Tetrahedron Vol. 41, No. 24, pp. 5879 to 5886, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

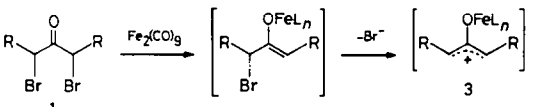
NATURAL PRODUCT SYNTHESIS VIA THE POLYBROMO KETONE–IRON CARBONYL REACTION

R. NOYORI* and Y. HAYAKAWA
Department of Chemistry and Chemical Instrument Center, Nagoya University, Chikusa, Nagoya 464, Japan

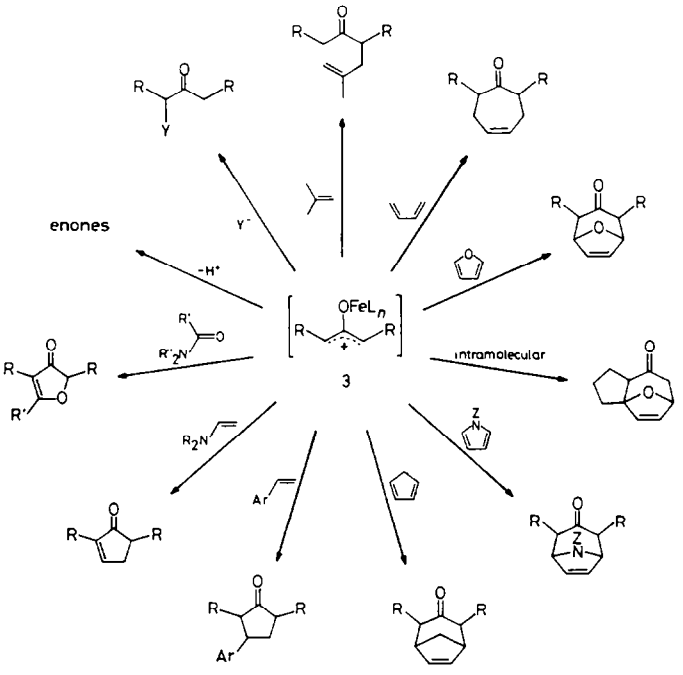
(*Received in USA* 11 *May* 1984)

Abstract—Application of the polybromo ketone–iron carbonyl reaction to natural product synthesis is summarized. The general synthesis of tropane alkaloids has been achieved via the reductive [3+4] cyclocoupling of *sym*-tetrabromoacetone with N-methoxycarbonylpyrrole as the key step. Ready availability of 8-oxabicyclo[3.2.1]oct-6-en-3-one from the tetrabromoacetone and furan has opened a new, efficient entry to natural C-nucleosides including pseudouridine, pseudocytidine, and showdomycin. The artificial analogues such as 2-thiopseudouridine, 6-azapseudouridine, pseudoisocytidine, etc., are also obtainable. The oxabicyclic ketones bearing an isopropyl substituent at the appropriate position serve as intermediates for the synthesis of naturally occurring troponoids, nezukone, α-thujaplicin, and hinokitiol (β-thujaplicin). Carbocamphenilone and camphenic acid have been prepared through the [3+4] reaction of 1,1,3-tribromo-3-methylbutan-2-one and cyclopentadiene. The [3+2] cyclocondensation of an α,α'-dibromo ketone and a styrene derivative leads to the single-step synthesis of α-cuparenone. 1,3-Dibromo-3,7-dimethyloct-6-en-2-one derived from nerol (or geraniol) undergoes the biogenetic-type double cyclization. The iron carbonyl-assisted intramolecular [3+2] cyclocoupling gives camphor accompanied by other monoterpenic ketones. A mixture of campherenone and epicampherenone has been obtained from related dibromo ketone prepared from farnesols. The hetero [3+2] reaction by use of dibromo ketones and N,N-dimethylcarboxamides, forming 3 (2H)-furanones, is employable for the preparation of muscarine alkaloid derivatives.

The chemistry of transition-metal carbonyls originates from the discovery of nickel carbonyl by Mond in 1890. During the next one hundred years, there have been elaborated numerous complexes having versatile reactivity applicable both as catalysts and as stoichiometric reagents to a wide range of organic syntheses; for example, activation or protection of unsaturated compounds, isomerization of dienic substrates, fixation of unstable molecules such as cyclobutadienes[1] and carbenes,[2] carbonylation, etc.[3] Additional utility of such neutral metal carbonyls arises from the high reducibility or nucleophilicity based on the low oxidation states of the central metal atoms. Here, the reduction generally requires the stoichiometric use of reagents, and therefore iron carbonyls, perhaps the lowest-cost metal carbonyls, may be among the most conveniently employable for this purpose. In fact, the reduction with iron carbonyls has been frequently applied as the key process to a number of organic syntheses.[4] The successful preparation of trimethylenemethane–iron carbonyl complex by the $Fe_2(CO)_9$-reduction of 1,3-dichloro-2-methylenepropane[5] incited us to examine the reduction of α,α'-dibromo ketones (oxo analogues of the dihalo olefin) with iron carbonyls in hopes of generating a new reactive species usable for organic syntheses. The mechanistic investigation has provided many lines of evidence for the reduction initiated by two-electron reduction of the dibromo ketone **1** (directly or via oxidative addition of the C–Br bond) to give the enolate **2**, which then eliminates the allylic bromine atom to produce the oxyallyl–iron(II) complex **3**.[6] The reaction proceeds smoothly even in hydrocarbon solvents. Usually, both mononuclear $Fe(CO)_5$ and dinuclear $Fe_2(CO)_9$ may be used for the reduction, but



the latter is of general use. The unique reactivity of this new type of allylic dipolar species, acting as both a uni- and bifunctional three-carbon electrophile, relies heavily on the presence of the central oxygen group. Particularly noteworthy is the endowment of electrophilic character to a carbon α to the original keto group. Thus the parent ketones can be functionalized in a variety of ways in a nonbasic environment. Scheme 1 illustrates various kinds of valuable reactions.[7] Among all, the most important property is the capability of undergoing the cycloaddition with a variety of unsaturated substrates.[7] For instance, **3** underwent [3+4] cycloaddition with open-chain dienes producing substituted 4-cycloheptenones.[8,9] In addition, the cycloaddition with cyclic dienes including cyclopentadiene[8,10] and hetero aromatics such as pyrroles[8,11] and furans[8,12] gives bridged ketone systems. The [3+4] annulation is classified as the symmetry-allowed [$_\pi 2 + _\pi 4$] process related to well-known Diels–Alder reaction. The reaction with furans proceeds by a concerted process with the regioselectivity controlled by the frontier molecular orbitals of the two reactants.[13] Behavior of the C_3 unit in cycloaddition is reminiscent of reactivities of some highly electron-deficient olefins such as tetracyanoethylene. The oxyallyl cations react with not only dienes but also certain olefins in a [3+2] manner, producing five-membered ketones.[14,15] The symmetry-forbidden reaction occurs in a stepwise



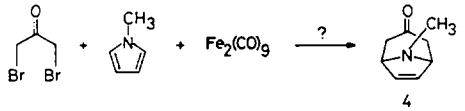
Scheme 1.

fashion, where regioselectivity is determined by the relative stability of the zwitterionic intermediates.[13] The hetero [3+2] cycloadditions are also possible with some substrates possessing a C=X bond (X = hetero atom).[16]

The discovery of the iron carbonyl-promoted [3+2] and [3+4] annulations has enabled us to make a wide range of organic frameworks. This paper will survey the application to the synthesis of a variety of naturally occurring products.

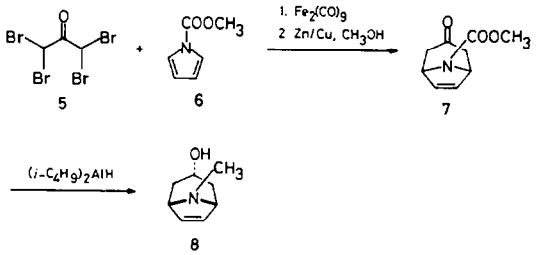
Alkaloids

Of synthetical importance is the presence of an olefinic bond in the [3+4] adducts which serves as a key for the further functionalization. The utility of the [3+4] reaction was displayed by realization of a general synthesis of tropane alkaloids having an 8-azabicyclo[3.2.1]octane system.[17] What appeared to be solved in the original synthetic design outlined below were: (1) incapability of dibromoacetone of generating the oxyallyl species,[6] (2) predominant aromatic rather than dienic character of N-methylpyrrole which results in electrophilic substitution instead of the desired cycloaddition,[8,12] and (3) instability of **4** under the reaction conditions. These

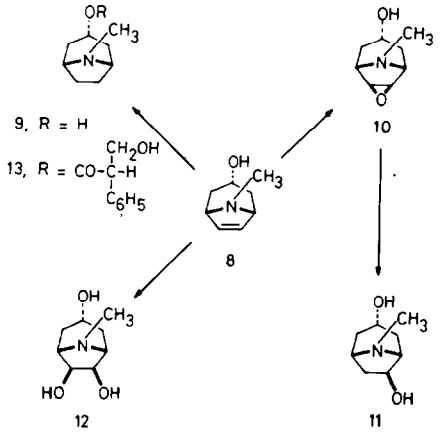


4

problems were overcome simply by replacing dibromoacetone by *sym*-tetrabromoacetone (**5**)[8] and N-methylpyrrole by N-methoxycarbonylpyrrole (**6**).[8,12] The electron-accepting alkoxycarbonyl group increases the diene character in the starting pyrrole derivative and the stability of the [3+4] adducts. Thus, when **5** was treated with $Fe_2(CO)_9$ in the presence of **6** followed by Zn/Cu couple in methanol, the azabicyclic ketone **7** was obtained in 57% yield. Reduction of **7** with diisobutylaluminum hydride gave stereoselectively 6,7-dehydrotropine (**8**) having the natural α-hydroxyl

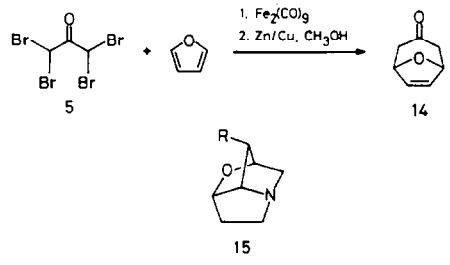


function in 92% yield ($\alpha/\beta = 93:7$).[18] The carbamate moiety was reduced to N-methyl at the same time. The alcohol **8** is convertible through appropriate reductive or oxidative modification of the double bond to most naturally occurring tropane alkaloids such as tropine (**9**), scopine (**10**), tropanediol (**11**), teloidine (**12**), etc.[19]



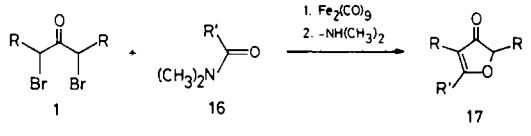
(−)-Hyosciamine (**13**) was prepared via esterification of **8** with (−)-O-acetyltropyl chloride followed by deacetylation with hydrochloric acid and catalytic hydrogenation over Pd/C.

The [3+4] cyclocondensation allows easy synthesis of the oxabicyclic ketone **14** from **5** and furan (63% yield).[8] The basic skeleton of lolium alkaloids (**15**) has been constructed from it.[20]



5 14 15

Iron carbonyls effect reductive coupling of α,α'-dibromo ketones and carboxamides of type **16**. The hetero [3+2] annulation involving the C=O linkage followed by elimination of dialkylamines gives 3 (2H)-furanones of type **17**.[16] An analogue of muscarine



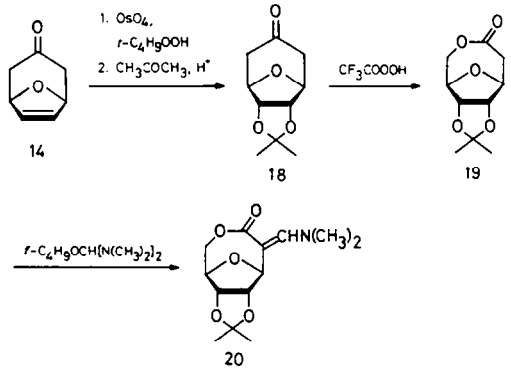
1 16 17

alkaloids was prepared from 2,4-dibromopentan-3-one and DMF by way of **17** (R = CH_3, R' = H).[16]

C-Nucleosides

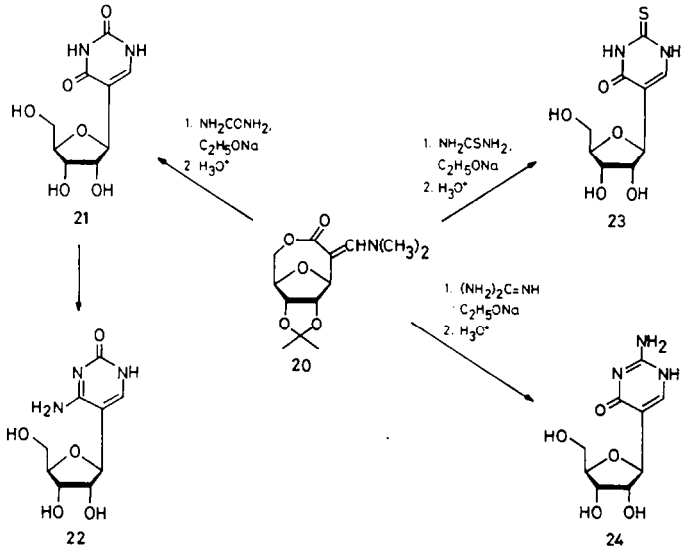
C-Nucleosides possess a multitude of biological properties such as antibiotic as well as anticancer and antiviral activities,[21] and the chemical synthesis is a subject of current interest. Creation of the four contiguous chiral centers in the ribose skeleton and control of the C-1' stereochemistry are the major challenges issued to the approach starting from non-carbohydrate precursors. The successful use of *sym*-tetrabromoacetone as a C_3 unit in the iron carbonyl-aided [3+4] cyclocoupling process has opened a new route to such compounds.[22,23]

Our synthesis starts with the readily available oxabicyclic ketone **14**. When **14** was subjected to osmium tetraoxide-catalyzed dihydration using t-butyl hydroperoxide[24] followed by acetonidation, the oxygen functions were introduced to the double bond solely from the less hindered side to give the acetonide **18** as a single isomer in 68% yield. Subsequent Baeyer–Villiger oxidation of **18** with trifluoroperacetic acid[25] afforded in 81% yield the key compound **19** possessing an adequate C-β-glycoside structure. The optically pure lactone was obtained through methanolysis of racemic **19** to the seco acid, its optical resolution by the Pirkle's method,[26] and then relactonization. Reaction of the optically active lactone D-**19** with bis(dimethylamino)-t-butoxymethane[27] produced the α-dimethylaminomethylene lactone D-**20**, a common synthetic intermediate for pyrimidine C-nucleosides, in 91% yield. Exposure of D-**20** to urea in the presence of ethanolic sodium ethoxide, followed by removal of the glycol protective group with an acid furnished



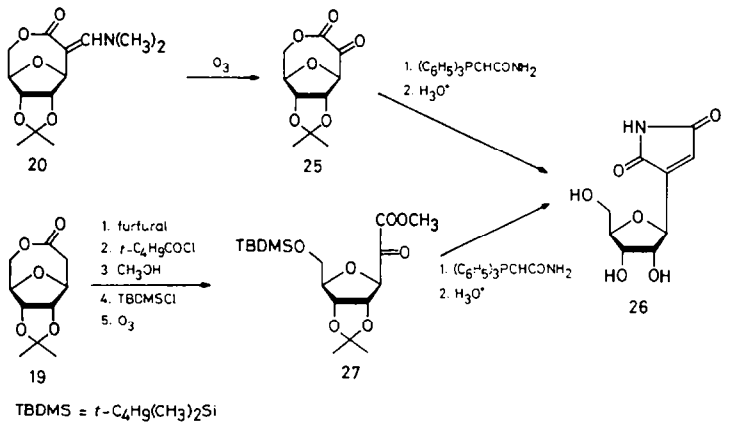
14 18 19 20

naturally occurring pseudouridine (**21**) in 60% yield. In addition, pseudouridine acetonide is convertible to pseudocytidine (**22**),[28] another natural product, and 6-azapseudouridine,[29] an artificial analogue. When D-**20** was treated with thiourea under the basic conditions and then with an acid, 2-thiopseudouridine (**23**) was produced in 60% yield. In a similar fashion, the base-assisted condensation of D-**20** with guanidine and the subsequent acid hydrolysis formed pseudoisocytidine (**24**), a chemotherapeutically significant synthetic C-nucleoside, in 70% yield.



21 22 23 20 24

Showdomycin (**26**), a natural maleimide C-nucleoside, was synthesized through D-**19** or D-**20** in two different ways. Ozonolysis of D-**20** followed by reductive workup with dimethyl sulfide gave the α-keto lactone, D-**25**. Its Wittig olefination with $(C_6H_5)_3P$-$CHCONH_2$, causing simultaneous ring closure to give a maleimide structure, followed by deprotection by acid treatment afforded the C-nucleoside **26** in 30% overall yield.[22] Another synthesis of **26** via D-**19** was achieved through the sequence which involves (1) aldol reaction with furfural followed by dehydration using pivaloyl chloride, yielding the corresponding α-furfurylidene lactone, (2) methanolysis of the lactone, (3) t-butyldimethylsilylation of the 5'-hydroxyl of the resulting ribosyl derivative, (4) ozonolysis giving D-**27**, (5) the Wittig condensation using $(C_5H_5)_3PCHCONH_2$, and (6) deprotection by acid hydrolysis.[30]

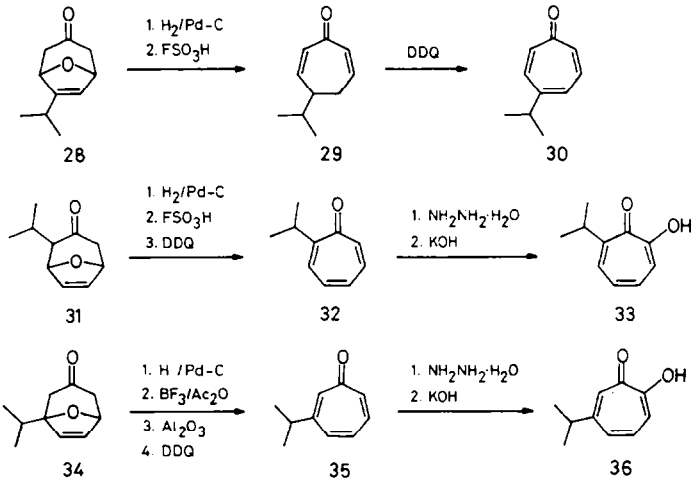


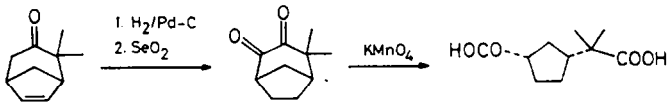
Thus, the highly chiral C-nucleosides were prepared expeditiously from simple, achiral materials, acetone and furan. The salient feature of this total synthesis is use of the rigid bicyclic system, resulting in preservation of the natural stereochemical integrity at the C-1' position of the ribose skeleton throughout the overall transformation. Most synthetic approaches presented so far are based on introduction of the heterocyclic base into the ribose aomeric center, and does not allow strict stereochemical control.[31] Furthermore, since the key [3+4] cyclocondensation is applicable to a wide range of polybromo ketones and furans, this approach is capable of preparing various kinds of artificial C-nucleoside analogues, particularly those with unnatural carbohydrates possessing alkyl or hydroxyalkyl substituents at the appropriate positions.[32] Homo-C-nucleosides were also obtained by similar synthetic operations.[33]

Terpenes

The new cyclocoupling was further applied to the syntheses of terpenoids and related compounds. An example is the synthesis of naturally occurring troponoids achieved via sequence of simple reactions starting from [3+4] adducts of the polybromo ketones and furan derivatives.[34] Thus, nezukone (**30**) was conveniently prepared using **28** as the starting material, obtainable from *sym*-tetrabromoacetone and 3-isopropylfuran, through its hydrogenation on Pd/C, dehydration with fluorosulfonic acid, giving the cross conjugated dienone **29**, and then dehydrogenation using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[34,35] In a similar fashion, the bicyclic adduct **31** was converted to 2-isopropyltropone (**32**), and its α-hydroxylation according to the standard method, viz., α-amination with hydrazine hydrate followed by basic hydrolysis, produced α-thujaplicin (**33**).[34,36] Hinokitiol (β-thujaplicin) (**36**) was also synthesized via similar reaction sequence involving **34** and **35** as the key intermediates.[34,36]

The product **37**, derived from methyl isopropyl

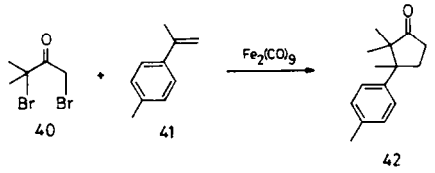




37 38 39

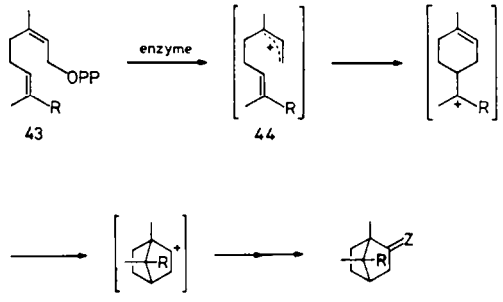
ketone tribromide and cyclopentadiene, was employed for the synthesis of (±)-carbocamphenilone (**38**).[10] Thus, catalytic hydrogenation of **37** and the subsequent selenium dioxide oxidation afforded **38** in 80% overall yield. Potassium permanganate oxidation of **38** led to (±)-camphenic acid (**39**).[37]

α,α'-Dibromo ketones underwent the [3+2] cyclocoupling with aromatic olefins, producing 3-arylated cyclopentanones.[14] The regioselective reaction of unsymmetrically substituted dibromides allowed the single-step synthesis of a cuparane-type sesquiterpene. Thus, (±)-α-cuparenone (**42**) was directly prepared though in 18% yield by the reaction of the dibromide **40** and the olefin **41** with the aid of $Fe_2(CO)_9$.[38]



40 41 42

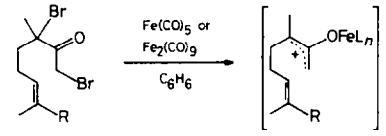
Terpenes bearing a bicyclo[2.2.1]heptane skeleton like **45** are conceived to be biosynthesized by the double cyclization of the allylic cation **44** generated from the pyrophosphate **43**. The iron carbonyl-promoted



43 44

45, Z = H, OH, or O

intramolecular [3+2] process provided a chemical analogue of this bioconversion.[39] When the C_{10} dibromo ketone **46** was reduced with $Fe_2(CO)_9$, (±)-camphor (**47**) among other minor monoterpenic ketones was obtained in 38% yield. Here, besides the oxygen atom, the methyl substituents are crucially important for the oxyallyl intermediate to undergo the double cyclization.[39,40] In a similar manner, the reduction of the C_{15} analogue **48** with $Fe(CO)_5$ gave (±)-campherenone (**49**) accompanied by (±)-epicampherenone (**50**) (**49**/**50** = 2:1 ratio) in 58% combined yield. The reaction using the geometrical isomer, (*Z*)-**48**, afforded a 1:2 mixture of **49** and **50** in 38% yield.[39]

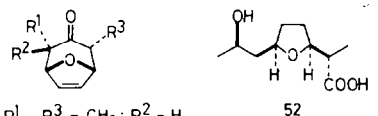


46, R = CH_3
48, R = $CH_2CH_2CH{=}C(CH_3)_2$

47, $R^1 = R^2 = CH_3$
49, $R^1 = CH_3$; $R^2 = CH_2CH_2CH{=}C(CH_3)_2$
50, $R^1 = CH_2CH_2CH{=}C(CH_3)_2$; $R^2 = CH_3$

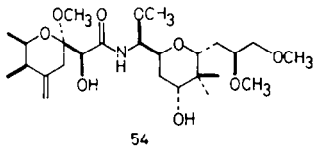
Others

There have been also achieved syntheses of other natural products and their analogues via the [3+4] reaction of the polybromo ketones and furan as the key step. (±)-Nonactic acid (**52**) was synthesized[41] through **51**.[8] The ketone **53**[8] served for the construction of the right-half block of (±)-pederin (**54**).[42] Preparation of a thromboxane A_1 analogue **55**[43] was accomplished starting from **14**.[8]

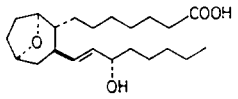


51, $R^1 = R^3 = CH_3$; $R^2 = H$
53, $R^1 = R^2 = CH_3$; $R^3 = H$

52



54



55

EXPERIMENTAL

Because of the space limitation, herein only procedures of the key iron carbonyl-promoted cyclocoupling reactions are described. Original papers cited in the text report the experimental detail of other standard reactions. The original reports also mention the spectral characteristics of products, which are omitted here. Diiron enneacarbonyl [$Fe_2(CO)_9$], though commercially available, was prepared by the method of King[44] and used after drying over KOH in a vacuum desiccator. All reactions were performed under argon atmosphere. Unless otherwise noted, the reaction mixture was usually worked up as follows: (1) quenching with saturated disodium dihydrogen ethylenediaminetetraacetate (Na_2H_2edta) soln, (2) extraction by suitable organic solvents and, if necessary, filtration, (3) dryness of the extracts, and (4) concentration. Chromatography was done on a silica-gel column.

8-*Methoxycarbonyl*-8-*azabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**7**)

The key intermediate for the tropane alkaloids synthesis. A mixture of *sym*-**5** (11.2 g, 30.0 mmol) and $Fe_2(CO)_9$ (10.9 g, 30.0 mmol) in benzene (50 ml) was stirred at 50°. After 5 min, to the resulting mixture was added **6** (12.5 g, 10.0 mmol) and stirring was continued at the same temp for an additional 72 hr. Usual workup afforded a viscous oil (*ca* 10 g), which was dissolved in CH_2Cl_2 (100 ml) and then to the soln was added NH_4Cl-saturated MeOH (100 ml). Subsequently, Zn/Cu couple (20.0 g, 308 mg-atoms) was added in small portions over 10 min with vigorous stirring. After the addition was completed, stirring was continued at room temp for 3 hr. The mixture was usually worked up to leave a black tar (*ca* 2.5 g), whose column chromatography (1 : 3 EtOAc–hexane) produced **7** as crystals (1.03 g, 57% yield), m.p. 69–70°.

8-*Oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**14**)

The key intermediate for the synthesis of C-nucleosides and the basic skeleton of lolium alkaloids. A mixture of **5** (3.73 g, 10.0 mmol) and $Fe_2(CO)_9$ (3.46 g, 10.0 mmol) in furan (40 ml) was stirred at refluxing temp for 48 hr. The mixture was worked up in a usual manner to afford a brown oil, which was subjected to column chromatography (1 : 10 EtOAc–hexane), giving a diastereomeric mixture of 2,4-dibromo-8-oxabicyclo[3.2.1]oct-6-en-3-ones (1.76 g, 63% yield) as colorless crystals. A mixture of the dibromides (300 mg, 1.06 mmol) was stirred with Zn/Cu couple (1.00 g, 15.3 mg-atoms) in MeOH (10 ml) saturated with NH_4Cl at room temp for 15 min. After removal of insoluble materials by filtration, the filtrate was subjected to usual extractive workup. The resulting organic extract was concentrated at atmospheric pressure through a 20-cm Vigreux column. Finally the residue was lightly sucked by an aspirator at room temp to leave **14** (130 mg, 100% yield from the dibromides). The pure crystalline sample, m.p. 37–39°, was obtained by bulb-to-bulb distillation at bath temp of 50–80° (0.01 mm). The ketone **14** was also conveniently accessible by using Zn/Ag couple as the reducing agent.[45]

2,4-*Dimethyl*-3(2H)-*furanone* (**17**, R = CH_3, R′ = H). A mixture of 2,4-dibromopentan-3-one (8.70 g, 35.6 mmol), $Fe_2(CO)_9$ (15.6 g, 42.8 mmol), and Na_2H_2edta (18.0 g, 53.3 mmol) in DMF (180 ml) was stirred at room temp for 12 hr. After the usual workup gave a brown oil (4.06 g), to which was added petroleum ether (80 ml), and the occurring ppts were removed by filtration. Evaporation of the filtrate followed by bulb-to-bulb distillation (25–70°, 0.2 mm) afforded 2,4-dimethyl-3(2H)-furanone (2.11 g, 53% yield).

6-*Isopropyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**28**)

The intermediate for nezukone synthesis. To a mixture of **5** (7.50 g, 20.0 mmol), 3-isopropylfuran (0.88 g, 8.00 mmol), and $Fe_2(CO)_9$ (5.50 g, 15.0 mmol) in benzene (20 ml) was stirred at 60° for 2.5 hr. The mixture was cooled and to this were added Zn/Cu couple (10.0 g, 150 mg-atoms), NH_4Cl-saturated MeOH (15 ml), and benzene (40 ml). The mixture was vigorously stirred at room temp for 20 min. Standard workup followed by purification by column chromatography (1 : 10 ether–benzene) afforded **28** (945 mg, 71% yield based on 3-isopropylfuran) as an oil.

2-*Isopropyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**31**)

The synthetic intermediate of α-thujaplicin. A mixture of 1,1,3-tribromo-4-methylpentan-2-one (1.68 g, 5.00 mmol), $Fe_2(CO)_9$ (2.20 g, 6.04 mmol), and furan (15 ml) was heated at refluxing temp for 16 hr and worked up in a usual manner to give a dark brown oil (1.3 g). Treatment of this oil with Zn/Cu couple (3.6 g, 55.0 mg-atoms) in NH_4Cl-saturated MeOH (15 ml) at room temp for 1.5 hr followed by preparative TLC (1 : 10 EtOAc–hexane) afforded **31** (290 mg, 35% yield).

1-*Isopropyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**34**)

The intermediate for preparation of hinokitiol. A mixture of **5** (40.0 g, 107 mmol), $Fe_2(CO)_9$ (27.3 g, 75.0 mmol), and 2-isopropylfuran (5.50 g, 50.0 mmol) in benzene (100 ml) was stirred at 60° for 2 hr. Usual workup followed by treatment with Zn/Cu couple (70.0 g, 1.07 g-atoms) in MeOH (300 ml) at room temp for 30 hr gave a brown oil (4.4 g). Purification of this crude material with a short alumina column left **34** (3.09 g, 47% yield based on 2-isopropylfuran), m.p. 35–37°.

2,2-*Dimethylbicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**37**)

The intermediate for preparation of carbocamphenilone and camphenic acid. To a stirred mixture of cyclopentadiene (1.0 ml), $Fe(CO)_5$ (1.17 g, 5.98 mmol), THF (1.0 ml), and benzene (10 ml) was added at 80° a soln of 1,1,3-tribromo-3-methylbutan-2-one (1.62 g, 50.0 mmol) in a 1 : 1 mixture of cyclopentadiene and benzene (7.5 ml) over 25 min. The resulting mixture was stirred for an additional 45-min period at the same temp. After cooling, the mixture was quenched by addition of NH_4Cl-saturated MeOH (12.0 ml) and shaken with Zn/Cu couple (3.80 g, 57.8 mg-atoms) for 20 min. Usual workup afforded an oily residue, which was dissolved in CH_2Cl_2 (20 ml). The soln was added in small portions to vigorously stirred hexane (200 ml) and the resulting insoluble ppts were removed by filtration. Concentration of the filtrate followed by column chromatography (1 : 10 EtOAc–hexane) gave an oily **37** (95% pure by ^{1}H-NMR, 520 mg, 66% yield), which produced a pure crystalline sample, m.p. 45–48°, by bulb-to-bulb distillation at 70–120° (bath temp) (2 mm).

α-Cuparenone (**42**). Solns of **40** (245 mg, 1.00 mmol) in benzene (1.5 ml) and **41** (528 mg, 4.00 mmol) in benzene (1.5 ml) were introduced separately using two motor-driven syringes to a vigorously stirred suspension of $Fe_2(CO)_9$ (510 mg, 1.40 mmol) in benzene (0.5 ml) over 40 min at 55°. The mixture was stirred at the same temp for an additional 15 hr and then worked up usually to give an oil (668 mg), which was subjected to column chromatography (1 : 10 ether–hexane) to yield a colorless oil (54 mg) containing **42** as the major component. Bulb-to-bulb distillation of the chromatographed material at 100–200° (bath temp) (0.1 mm) afforded a pure sample of **42** (42 mg, 18% yield).

Reaction of 1,3-*dibromo*-3,7-*dimethyloct*-6-*en*-2-*one* (**46**) *with* $Fe_2(CO)_9$

Formation of camphor. A mixture of **46** (156 mg, 0.50 mmol) and $Fe_2(CO)_9$ (218 mg, 0.60 mmol) in benzene (25 ml) in a pressure bottle was heated at 100–110° for 1.5 hr with magnetical stirring. The resulting mixture was treated with 2 M ceric ammonium nitrate soln in 80% aqueous acetonitrile (3 ml) at room temp for 1 hr. After usual workup, the resulting crude product was subjected to VPC [3 mm × 2 m 5% 1,2,3-tris(2-cycloethoxy)propane (TCEP), 130°], indicating the formation of **47** (t_R 5.8 min) in 38% yield, accompanied by other several minor products. Preparative VPC (7 mm × 3 m 10% Apiezon grease L, 130°) gave an analytical sample of **47**.

Reaction of (E)-1,3-*dibromo*-3,7,11-*trimethyldodeca*-6,10-*dien*-2-*one* (**48**) *and* $Fe(CO)_5$

Preparation of campherenone and epicampherenone. A mixture of **48** (380 mg, 1.00 mmol) and $Fe(CO)_5$ (196 mg, 1.00 mmol) in benzene (10 ml) in a pressure bottle was heated at 100° for 4.5 hr, and then worked up to give an oily product (300 mg). The VPC analysis (3 mm × 2 m 10% $AgNO_3$–10% TCEP, 100°) showed the formation of **49** (t_R 24 min) and **50** (t_R 26 min) in a 2 : 1 ratio in 58% combined yield. The pure samples of them were collected by preparative VPC (10 mm × 2 m 10% $AgNO_3$–10% TCEP, 110°).

2α,4α-*Dimethyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**51**) *and its* 2α,4β-*dimethyl isomer.* A mixture of 2,4-dibromopentan-3-one (1.22 g, 5.00 mmol), $Fe_2(CO)_9$ (2.18 g, 6.00 mmol), and furan (50 ml) was stirred at 40°. After 24 hr, the second portion of $Fe_2(CO)_9$ (1.09 g, 3.00 mmol) was added, and the mixture was maintained at this temp for an additional 29 hr. Workup afforded a 44 : 56 mixture of **51** and its 2α,4β-dimethyl isomer (883 mg, 90% combined yield). The derivative **51** was also obtainable as the single isomer by the reaction using Zn/Ag couple as the reducing agent.[45]

2,2-*Dimethyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**53**). A

mixture of 1,1,3-tribromo-3-methylbutan-2-one (646 mg, 2.00 mmol), $Fe_2(CO)_9$ (728 mg, 2.00 mmol), and furan (10 ml) was stirred at refluxing temp for 40 hr. Usual workup afforded 2α-bromo-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one as colorless crystals (371 mg, 93% yield), m.p. 93–94°. The cycloadduct (49 mg, 0.21 mmol) was then treated with Zn/Cu couple (400 mg, 6.12 mg-atoms) in NH_4Cl-saturated MeOH (2.0 ml) at 25° for 30 min. Removal of insoluble materials by filtration followed by extractive workup gave rise to the crystalline **53** (33 mg, 100% yield from the bicyclic bromide), m.p. 47–50°. The Zn/Ag couple-mediated cyclocondensation also afforded **53**.[45]

Acknowledgements—We are grateful to the highly talented coworkers, whose names are given in the appropriate references. We are particularly indebted to Professor H. Takaya for the valuable contribution at an early stage of this work. The synthesis of camphor and campherenone was done by collaboration with the group of Professors H. Nozaki and H. Yamamoto. We also acknowledge generous gifts of D-ribose from Ajinomoto Co., pseudouridine from Kyowa Hakko Co., pseudoisocytidine hydrochloride from Dr K. A. Watanabe, showdomycin from Shionogi Research Laboratory, nezukone from Professor Y. Hirose, α- and β-thujaplicins from Professors S. Ito and K. Takase and Drs T. Toda and H. Fujise, and campherenone from Professor T. Money.

REFERENCES

[1] G. F. Emerson, L. Watts and R. Pettit, *J. Am. Chem. Soc.* **87**, 131 (1965).

[2] For a comprehensive review: *Transition Metal Carbene Complexes.* Verlag Chemie GmbH, Weinheim (1983).

[3] Reviews: *Organic Syntheses via Metal Carbonyls* (Edited by I. Wender and P. Pino), Vols 1 and 2. Interscience, New York (1968 and 1977); R. F. Heck, *Organotransition Metal Chemistry.* Academic Press, New York (1974); J. Tsuji, *Organic Synthesis by Means of Transition Metal Complexes.* Springer, Berlin and New York (1975); J. Falbe, *Carbon Monoxide in Organic Synthesis.* Springer, 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 (1967); M. Ryang, *Organometal. Chem. Rev.* **A5**, 67 (1970); M. Ryang and S. Tsutsumi, *Synthesis* 55 (1971); R. Noyori, *Transition Metal Organometallics in Organic Synthesis* (Edited by H. Alper), Vol. 1, Chap. 2. Academic Press (1976); J. P. Collman and L. S. Hegedus, *Principles and Applications of Organotransition Metal Chemistry* (Edited by A. Kelly). University Science Books, Mill Valley (1980).

[4] Accounts on synthetic utility of iron carbonyl complexes: R. Pettit, *Proc. Robert A. Welch. Found. Conf. Chem. Rev.* **17**, 227 (1973); M. Rosenblum, *Acc. Chem. Res.* **7**, 122 (1974); J. P. Collman, *Ibid.* **8**, 342 (1975); E. Weissberger and P. Laszlo, *Ibid.* **9**, 209 (1976); A. J. Birch and I. D. Jenkins, *Transition Metal Organometallics in Organic Synthesis* (Edited by H. Alper), Vol. 1, Chap. 1. Academic Press, New York (1976).

[5] G. F. Emerson, K. Ehrlich, W. P. Giering and P. C. Lauterbur, *J. Am. Chem. Soc.* **88**, 3172 (1966).

[6] R. Noyori, Y. Hayakawa, H. Takaya, S. Murai, R. Kobayashi and N. Sonoda, *J. Am. Chem. Soc.* **100**, 1759 (1978); R. Noyori, Y. Hayakawa, M. Funakura, H. Takaya, S. Murai, R. Kobayashi and S. Tsutsumi, *Ibid.* **94**, 7202 (1972); R. Noyori, F. Shimizu and Y. Hayakawa, *Tetrahedron Lett.* 2091 (1978). See also H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **12**, 819 (1973); *Ibid.* **23**, 1 (1984) and refs cited.

[7] R. Noyori, *Acc. Chem. Res.* **12**, 61 (1979); R. Noyori and Y. Hayakawa, *Org. React.* **29**, 163 (1983).

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

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

[10] R. Noyori, T. Souchi and Y. Hayakawa, *J. Org. Chem.* **40**, 2681 (1975).

[11] R. Noyori, S. Makino, Y. Baba and Y. Hayakawa, *Tetrahedron Lett.* 1049 (1974).

[12] R. Noyori, Y. Baba, S. Makino and H. Takaya, *Tetrahedron Lett.* 1741 (1973).

[13] R. Noyori, F. Shimizu, K. Fukuta, H. Takaya and Y. Hayakawa, *J. Am. Chem. Soc.* **99**, 5196 (1977); R. Noyori, *Ann. N.Y. Acad. Sci.* **295**, 225 (1977).

[14] Y. Hayakawa, K. Yokoyama and R. Noyori, *J. Am. Chem. Soc.* **100**, 1791 (1978); R. Noyori, K. Yokoyama and Y. Hayakawa, *Ibid.* **95**, 2272 (1973); Y. Hayakawa, K. Yokoyama and R. Noyori, *Tetrahedron Lett.* 4347 (1976).

[15] Y. Hayakawa, K. Yokoyama and R. Noyori, *J. Am. Chem. Soc.* **100**, 1799 (1978); R. Noyori, K. Yokoyama, S. Makino and Y. Hayakawa, *Ibid.* **94**, 1722 (1972).

[16] Y. Hayakawa, H. Takaya, S. Makino, N. Hayakawa and R. Noyori, *Bull. Chem. Soc. Japan* **50**, 1990 (1977); R. Noyori, Y. Hayakawa, S. Makino, N. Hayakawa and H. Takaya, *J. Am. Chem. Soc.* **95**, 4103 (1973).

[17] Y. Hayakawa, Y. Baba, S. Makino and R. Noyori, *J. Am. Chem. Soc.* **100**, 1786 (1978); R. Noyori, Y. Baba and Y. Hayakawa, *Ibid.* **96**, 3336 (1974).

[18] Y. Hayakawa and R. Noyori, *Bull. Chem. Soc. Japan* **47**, 2617 (1974).

[19] G. Fodor, *Prog. Phytochem.* **1**, 491 (1968).

[20] R. S. Glass, D. R. Deardorff and L. H. Gains, *Tetrahedron Lett.* 2965 (1978); S. R. Wilson and R. A. Sawicki, *Ibid.* 2969 (1978).

[21] R. J. Suhadolnik, *Nucleoside Antibiotics,* Chaps 9–11. Wiley-Interscience, New York (1970); P. Roy-Burman, *Analogues of Nucleic Acid Components.* Springer, Berlin and New York (1970); S. Nakamura and H. Kondo, *Heterocycles* **8**, 583 (1977).

[22] R. Noyori, T. Sato and Y. Hayakawa, *J. Am. Chem. Soc.* **100**, 2561 (1978); *Bull. Chem. Soc. Japan* **57**, 2515 (1984).

[23] T. Sato, Y. Hayakawa and R. Noyori, *Nucleic Acid Chem.* (1985), in press.

[24] K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.* **98**, 1986 (1976); V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.* 1973 (1976).

[25] R. Noyori, T. Sato and H. Kobayashi, *Bull. Chem. Soc. Japan* **56**, 2661 (1983); R. Noyori, T. Sato and H. Kobayashi, *Tetrahedron Lett.* **21**, 2569 (1980); R. Noyori, H. Kobayashi and T. Sato, *Ibid.* **21**, 2573 (1980).

[26] W. H. Pirkle and M. S. Hoekstra, *J. Org. Chem.* **39**, 3904 (1974).

[27] H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann and P. Grieshaber, *Chem. Ber.* **101**, 41 (1968).

[28] A. M. Michelson and W. E. Cohn, *Biochem.* **1**, 490 (1962).

[29] M. Bobek, J. Farkaš and F. Šorm, *Coll. Czech. Chem. Commun.* **34**, 1690 (1969); *Tetrahedron Lett.* 1543 (1963).

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

[31] For comprehensive reviews: L. Goodman, *Basic Principles in Nucleic Acid Chemistry* (Edited by P. O. P. Tso), Vol. 1, p. 93. Academic Press, New York (1974); G. D. Daves, Jr. and C. Cheng, *Prog. Med. Chem.* **13**, 303 (1976); S. Hannessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.* **33**, 111 (1976); S. D. Gero, J. Cleophax, D. Mercier and A. Olesker, *Synthethic Methods for Carbohydrates* (Edited by H. S. El Khadam), p. 64. American Chemical Society, Washington, D.C. (1976); M. Ohno, *Anticancer Agents Based on Natural Product Models* (Edited by J. M. Cassady and J. D. Douros), pp. 73–84. Academic Press, New York (1980); J. G. Buchanan, *Prog. Chem. Org. Natural Products* **44**, 243 (1983).

[32] T. Sato, M. Watanabe, H. Kobayashi and R. Noyori, *Bull. Chem. Soc. Japan* **56**, 2680 (1983) and refs cited.

[33] T. Sato and R. Noyori, *Bull. Chem. Soc. Japan* **56**, 2700 (1983) and refs cited.

[34] H. Takaya, Y. Hayakawa, S. Makino and R. Noyori, *J. Am. Chem. Soc.* **100**, 1778 (1978).
[35] Y. Hayakawa, M. Sakai and R. Noyori, *Chem. Lett.* 509 (1975).
[36] R. Noyori, S. Makino, T. Okita and Y. Hayakawa, *J. Org. Chem.* **40**, 806 (1975).
[37] S. Ranganathan and B. B. Singh, *Chem. Commun.* 218 (1970); Y. Matsubara, *Nippon Kagaku Zasshi* **78**, 719 (1957).
[38] Y. Hayakawa, F. Shimizu and R. Noyori, *Tetrahedron Lett.* 993 (1978).
[39] R. Noyori, M. Nishizawa, F. Shimizu, Y. Hayakawa, K. Maruoka, S. Hashimoto, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.* **101**, 220 (1979).
[40] M. Nishizawa and R. Noyori, *Bull. Chem. Soc. Japan* **54**, 2233 (1981).
[41] M. J. Arco, M. H. Trammell and J. D. White, *J. Org. Chem.* **41**, 2075 (1976).
[42] J. Meinwald, *Pure Appl. Chem.* **49**, 1275 (1977); see also M. A. Adams, A. J. Duggan, J. Smolanoff and J. Meinwald, *J. Am. Chem. Soc.* **101**, 5364 (1979).
[43] M. F. Ansell, M. P. L. Caton and J. S. Mason, *Tetrahedron Lett.* **22**, 1141 (1981).
[44] R. B. King, *Organomet. Synth.* **1**, 93 (1965).
[45] T. Sato and R. Noyori, *Bull. Chem. Soc. Japan* **51**, 2745 (1978).