of ring openings of activated cyclopropanes.[10,11]

From this basis, John Dynak investigated the effects of intramolecularity on the facility of ring opening.[12] In particular, Dynak studied the relative preponderance of the *spiro* (cf. **11**) vs. the *fused* (cf. **12**) mode of in-



Samuel Danishefsky received his B.S. degree from Yeshiva University. His graduate training was taken at Harvard University, leading to a Ph.D. degree in 1962. After an NIH Postdoctoral Fellowship at Columbia University, he joined the faculty at the University of Pittsburgh, where he is now Professor of Chemistry. His research interests have been directed toward the synthesis of natural products and the development of new synthetic processes pursuant to these objectives.

(1) W. A. Bone and W. H. Perkin, *J. Chem. Soc.*, **67**, 108 (1895).
(2) R. Best and J. F. Thorpe, *J. Chem. Soc.*, 685 (1909).
(3) While we have not reinvestigated this reaction, more current notions of tautomerism would suggest an enamine, rather than imine formulation.
(4) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610, 3616 (1952).
(5) R. Cavanaugh, Ph.D. Thesis, University of Pittsburgh, 1968.
(6) J. E. Dolfini, K. Menich, P. Corliss, R. Cavanaugh, and S. Danishefsky, *Tetrahedron Lett.*, 4421 (1966).
(7) S. Danishefsky, G. Rovnyak, and R. Cavanaugh, *Chem. Commun.*, 636 (1969).
(8) G. Rovnyak, Ph.D. Thesis, University of Pittsburgh (1970).
(9) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 821 (1972).
(10) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 820 (1972).
(11) S. Danishefsky and G. Rovnyak, *J. Org. Chem.*, **40**, 114 (1975).
(12) J. Dynak, Ph.D. Thesis, University of Pittsburgh, 1975.

0001-4842/79/0112-0066$01.00/0