General Synthesis of Tropane Alkaloids via the Polybromo Ketone–Iron Carbonyl Reaction[1,2]

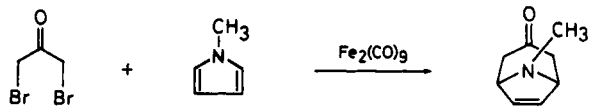
Y. Hayakawa, Y. Baba, S. Makino, and R. Noyori*

Contribution from the Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan. *Received February 28, 1977*

Abstract: The iron carbonyl promoted reaction of polybromo ketones and pyrrole derivatives is applied to the synthesis of tropane alkaloids. The [3 + 4] cyclocoupling between $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and *N*-carbomethoxypyrrole leads to *N*-carbomethoxy-2,4-dibromo-8-azabicyclo[3.2.1]oct-6-en-3-ones. Hydrogenation of the adducts in ethanol over Pd/C gives *N*-carbomethoxy-8-azabicyclo[3.2.1]octan-3-one, which is reduced with diisobutylaluminum hydride to tropine. Treatment of the unsaturated bicyclic dibromo adducts with zinc–copper couple in methanol containing ammonium chloride affords *N*-carbomethoxy-8-azabicyclo[3.2.1]oct-6-en-3-one, which upon reduction with diisobutylaluminum hydride is converted selectively to *N*-methyl-8-azabicyclo[3.2.1]oct-6-en-3α-ol (6,7-dehydrotropine). Since the product can be transformed to all naturally occurring tropane derivatives, the present procedure marks the realization of a new, general synthesis of the alkaloid family.

Tropane alkaloids[3-5] have received a great deal of attention because of their remarkable pharmaceutical significance. Therefore a variety of synthetic approaches to tropane alkaloids have been investigated.[6,7] We feel, however, that most of them reported so far are able to produce derivatives of only certain types. This paper describes a new synthesis of tropane alkaloids based on the polybromo ketone–iron carbonyl reaction[1,8] which allows the preparation of a wide variety of natural and unnatural alkaloids.

Basic Design. Since the first discovery of the 4-cycloheptenone synthesis via the iron carbonyl promoted cyclocoupling between α,α'-dibromo ketones and 1,3-dienes,[9] we have hoped to apply the reaction to the synthesis of tropanes. The cyclocoupling reaction with cyclic dienes such as furan[10] and cyclopentadiene[9] proceeds quite facilely, yielding the bicyclic [3 + 4] adducts. Therefore, we expected that the cyclocoupling of dibromoacetone and *N*-methylpyrrole as cyclic 1,3-diene may lead directly to 6,7-dehydrotropinone (**1**). At the outset



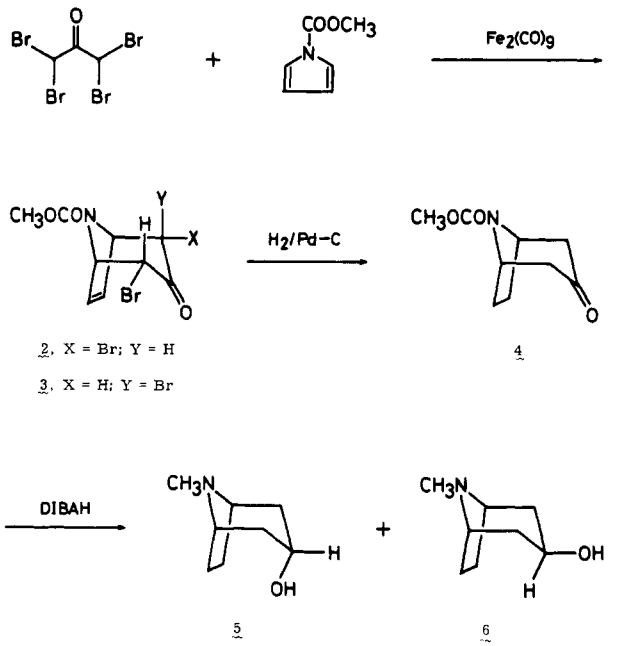
1

of the examination, however, the original plan resulted totally in failure because of the following three limitations. The first is that dibromoacetone, unlike ordinary dibromo ketones with long alkyls, does not react with dienes for the reasons described previously.[8] The second is that reaction of α,α'-dibromo ketones and *N*-methylpyrrole cannot afford the expected cyclocoupling products but gives the monocyclic substitution products.[8,11] The third limitation arises from the instability of 6,7-dehydrotropinones under the present reaction conditions that form $FeBr_2$ with the progress of reaction.[12,13]

Fortunately, we could unravel these problems by adopting the following modifications. The first impediment was removed by the use of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone as the starting three-carbon unit followed by removal of bromine atoms from the initially formed diene adduct.[1,8] The second and third problems, which are likely caused by the presence of free lone pair electrons on the nitrogen atom, were concurrently solved by the use of *N*-carbomethoxypyrrole in place of *N*-methylpyrrole.[8,11]

Synthesis of Tropine. Scheme I shows a new route to tropine. The $Fe_2(CO)_9$-aided reaction of tetrabromoacetone and *N*-carbomethoxypyrrole (3:3:1 mole ratio) in benzene at 50 °C gave a 2:1 mixture of the desired cycloadducts **2** and **3** having a tropane skeleton in 70% yield (52% isolated). Both diastereomers were quite stable during usual workup and silica gel

Scheme I



chromatography. Stereochemistry of these isomers was verified on the basis of the NMR signals due to the CHBr protons.[15] The cis isomer **2** showed a two-proton doublet (J = 4.0 Hz) at δ 4.80, indicating the presence of two equivalent methine protons at C_2 and C_4, whereas the trans isomer **3** exhibited two one-proton doublets at δ 4.27 (J = 2.0 Hz) and 5.11 (J = 3.5 Hz) arising from the two nonequivalent methine protons. Other signals of **2** occurred with a symmetrical pattern, but those of **3** did not.

The yield of the cyclocoupling products was affected by the mole ratio of the starting materials employed. When $Fe_2(CO)_9$ was used in excess to the tetrabromide, overreduction of the resulting **2** and **3** occurred to afford a monobromide. The use of an excess of *N*-carbomethoxypyrrole to the tetrabromide caused a drastic decrease in yield of the products. For example, the desired adducts **2** and **3** were obtained in <10% yield in the reduction using the pyrrole and tetrabromoacetone in 3–7:1 mole ratio. $Fe(CO)_5$ in place of $Fe_2(CO)_9$ failed to give the cyclocoupling products in satisfactory yield. Zinc–copper couple may be used as reducing agent.[16] Thus, when the reduction of tetrabromoacetone with zinc–copper couple in the presence of *N*-carbomethoxypyrrole (1:1.2:2 mole ratio) was performed in 1,2-dimethoxyethane (DME) at −5 °C to room

0002-7863/78/1500-1786$01.00/0

Table I. Stereoselectivity in the Reduction of *N*-Carbomethoxynortropinone (**4**)[a]

Run	Reducing agent	Solvent	Temp, °C (time, h)	Product ratio, **5**/**6**[b]
1	DIBAH	THF	−78 (10) and 25 (10)	90:10
2	DIBAH	1:1 THF–pentane	−20 (19) and 25 (24)	80:20
3	DIBAH	1:1 THF–pentane	25 (22)	70:30
4	DIBAH	1:1 ether–pentane	25 (24)	65:35
5	DIBAH	1:1 2-MeTHF[c]–pentane	25 (22)	65:35
6	DIBAH	1:1 DME–pentane	25 (2)	60:40
7	DIBAH	1:1 benzene–pentane	25 (19)	60:40
8	$LiAl(O\text{-}t\text{-}C_4H_9)_2H_2$[d]	THF	25 (18)	60:40
9	$LiAl(O\text{-}t\text{-}C_4H_9)_3H$[d]	THF	25 (18)	60:40
10	$NaAl(OCH_2CH_2OCH_3)_2H_2$	Benzene	25 (22)	60:40
11	$LiAlH_4$	THF	25 (5)	55:45
12[e]	TIBA	1:1 benzene–pentane	25 (23)	80:20

[a] Unless otherwise stated, the experiment afforded **5** and **6** in >90% yield. [b] Determined by NMR analysis (benzene as internal standard). [c] 2-Methyltetrahydrofuran. [d] This reagent did not reduce the carbamate function. Further reduction was achieved by adding $LiAlH_4$ after completion of the carbonyl reduction. [e] Result obtained with tropinone.

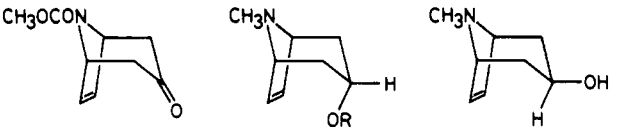
temperature, **2** was obtained as a single product in 25–30% yield.

The cycloadducts **2** and **3** can be transformed via only two steps to tropine (**5**), a representative naturally occurring alkaloid. Catalytic reduction of a mixture of **2** and **3** over 10% Pd/C in ethanol afforded the ketone **4** in quantitative yield. The structure of **4** was confirmed by comparison of all respects with an authentic sample which had been independently prepared from tropinone and methyl chloroformate.[17]

Diisobutylaluminum hydride (DIBAH) can readily transform a carbonyl group into a secondary hydroxyl and at the same time a carbamate function into *N*-methyl.[18] Thus the ketone **4** was reduced with 10 equiv of DIBAH in tetrahydrofuran (THF) at −78 °C for 10 h and then at room temperature for 10 h, producing a 90:10 mixture of tropine (**5**) and pseudotropine (**6**) in 96% combined yield.[19] Both compounds corresponded to authentic samples in all respects.[20] In order to gain the desired α alcohol selectively, choice of the reaction conditions is crucial. The degree of stereoselectivity of the reduction, **5** (α alcohol)/**6** (β alcohol), was highly dependent on the reagent, solvent, and temperature used. As shown in Table I, the use of DIBAH as reducing agent and THF as solvent gave the greatest selectivity. Use of nonpolar solvents such as hydrocarbons resulted in lower selectivity. Attempted hydrogenation of **4** over Pd catalysts (10 atm, 25 °C, ethanol) failed to afford the alcoholic products but resulted in recovery of the starting compound.[21]

General Tropane Synthesis. When the dibromo ketones **2** and **3** were treated with zinc–copper in methanol saturated with ammonium chloride at room temperature for a short period, the debromination product **7** was obtained in quantitative yield. In actual practice, rigorous purification of **2** and **3** is not necessary; the [3 + 4] cyclocoupling between tetrabromoacetone and *N*-carbomethoxypyrrole followed by direct zinc–copper couple reduction gave **7** in 57% overall yield. The ketones **7** and **1** (or the C_2 or C_4 alkylated derivatives) equally have a trop-6-en-3-one structure but show marked difference in stability. The bicyclic ketone **7**, having an electron-withdrawing group at the nitrogen atom, is much more stable than the *N*-methyl derivatives and can exist without any decomposition under the Lewis acid forming reaction conditions as well as workup conditions.

Reduction of **7** with an excess of DIBAH in THF at −78 °C and then at room temperature led to a mixture of the alcohols **8**, melting at 36 °C,[22,23] and **9** in 92% combined yield. Here again the α alcohol **8** was produced stereoselectively (93:7 ratio). Stereochemical elucidation of these isomers was aided by NMR analysis. Catalytic hydrogenation of **8** and **9** over



7 **8**, R = H **9**

10, R = CO-C(CH2OH)(H)-C6H5

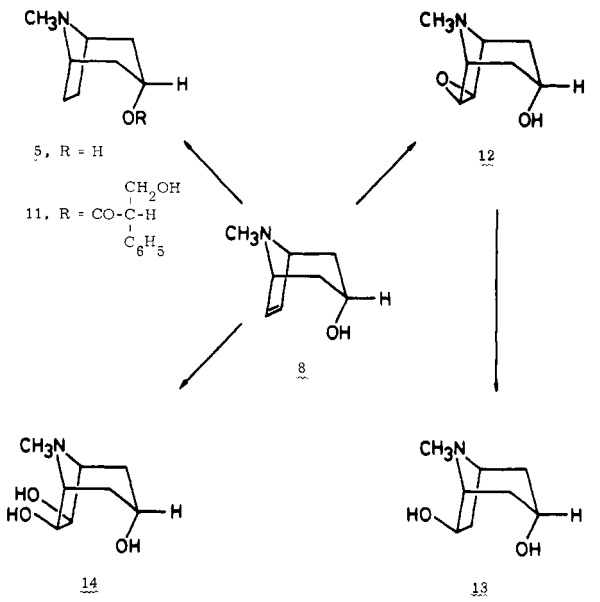
10% Pt/C in ethanol led to tropine (**5**) and pseudotropine (**6**), respectively.

Esterification of **8** can be attained readily. For instance, (−)-dehydrohyoscyamine (**10**)[25] was prepared in 88% yield by treatment of the *p*-toluenesulfonic acid salt of **8** with (−)-*O*-acetyltropyl chloride followed by removal of the acetyl group with hydrochloric acid.[26] The unsaturated amine **10** upon catalytic hydrogenation over Pd/C afforded hyoscyamine (**11**).

6,7-Dehydrotropine (**8**) is a very important compound as a common intermediate for the tropane alkaloid synthesis, as shown in Scheme II.[3b,4] This compound is generally converted to alkaloids bearing oxygen function(s) at the C_6 (AND C_7) position(s) by a suitable oxidative modification of the double bond. Scopine (**12**) can be synthesized by epoxidation with trifluoroperacetic acid,[22,25b,27] hydrogen peroxide in formic acid,[25b] or hydrogen peroxide in the presence of tungstic acid.[25c] Valerine (or tropanediol) (**13**) is obtained by hydrogenolysis of the epoxide function of **12** over Raney nickel[27] or Pd catalysts.[29] Oxidation with potassium permanganate yields teloidine (**14**).[4]

Apparently the success of the new synthesis of **8** depends on both effectiveness of the [3 + 4] cyclocoupling reaction constructing the azabicyclic skeleton and the high stereoselectivity in the carbonyl reduction affording the secondary alcohol of α stereochemistry. A great deal of effort was directed toward the stereoselective preparation of α alcohols, because most tropane bases occurring in natural field have this configuration. Nevertheless, few methods have been offered as the practical tool of the selective transformation. As to the reduction of tropinone, only *catalytic* hydrogenation has been employed for this purpose,[21] whereas *chemical* reductions, irrespective of kinetically controlled (metal hydrides[20,30]) or thermodynamically controlled ones (sodium in alcoholic solvents[20]), are known to produce unnatural pseudotropine (**6**) predominantly. Treatment with zinc–hydriodic acid leads to the preferential formation of the α alcohol **5** but the selectivity is rather poor (**5**:**6** = 5:2).[6] In contrast, DIBAH serves as a practical reagent

Scheme II



that produces the α alcohol with a high stereoselectivity; reduction of tropinone with DIBAH in THF at −78 °C gave a 97:3 mixture of **5** and **6** in high yield.[31] The reagent thus effects the desired stereoselective reduction of a carbonyl moiety of a trop-6-en-3-one *leaving the carbon–carbon double bond intact.*

Advantages of the Present Tropane Synthesis. The present approach to tropane alkaloids has the following attractive features compared with the existing synthetic processes: (1) the directness, (2) the ready, economical availability of the starting materials, (3) the efficiency of the general synthesis of various alkaloids via a single common intermediate, and (4) the flexibility which allows the preparation of a number of artificial analogues not occurring in plant tissues. Among the syntheses so far reported, the Robinson method has the widest generality and can prepare a number of tropinone-like compounds by the use of various four-carbon dialdehydes or keto aldehydes.[32] Unfortunately, however, the method failed to employ malealdehyde[33,37] and epoxysuccinaldehyde,[38] and hence it could not produce directly scopine (**12**) (one of the most important alkaloids in the tropane family) and **8** (a precursor of **12**). The present general synthesis can construct any natural alkaloids, including **12**, through the intermediate **8**. Synthetic flexibility is the key in achieving an effective drug design, because skeletal modification of natural products often increases or improves the specific physiological activities.[39] The present method has found widespread utility in the synthesis of not only natural products but also various unnatural analogues bearing alkyl and other substituents,[11] and discovery of novel physiological activities is expected with these analogues.

Experimental Section

General. All melting points are uncorrected. Infrared (IR) and nuclear magnetic resonance (NMR) spectra were taken in chloroform and deuteriochloroform solutions, respectively. IR spectra were obtained on a JASCO Model IRA-I or JASCO Model DS-402G spectrometer. A JEOL Model C-60H or Varian Model HA-100D spectrometer was used for NMR measurement. Mass spectra were determined on a Hitachi RMU-6C mass spectrometer with a heating or direct inlet system operating at an ionization energy of 70 eV. A JASCO Model DIP-4 spectrometer was used for measurement of degree of optical rotation. Elemental analyses were performed at the Research Laboratory of Fujisawa Pharmaceutical Co. E. Merck GF_{254} silica gel plates (0.25 mm) or Woelm basic alumina (activity I) plates (0.25 mm) were used for analytical thin layer chromatography (TLC). Preparative scale TLC was done with a plate coated with 1.0-mm thickness of E. Merck GF_{254} silica gel. Column chromatography was performed by the use of Kieselgel 60 (70–230 mesh) or basic alumina (activity II–III) purchased from E. Merck Co. Catalytic hydrogenation was carried out using a simple balloon technique.

Materials. $\alpha,\alpha,\alpha',\alpha'$-Tetrabromoacetone,[40] *N*-carbomethoxypyrrole,[41] $Fe_2(CO)_9$,[42] zinc–copper couple,[43] $LiAl(O\text{-}t\text{-}C_4H_9)_2H_2$,[44] $LiAl(O\text{-}t\text{-}C_4H_9)_3H$,[44] and *O*-acetyltropic acid[45] were prepared by the known procedures. Tropine (Tokyo Kasei), tropinone (Aldrich), DIBAH (Alfa Inorganics), 15% TIBA in hexane solution (Tokyo Kasei), 70% $NaAl(OCH_2CH_2OCH_3)_2H_2$ in benzene solution (Aldrich), tropic acid (Tokyo Kasei), and all other common reagents were used as supplied commercially. Aprotic solvents (pentane, benzene, ether, THF, 2-MeTHF, and DME) were used for reactions after distillation from $LiAlH_4$. Anhydrous Na_2SO_4 was used as a drying agent of organic extracts.

Reaction of *N*-Carbomethoxypyrrole and Tetrabromoacetone. A. With $Fe_2(CO)_9$. Into $Fe_2(CO)_9$ (1.09 g, 3.00 mmol) was poured a solution of tetrabromoacetone (1.13 g, 3.00 mmol) in benzene (7.5 mL). The mixture was heated at 50 °C with stirring for 5 min. To the resulting mixture was added *N*-carbomethoxypyrrole (125 mg, 1.00 mmol) and then the mixture was allowed to stand at the same temperature with stirring for 72 h. The dark brown reaction mixture was diluted with ethyl acetate (15 mL) and the remaining insoluble materials were removed by filtration through a Celite 545 pad. The filtrate was concentrated under reduced pressure leaving a black, tarry residue. The NMR analysis by use of 1,1,2,2-tetrachloroethane as standard showed that the desired 1:1 adducts, *N*-carbomethoxy-2α,4α-dibromo-8-azabicyclo[3.2.1]oct-6-en-3-one (**2**) and *N*-carbomethoxy-2α,4β-dibromo-8-azabicyclo[3.2.1]oct-6-en-3-one (**3**), were formed in 70% yield (2:1 ratio). Preparative TLC of the tar with 1:3 ethyl acetate–hexane afforded a mixture of **2** and **3** (R_f 0.6–0.7, 145 mg, 52% yield). Fractional recrystallizations from ethyl acetate–hexane afforded an analytical sample of **2** as colorless crystals, mp 155–157 °C. The mother liquor was concentrated and subjected to further TLC using 1:3 ethyl acetate–hexane as eluent, yielding pure **3** (R_f 0.60), mp 112–114 °C from ethyl acetate–hexane.

2: IR 1748 (C=O), 1710 cm^{-1} ($NCOOCH_3$); NMR δ 3.82 (s, OCH_3), 4.80 (d, J = 4.0 Hz, CHBr), 5.11 (dd, J = 1.0 and 4.0 Hz, NCH), 6.53 (t-like, J = 1.0 Hz, =CH); mass spectrum *m/e* 341, 339, 337 (1:2:1 ratio, M^+), 310, 308, 306 (1:2:1 ratio, $M^+ - OCH_3$), 282, 280, 278 (1:2:1 ratio, $M^+ - COOCH_3$), 260, 258 (base peaks, 1:1 ratio, $M^+ - Br$). Anal. ($C_9H_9NO_3Br_2$) C, H, N, Br.

3: IR 1740 (C=O), 1710 cm^{-1} ($NCOOCH_3$); NMR δ 3.82 (s, OCH_3), 4.27 (d, J = 2.0 Hz, $CH_{eq}Br$), 5.11 (d, J = 3.5 Hz, $CH_{ax}Br$), 5.0–5.3 (m, NCH), 6.36 and 6.61 (dd, J = 2.0 and 6.0 Hz, 1 H each, =CH); mass spectrum *m/e* 341, 339, 337 (1:2:1 ratio, M^+), 310, 308, 306 (1:2:1 ratio, $M^+ - OCH_3$), 282, 280, 278 (1:2:1 ratio, $M^+ - COOCH_3$), 260, 258 (base peaks, 1:1 ratio, $M^+ - Br$). Anal. ($C_9H_9NO_3Br_2$) C, H, N, Br.

B. With Zinc–Copper Couple. In a round-bottomed flask were placed zinc–copper couple (1.60 g, 24.0 mg-atoms), DME (20 mL), and *N*-carbomethoxypyrrole (5.00 g, 40.0 mmol). The mixture was cooled at −5 °C and then a solution of tetrabromoacetone (7.50 g, 20.0 mmol) in DME (20 mL) was added dropwise over a 30-min period with stirring. Stirring was continued at the same temperature for 30 min and then at room temperature for 2 h. The reaction mixture was evaporated under reduced pressure and the residue was diluted with water (80 mL). The insoluble materials were filtered off and the filter cake was rinsed with ethyl acetate. The filtrate was diluted with ethyl acetate (30 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (30 mL × 3). The organic extracts were combined, washed with brine, dried, and concentrated to afford a dark brown oil (10 g). Its NMR analysis (1,1,2,2-tetrachloroethane as internal standard) showed that **2** (a sole 1:1 adduct) was produced in 25–30% yield. Column chromatography (silica gel, 400 g, 1:20, and then 1:1 ethyl acetate–hexane as eluent) of the oil gave **2** (ca. 1.8 g) contaminated with a considerable amount of *N*-carbomethoxypyrrole. The pure product (680 mg, 10% yield) was obtained by recrystallization from ethyl acetate–hexane.

Hydrogenation of a Mixture of 2 and 3 in Ethanol. A mixture of **2** and **3** (200 mg, 0.59 mmol) and 10% Pd/C (100 mg) in ethanol (4.0 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure, producing a yellow

oil. The residue was dissolved in ethyl acetate (10 mL) and the solution was treated with solid $NaHCO_3$ for a few minutes. The insoluble materials were filtered off. Concentration of the filtrate left *N*-carbomethoxy-8-azabicyclo[3.2.1]octan-3-one (**4**) as colorless crystals (115 mg). Recrystallization from benzene–hexane at −20 °C afforded an analytical sample (99 mg, 92% yield): mp 60–61 °C; IR 1713 (C=O), 1695 cm^{-1} ($NCOOCH_3$); NMR δ 1.5–3.0 (m, CH_2), 3.76 (s, OCH_3), 4.55 (m, NCH); mass spectrum *m/e* 183 (M^+). Anal. ($C_9H_{13}NO_3$) C, H, N.

Reduction of 2 with DIBAH. To a solution of **3** (166 mg, 0.91 mmol) in THF (3.0 mL) chilled at −78 °C was added a 1 M THF solution of DIBAH (9.00 mL, 9.00 mmol). The mixture was stirred for 10 h at −78 °C and for an additional 10 h at room temperature, and then quenched by adding a few drops of water. After stirring at room temperature for 30 min, the resulting voluminous gel was well crashed and extracted with ethyl acetate thoroughly. The organic washings were dried and concentrated, affording a colorless oil (180 mg) which consisted of tropine (**5**) and pseudotropine (**6**) (90:10 ratio as determined by NMR analysis). The oil was subjected to column chromatography on alumina (7.2 g) using ethyl acetate and then 5:95 methanol–ethyl acetate as eluent. The course of elution was monitored by analytical TLC on alumina. Concentration of fractions that contained only **5** afforded colorless crystals (111 mg, 86% yield). Recrystallization from benzene produced an analytical sample, mp and mmp 62–63 °C (lit.[20,46] 63–64 °C), identical with natural **5**. Then there was collected a ca. 1:1 mixture of **5** and **6** (8 mg). Fractions containing only **6** were evaporated to give colorless crystals (8 mg, 5% yield). Recrystallization from benzene–hexane left an analytical sample, mp and mmp 106–108 °C (lit. 108,[6] 109–110 °C[20]), superimposable in all respects on an authentic sample.

Conversion of the Dibromides 2 and 3 to 7. A mixture of **2** and **3** (300 mg, 0.87 mmol) and zinc–copper couple (750 mg, 11.5 mg-atoms) in methanol (15 mL) saturated with NH_4Cl was stirred at room temperature for 10 min. To this mixture was added ethyl acetate (30 mL) and insoluble materials were removed by filtration. The filtrate was concentrated to afford an oil containing some solid, to which was added 1:1 ethyl acetate–hexane (20 mL). Remaining insoluble precipitates were removed by decantation and rinsed with 1:1 ethyl acetate–hexane. The organic layers were combined, washed with a small amount of water, dried, and evaporated to give *N*-carbomethoxy-8-azabicyclo[3.2.1]oct-6-en-3-one (**7**, 160 mg, 100% yield) as colorless crystals. Recrystallization from hexane produced an analytical specimen: mp 69–70 °C; IR 3005 (=C–H), 1700–1710 (C=O and $NCOOCH_3$), 1600 cm^{-1} (C=C); NMR δ 2.40 (dd, J = 16.5 and 1.5 Hz, equatorial protons at C_2 and C_4), 2.80 (dd, J = 16.5 and 4.5 Hz, axial protons at C_2 and C_4), 3.84 (s, OCH_3), 4.90 (br d, J = 4.5 Hz, NCH), 6.27 (t-like, J = 1.0 Hz, =CH); mass spectrum *m/e* 181 (M^+), 138. Anal. ($C_9H_{11}NO_3$) C, H, N.

Simple Synthesis of 7. A. With $Fe_2(CO)_9$. A mixture of $Fe_2(CO)_9$ (10.9 g, 30.0 mmol) and tetrabromoacetone (11.2 g, 30.0 mmol) in benzene (50 mL) was heated at 50 °C for 5 min with stirring under nitrogen and then was added a solution of *N*-carbomethoxypyrrole (1.25 g, 10.0 mmol) in benzene (50 mL). The resulting mixture was stirred at the same temperature for 72 h. The mixture was diluted with methylene chloride (200 mL), washed with saturated ethylenediaminetetraacetic acid disodium salt (Na_2H_2edta) solution (100 mL × 2) and brine (20 mL). The organic layer was dried and concentrated to afford a resinous material (ca. 10 g). This residue was dissolved in methylene chloride (100 mL) and then methanol (100 mL) saturated with NH_4Cl was added. Then zinc–copper couple (20.0 g, 308 mg-atoms) was added in small portions over 10 min with vigorous stirring. After the addition was complete, stirring was continued at room temperature for 3 h. The reaction mixture was quenched with saturated Na_2H_2edta solution. The resulting insoluble materials were removed by passing through a Celite 545 pad (16.5 cm diameter × 2 cm thickness) and the pad was washed with methylene chloride thoroughly (ca. 300 mL). The organic layer was separated and the aqueous layer was extracted with methylene chloride (10 mL × 3). The organic layers were combined, washed with brine (30 mL), and dried. Removal of the solvent left a black, tarry oil (ca. 2.5 g). Column chromatography of the oil (silica gel, 100 g, 1:3 ethyl acetate–hexane) gave crystalline **7** (1.03 g, 57% yield), R_f 0.3 on analytical TLC with 1:1 ethyl acetate–hexane. An analytical specimen, mp 69–70 °C, was obtained by recrystallization from hexane.

B. With Zinc–Copper Couple. To a stirred mixture of zinc–copper couple (300 mg, 4.62 mg-atoms) and *N*-carbomethoxypyrrole (500 mg, 4.00 mmol) in DME (4.0 mL) was added dropwise a solution of tetrabromoacetone (1.50 g, 4.00 mmol) in DME (20 mL) at −5 to 0 °C over a period of 30 min. The resulting brown mixture was stirred at the same temperature for an additional 30 min, warmed up gradually to room temperature, and maintained for 2 h. The whole mixture was evaporated directly to give a dark brown oil which contained mainly *N*-carbomethoxypyrrole (R_f 0.7) and **2** (R_f 0.5) (TLC on silica gel, 1:3 ether–hexane). The oil was dissolved in methanol (5 mL) and to the solution with vigorous stirring was added zinc–copper couple (600 mg, 9.24 mg-atoms) in ca. 100-mg portions over 5 min at room temperature. The resulting mixture was stirred for an additional 30 min. On concentration of the reaction mixture there was obtained a brown liquid. This was diluted with ethyl acetate and washed with Na_2H_2 edta solution. The aqueous layer was extracted with a small portion of ethyl acetate. The organic layers were combined and dried. Residual oil obtained after removal of the solvent was treated with ether. The resulting insoluble materials were removed by filtration and the filtrate was concentrated, yielding a black oil (500 mg). Subsequent preparative TLC (1:1 ethyl acetate–hexane, two developments) produced **7** (R_f 0.3, 180 mg, 25% yield) as crystals. Recrystallization from hexane gave an analytical sample, mp 69–70 °C.

Reduction of 7 with DIBAH. A solution of **7** (400 mg, 2.21 mmol) in THF (1.0 mL) was cooled at −78 °C and to this was added 1 M solution of DIBAH in THF (22.0 mL, 22.0 mmol) in a dropwise manner. The mixture was stirred at the same temperature for 23 h and then warmed to room temperature. After 3 h addition of the DIBAH solution (5.0 mL, 5.0 mmol) was renewed and stirring was continued for 5 h. The resulting mixture was quenched by the addition of water (ca. 1 mL) over a 30-min period and allowed to stand for 30 min, resulting in the formation of a voluminous gel. The gel was mixed with ethyl acetate and filtered through a Celite 545 pad. The pad was washed with ethyl acetate repeatedly and the filtrate and washings were combined, dried, and evaporated, affording an oily residue (ca. 400 mg). NMR analysis showed that the oil contained a 93:7 mixture of dehydrotropine (**8**) and pseudodehydrotropine (**9**). The oil was subjected to column chromatography on alumina (16 g) with ethyl acetate, 1:10 methanol–ethyl acetate, and 1:5 methanol–ethyl acetate as eluent. The elution course was monitored by analytical TLC on alumina plates and fractions were collected. The α alcohol **8** (268 mg, 87% yield) was obtained from fractions eluted with ethyl acetate and 1:10 methanol–ethyl acetate. An analytical sample was obtained as colorless crystals by bulb-to-bulb distillation (bath temperature 70–90 °C, 0.2 mm), mp 36 °C (lit.[22] an oil). Its picrate melted at 273 °C (lit.[22] 278 °C). Spectral characteristics of **8** follow: IR 3600 (OH), 3060 cm^{-1} (=C–H); NMR δ 1.69 (br d, J = 14 Hz, equatorial protons at C_2 and C_4), 1.8–2.5 (m, OH and axial protons at C_2 and C_4), 2.18 (s, NCH_3), 3.33 (m, NCH), 3.71 (t, J = 6.3 Hz, C*H*OH), 6.17 (narrow m, $W/2$ = 2.2 Hz, =CH); mass spectrum *m/e* 139 (M^+), 122 (M^+ − OH). Fractions eluted with 1:5 methanol–ethyl acetate gave the β alcohol **9** as a semisolid (16 mg, 5% yield) contaminated with a trace amount of **8**: IR 3600 (OH), 3060 cm^{-1} (=C–H); NMR δ 1.47 (ddd, J = 12, 9.5, and 3.0 Hz, equatorial protons at C_2 and C_4), 1.84 (ddd, J = 12, 6.5, and 2.5 Hz, axial protons at C_2 and C_4), 2.14 (s, NCH_3), 2.30 (br s, OH), 3.40 (m, NCH), 3.56 (dd, J = 9.5 and 6.5 Hz, C*H*OH), 5.82 (narrow m, $W/2$ = 2.0 Hz, =CH); mass spectrum *m/e* 139 (M^+), 122 (M^+ − OH).

Hydrogenation of 8. The unsaturated alcohol **8** (4.0 mg, 0.03 mmol) and a catalytic amount of 10% Pt/C were mixed in ethanol (0.5 mL) and stirred at room temperature under atmospheric pressure of hydrogen for 16 h. The mixture was passed through a Celite 545 pad. Removal of the solvent afforded tropine (**5**) as an oil (4 mg, 100% yield). Its spectral properties (IR, NMR, and mass spectra) and chromatographic behavior (TLC on alumina with 1:10 methanol–ethyl acetate, R_f 0.4) were identical with those of the natural one.

Hydrogenation of 9. A mixture of **9** (4.0 mg, 0.03 mmol) and a catalytic amount of 10% Pt/C in ethanol (0.5 mL) was left at room temperature under 1 atm hydrogen with stirring. After 16 h, the catalyst was removed by filtration and the filtrate was concentrated. The resulting oil was taken up in a small amount of ethyl acetate and the occurring insoluble materials were filtered off. Evaporation of the filtrate gave pseudotropine (**6**, 4 mg, 100% yield) as an oil, whose spectral (IR, NMR, and mass spectra) and TLC behaviors (alumina, 1:10 methanol–ethyl acetate, R_f 0.2) were identical with those of an authentic sample.[20]

Synthesis of (−)-Dehydrohyoscyamine (10). A mixture of (−)-*O*-

acetyltropic acid ($[\alpha]^{20}_D$ −72°, C_2H_5OH, *c* 1.50) (60 mg, 0.28 mmol), thionyl chloride (160 mg, 1.30 mmol), and benzene (0.10 ml) was heated at 60 °C for 2.5 h under nitrogen and then evaporated (25 °C, 2 mm). To the resulting viscous oil was added dehydrotropinium *p*-toluenesulfonate (89 mg, 0.28 mmol) and the mixture was heated at 82 °C for 2 h under nitrogen, giving a viscous, colorless oil. The oil was mixed with 6 N HCl (0.3 mL) and allowed to stand at room temperature for 6 h. The reaction mixture was dissolved in 1:1 methanol-chloroform (10 mL) and dried over Na_2SO_4. The organic layer was concentrated to afford an oil, which was diluted with 1:5 methanol-chloroform (20 mL). Crystals formed by this treatment were removed by decantation and the organic solution was passed through a short alumina-Na_2SO_4 column. Evaporation of the organic solution yielded a pale yellow oil (320 mg), which was subjected to column chromatography (alumina, 15 g, chloroform), giving rise to **10** (71 mg, 88% yield) as a semisolid, $[\alpha]^{22}_D$ −13° (CH_3OH, *c* 0.268). Recrystallizations from hexane afforded an analytical sample as plates, mp 63–64 °C, $[\alpha]^{23}_D$ −14° (CH_3OH, *c* 0.130). This product displayed a mass spectrum identical with the reported one.[25a] The IR and NMR data (unreported so far) follow: IR 3600 (OH), 1720 cm^{-1} (ester C=O); NMR δ 1.57 (br t, *J* = 15 Hz, equatorial protons of $NCHCH_2$), 1.9–2.4 (m, axial protons of $NCHCH_2$), 2.30 (s, NCH_3), 3.25 (br s, OH), 3.36 (m, NCH), 3.4–4.2 (ABC-type m, $COCHCH_2$), 4.99 (t, *J* = 5.0 Hz, COOCH), 5.44 and 5.83 (dd, *J* = 5.0 and 2.0 Hz, 1 H each, $NCHCH=$), 7.28 (m, C_6H_5). Anal. ($C_{17}H_{21}NO_3$) C, H, N.

Hydrogenation of 10. A balloon technique was employed for this catalytic hydrogenation. A mixture of **10** (22 mg, 7.67×10^{-2} mmol) and 10% Pd/C (10 mg) in ethanol (1.3 mL) was magnetically stirred under 1 atm hydrogen at room temperature for 22 h. The catalyst was removed by passing through a short alumina column and washed with chloroform (10 mL). The combined filtrates were evaporated, affording hyoscyamine (**11**, 22 mg, 99% yield) as colorless crystals, mp 101–105 °C. The magnitude of rotation of the crude material, $[\alpha]^{22}_D$, was −20° (CH_3OH, *c* 0.202), and identical with that of natural hyoscyamine, $[\alpha]^{20}_D$ −20° (CH_3OH, *c* 0.200). The NMR spectrum was superimposable on that of authentic natural product. Recrystallizations from hexane gave a pure specimen, mp and mmp 106–107 °C, $[\alpha]^{22}_D$ −20° (CH_3OH, *c* 0.232).

Acknowledgments. Thanks are due to the Ministry of Education of the Japanese Government for support of this investigation (Grants 984014 and 147022). The author (R.N.) also gratefully acknowledges the partial support received from the Takeda Science Foundation.

References and Notes

(1) Carbon–Carbon Bond Formations Promoted by Transition Metal Carbonyls. 19. Part 18: H. Takaya, Y. Hayakawa, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) For preliminary communication, see R. Noyori, Y. Baba, and Y. Hayakawa, *J. Am. Chem. Soc.*, **96**, 3336 (1974).

(3) General reviews of tropane alkaloids: (a) G. Fodor, "Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand-Reinhold, Princeton, N.J., 1970, Chapter 15: (b) G. Fodor *Prog. Phytochem.*, **1**, 491 (1968); (c) H. L. Holmes, "The Alkaloids, Chemistry and Physiology", Vol. 1, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, New York, N.Y., 1950, Chapter 6; (d) D. Fodor, *ibid.*, Vol. 6, 1960, Chapter 5; (e) *ibid.*, Vol. 9, 1967, Chapter 7; (f) *ibid.*, Vol. 13, 1971, Chapter 8.

(4) Reviews for the synthesis: A. Stoll and E. Jucker, *Angew. Chem.*, **66**, 376 (1954); G. Fodor, *Acta Chim. Acad. Sci. Hung.*, **5**, 379 (1955); *Chem. Abstr.*, **49**, 11673 (1955); *Experientia*, **11**, 129 (1955); *Tetrahedron*, **1**, 86 (1957); *Chem. Ind. (London)*, 1500 (1961); *Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.*, 93 (1957); *Chem. Abstr.*, **52**, 16390 (1958); *Magy. Tud. Akad. Kem. Tud. Oszt. Kozl.*, **7**, 467 (1956); *Chem. Abstr.*, **52**, 9168 (1958); G. Fodor, G. Janzsó, P. Dobó, and J. Koczor, *Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.*, 187 (1964); *Chem. Abstr.*, **61**, 4405 (1964); I. Fleming, "Selected Organic Syntheses, A Guide Book for Organic Chemists", Wiley, New York, N.Y., 1973, pp 15–23.

(5) For pharmaceutical properties: K. Nádor, *Recent Dev. Chem. Nat. Carbon Compd.*, **1**, 163 (1965); *Chem. Abstr.*, **65**, 2836 (1966); K. Nádor, "Fortschritte der Arzneimittelforschung", Vol. 2, E. Jucker, Ed., Birkhäuser, Basel, 1960; L. Gyermek and K. Nádor, *J. Pharm. Pharmacol.*, **9**, 209 (1957); *Chem. Abstr.*, **51**, 10742 (1957); M. Doda, L. Gyorgy, and K. Nádor, *Arch. Int. Pharmacodyn.*, **145**, 264 (1963); *Chem. Abstr.*, **60**, 2221 (1964); B. Issekutz, Sr., *Pol. Tyg. Lek.*, **18**, 670 (1963); *Chem. Abstr.*, **61**, 6210 (1964); M. Tishler, *Adv. Chem. Ser.*, **No. 45**, 1 (1964). For biosynthesis: A. Romeike, *Pharmazie*, **15**, 655 (1960); *Chem. Abstr.*, **56**, 10277 (1962); J. H. van Soeren, *Pharm. Weekbl.*, **97**, 721 (1962); *Chem. Abstr.*, **58**, 10441 (1963). For stereochemical studies on N-quaternary salts: J. H. Supple and E. Eklum, *J. Am. Chem. Soc.*, **93**, 6684 (1971); G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *ibid.*, **93**, 403 (1971); P. Benci, C. H. Stam, and C. H. MacGillavry, *Tetrahedron Lett.*, 243 (1971); U. O. de la Camp, A. T. Bottini, C. C. Thut, J. Gal, and A. G. Bellettini, *J. Org. Chem.*, **37**, 324 (1972).

(6) R. Willstätter, *Ber.*, **29**, 936 (1896); **34**, 129, 3163 (1901); *Justus Liebigs Ann. Chem.*, **317**, 204, 267, 307 (1901); **326**, 23 (1903); R. Willstätter and F. Iglauer, *Ber.*, **33**, 1170 (1900).

(7) (a) R. Robinson, *J. Chem. Soc.*, 762 (1917); C. Schöpf, *Angew. Chem.*, **50**, 779 (1937); C. Schöpf and G. Lehmann, *Justus Liebigs Ann. Chem.*, **518**, 5 (1935); (b) F. Galinovsky, *Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.*, 98 (1957); *Chem. Abstr.*, **52**, 15654 (1958); (c) R. Willstätter and A. Pfannenstiel, *Justus Liebigs Ann. Chem.*, **422**, 1 (1920); (d) V. Horák and P. Zuman, *Tetrahedron Lett.*, 746 (1961); V. Horák, *Collect. Czech. Chem. Commun.*, **28**, 1614 (1963); A. T. Bottini and J. Gal, *J. Org. Chem.*, **36**, 1718 (1971); T. Sato, K. Sato, and T. Mukai, *Bull. Chem. Soc. Jpn.*, **44**, 1708 (1971); (e) G. R. Wiger and M. F. Rettig, *J. Am. Chem. Soc.*, **98**, 4168 (1976); (f) N. J. Turro and S. S. Edelson, *ibid.*, **90**, 4499 (1968); (g) G. Fierz, R. Chidgey, and H. M. R. Hoffmann, *Angew. Chem.*, **86**, 444 (1974).

(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, Y. Baba, S. Makino, and H. Takaya, *Tetrahedron Lett.*, 1741 (1973).

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

(12) Reference 7f. However, **1** is tolerable under neutral or basic conditions. See G. Fodor, S. Kiss, and A. Heusner, *Chem. Ind. (London)*, 372 (1963); N. A. Preobrazhenskii, I. A. Rubtsov, T. F. Dankova, and V. P. Pavlov, *J. Gen. Chem. USSR (Engl. Transl.)*, **15**, 952 (1945); *Chem. Abstr.*, **40**, 6488 (1946).

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

(14) The ratio of diastereomers was dependent on the reaction conditions (temperature, period, etc.).

(15) R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *J. Chem. Soc. C*, 437 (1967); J. P. Zahra, J. Casanova, B. Waegell, R. Gassend, and C. W. Jefford, *Bull. Soc. Chim. Fr*, 2247 (1974); B. Waegell and C. W. Jefford, *ibid.*, 844 (1964); M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); D. H. Williams and N. S. Bhacca, *ibid.*, **86**, 2742 (1964).

(16) Cf. H. M. R. Hoffmann, K. E. Clemens, and R. H. Smithers, *J. Am. Chem. Soc.*, **94**, 3940 (1972).

(17) G. Kraiss and K. Nádor, *Tetrahedron Lett.*, 57 (1971).

(18) W. Nagata, T. Wakabayashi, and N. Haga, *Synth. Commun.*, **2**, 11 (1972).

(19) Stereoisomeric composition of products was determined on the basis of NMR analysis by comparing the intensity of singlets arising from NCH_3 group appearing at δ 2.16 in **5** and δ 2.22 in **6**, respectively. For the detail of the NMR data of some tropane alkaloids, see ref 3a, p 445, and G. S. Chappell, B. F. Grabowski, R. A. Sandmann, and D. M. Yourtee, *J. Pharm. Sci.*, **62**, 414 (1973).

(20) Pseudotropine was produced from tropine according to the reported procedure. A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959). See also, A. Nickon and L. F. Fieser, *J. Am. Chem. Soc.*, **74**, 5566 (1952).

(21) Tropinone can be reduced to tropine under comparable condition: L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).

(22) This compound was reported to be an oil [P. Dobó, G. Fodor, G. Janzsó, I. Koczor, J. Tóth, and I. Vincze, *J. Chem. Soc.*, 3461 (1959)].

(23) There have been only two methods for the selective synthesis of **8**. The one is a four-step conversion of natural valerine (**13**)[22,24] and the other is a seven-step transformation of 6-hydroxytropan-3-one produced by the Robinson method. Both methods are neither direct nor practical in view of the poor yield.

(24) G. Fodor, J. Tóth, I. Koczor, and I. Vincze, *Chem. Ind. (London)*, 1260 (1955).

(25) (a) E. C. Blossey, H. Budzikiewicz, M. Ohashi, G. Fodor, and C. Djerassi, *Tetrahedron*, **20**, 585 (1963); (b) G. Fodor, J. Tóth, A. Romeike, I. Vincze, P. Dobó, and G. Janzsó, *Angew. Chem.*, **69**, 678 (1957); (c) G. Fodor, S. Kiss, and J. Rákóczi, *Chim. Ind. (Paris)*, **90**, 225 (1963).

(26) V. A. Fung and J. I. DeGraw, *Synthesis*, 311 (1976).

(27) G. Fodor, J. Tóth, I. Koczor, P. Dobó, and I. Vincze, *Chem. Ind. (London)*, 764 (1956).

(28) G. Fodor and Ö. Kovácz, *J. Chem. Soc.*, 2341 (1953); G. Fodor, I. Koczor, and G. Janzsó, *Arch. Pharm. (Weinheim, Ger.)*, **295**, 91 (1962); *Chem. Abstr.*, **57**, 12561 (1962).

(29) G. Fodor, Ö. Kovácz, and L. Mészáros, *Research (London)*, **5**, 534 (1952).

(30) R. Mirza, *Nature (London)*, **170**, 630 (1952).

(31) Y. Hayakawa and R. Noyori, *Bull. Chem. Soc. Jpn.*, **47**, 2617 (1974).

(32) The following dialdehydes and keto aldehydes are employable: tartaraldehyde giving teloidinone,[33] alkoxysuccinaldehydes yielding 6-alkoxytropinones,[34] malaldehyde affording valerinone,[35] and levulinaldehyde and its derivative[36] producing 1-substituted tropinones.

(33) C. Schöpf and W. Arnold, *Justus Liebigs Ann. Chem.*, **558**, 109 (1947).

(34) A. Stoll, E. Jucker, and A. Lindenmann, *Helv. Chim. Acta*, **37**, 495 (1954); **37**, 649 (1954).

(35) A. Stoll, B. Becker, and E. Jucker, *Helv. Chim. Acta*, **35**, 1263 (1952).

(36) J. Kebrle and P. Karrer, *Helv. Chim. Acta*, **37**, 484 (1954).

(37) A. Stoll and E. Jucker, *Chimia*, **9**, 25 (1955).

(38) C. Schöpf and A. Schmetterling, *Angew. Chem.*, **64**, 591 (1952).

(39) E. M. Trautner, *Aust. Chem. Inst. J.*, **14**, 411 (1947). See, with respect to N-quaternized bases, B. T. Cromwell, *Biochem. J.*, **37**, 717 (1944); N. A. Preobrazhenskii and E. Denkin, "Chemistry of Organic Pharmaceutical Compounds", Gozchimizdat, Moscow, 1953, p 177; M. Shimizu and F. Uchimaru, *Chem. Pharm. Bull.*, **9**, 300, 304, 313 (1961); Japanese Patent 6491 (1963); *Chem. Abstr.*, **59**, 11440 (1963); and as to C-substituted

analogues, ref 35 (1-substituted tropanols) and 33 (6-alkoxytropeines), respectively.
(40) C. Rappe, *Acta Chem. Scand.*, **16**, 2467 (1962).
(41) R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 457 (1961).
(42) R. B. King, *Organomet. Synth.*, **1**, 93 (1965).
(43) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).
(44) H. C. Brown and C. J. Shoaf, *J. Am. Chem. Soc.*, **86**, 1079 (1964).
(45) G. Fodor, J. Rakoczi, and Gy. Csepreghy, *Acta Chim. Acad. Sci. Hung.*, **28**, 409 (1961); *Chem. Abstr.*, **61**, 1903 (1964).
(46) A. Orechoff and R. Konowalwa, *Ber.*, **67**, 1153 (1934).

Iron Carbonyl Promoted Reaction of α,α′-Dibromo Ketones and Aromatic Olefins Leading to 3-Arylcyclopentanones. The [3 + 2] Cycloaddition Involving an Allylic Cation[1,2]

Y. Hayakawa, K. Yokoyama, and R. Noyori*

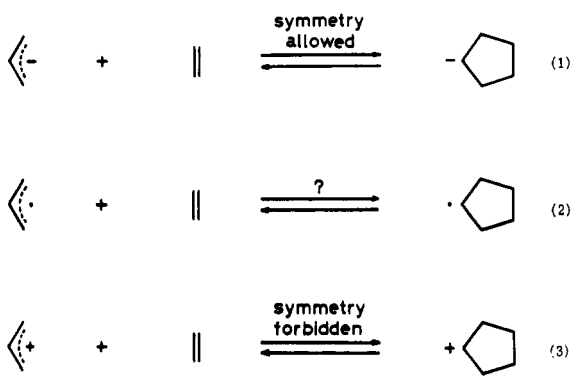
Contribution from the Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan. *Received February 28, 1977*

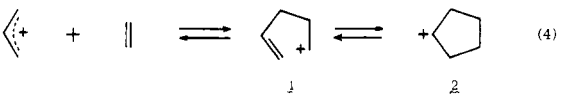
Abstract: Reactive oxyallyl–Fe(II) intermediates, generated from secondary or tertiary α,α′-dibromo ketones and iron carbonyls, cycloadd across aryl-substituted olefins in 3 + 2 → 5 manner, producing 3-arylcyclopentanones in fair to good yields. As the by-product open-chain olefinic ketones via electrophilic olefinic substitution are formed. In certain cases, 2-alkylidenetetrahydrofurans are produced as well. As the olefinic substrate, styrene, alkylated styrenes, anethole, indene, 1,1- and 1,2-diphenylethylene, ferrocenylethylene, etc., may be used. In order to achieve smooth reaction, placement of a carbocation-stabilizing group at the arylated olefinic carbon or in the aromatic ring is favorable. Competition experiments have revealed that the relative reactivities decrease in the order of α-methylstyrene > styrene > β-methylstyrene, implying that both electronic and steric factors are controlling the ease of the cycloaddition. The [$_\pi$2 + $_\pi$2]-type cycloaddition forming cyclopentanones is fully accounted for in terms of a stepwise mechanism involving a zwitterionic intermediate. The experiment by use of *cis*-β-deuteriostyrene has indicated that the [3 + 2] cycloaddition proceeds in a stereospecific fashion regardless of the stepwise nature, whereas the electrophilic substitution goes in a nonstereospecific manner. Possible structures of the zwitterions involved in these reactions are discussed.

Synthesis of five-membered carbocycles is usually accomplished by intramolecular cyclization of open-chain bifunctional compounds.[3,4] In certain cases, ring contraction of cyclohexanones[5] and ring enlargement of cyclobutane derivatives[6] are employed for this purpose. In contrast, there are only little syntheses by intermolecular cyclocombination of odd- and even-numbered carbon units, viz., a 1 + 4 → 5 or 3 + 2 → 5 manner.[3,7] The latter is apparently ascribed to the scarcity of odd-numbered reactive species which are capable of participating in such cyclocoupling reactions. This paper describes a new reaction which falls into this category.

General Consideration

Recently reactive allylic moieties have been highlighted as a promising three-carbon unit. Their cycloaddition across olefinic double bonds has received considerable attention from not only theoretical or mechanistic interest but also from synthetic importance. The possible [3 + 2] cycloadditions are formally classified into three cases, eq 1–3, according to the number of π electrons present in the allylic system. Among them the cycloaddition between allyl anions and olefins, eq 1, is regarded as a thermally allowed [$_\pi$4$_s$ + $_\pi$2$_s$] reaction,[8] and several examples of this anionic cycloaddition are known.[9] Cycloaddition of an allyl radical and olefin, given by eq 2, is viewed as a [$_\pi$3$_s$ + $_\pi$2$_s$] process and might be taken as a thermally allowed reaction according to the simple orbital-symmetry consideration[8] but some doubts arose about this analysis as well.[10] In practice, no example is known for the cycloaddition of this type. The relevant reverse reaction, decomposition of cyclopentyl radicals to allyl radicals and olefins, was examined in some detail and the stereochemical results indicated the retrocycloaddition to be stepwise in nature.[11] The third type of reaction via a four-electron transition state, eq 3, is imposed to be thermally forbidden by the orbital symmetry factors and has not been investigated to any great extent. To date, no evidence has been provided for the cationic [3 + 2] cycloaddition occurring in a concerted manner. This type of cycloaddition, though not attained in a synchronous fashion, may take place by a two-step mechanism under certain circumstances, however.[12] Such scheme, as outlined in eq 4, consists of initial electrophilic attack of an allyl cation onto olefinic substrate and subsequent cyclization of the cationic intermediate **1** to form the cyclopentyl cation **2**. Each step in this process is in principle microscopically reversible and hence the following demands must be satisfied in order that the equilibrium shifts so far to the right, thereby completing the formal [3 + 2] cycloaddition. Firstly, the intermediate **1** must have stability





0002-7863/78/1500-1791$01.00/0