Table I. Regioselectivity with Isoprene

dienophile	X	catalyst	time	yield, %	8/9	rel rate[a]
2	O		7 mo[b]	54[b]	70:30[c,d]	1
2	O	$AlCl_3$	3 h	50[d]	95:5[d]	7.4×10^5 [e]
5	$Cr(CO)_5$		3 h	70[f]	92:8[g]	2.1×10^4 [h]
6	$Mo(CO)_5$		1 h	61[f]	94:6[g]	
7	$W(CO)_5$		2 h	87[f]	91:9[g]	2.6×10^4 [h]

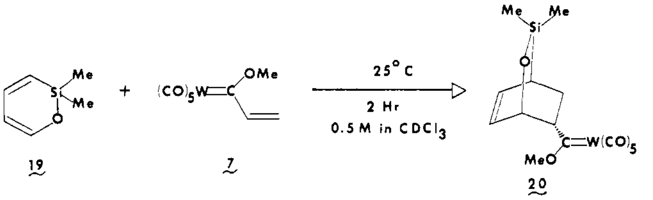
[a] Ratio of rate constants. [b] Reference 9. [c] Reference 21. [d] References 10 and 22. [e] Reference 23. [f] Yield of complexes isolated by flash chromatography. [g] Determined after oxidation to the known methyl esters. [h] Reaction followed with 0.05 M complex in benzene with 1.0 M isoprene at 25 °C; presuming a second-order reaction the rate constants are $4.9 \pm 0.4 \times 10^{-4}$ L mol^{-1} s^{-1} for **7** and $4.0 \pm 0.4 \times 10^{-4}$ L mol^{-1} s^{-1} for **5**.

Table II. Stereoselectivity with Cyclopentadiene

dienophile	X	catalyst	temp, °C	time	yield, %	10/11
2	O		30	7.5 h		78:22[a]
2	O	$AlCl_3$	30	1.0 h		94:6[a]
5	$Cr(CO)_5$		25	3 min	78[b]	94:6[b,c]
7	$W(CO)_5$		25	3 min	93[b]	93:7[b,c]

[a] Reference 11. [b] Yields of complexes isolated by flash chromatography. [c] Determined after oxidation to the known methyl esters.

Scheme II



oxide.[13] The methyl ester **14** is formed in excellent yields from either **12** or **13** by simple treatment with dimethyl sulfoxide at room temperature. The aldehyde **15** can be obtained in good yield from the reaction with hydrogen bromide.[14] The methyl vinyl ether **16** can be obtained by heating either **12** or **13** with pyridine.[16] Reaction with diazomethane[17] results in clean formation of the enol ether **17**, and thus **5** and **7** can serve as synthons for 2-methoxybutadiene as a dienophile. The metal can also be reductively removed by treatment with hydrogen where the metal center can serve to activate and deliver hydrogen thus allowing the double bond in **18** to survive intact.[18]

These results suggest that the combination of the high dienophilicity of Fischer carbene complexes and their relative stability to sensitive functionality[12] may be sufficient to allow for Diels–Alder reactions with the silapyran **19**.[19,20] Indeed, the tungsten complex **7** reacts with the silapyran **19** at 25 °C with clean formation of the cycloadduct **20** as evidenced by ^1H NMR (Scheme II). It can be further anticipated that Diels–Alder reactions of Fischer carbene complexes will have a broad range of applications in synthetic chemistry especially in combination with other reactions indigenous to organometallic compounds of the group 6 metals. We will report further on the scope of these and related cycloaddition reactions of Fischer carbene complexes and on their applications to natural product synthesis.

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Supplementary Material Available: Spectroscopic data and experimental details for compounds **5**–**20** (11 pages). Ordering information is given on any current masthead page.

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(14) Aldehydes have been detected but not isolated from the reaction of Fischer carbene complexes and hydrogen halides.[15]

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(19) Hussman, G.; Wulff, W. D.; Barton, T. J. *J. Am. Chem. Soc.* **1983**, *105*, 1263.

(20) The silapyran **19** reacts with methyl acrylate at 120 °C in 48 h, however, the cycloadduct is not thermally stable at these conditions. Lewis acid ($AlCl_3$, $ZnCl_2$) catalyzed reactions of **19** and **7** also fail perhaps due to the sensitive nature of either **19** or the cycloadduct. It thus appears that there will only be substantially limited utility for the silapyran **19** in cycloaddition reactions with current Diels–Alder technologies.

(21) Hennis, H. E. *J. Org. Chem.* **1963**, *28*, 2570.

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2-Carbomethoxy-3-tropinone: An Advanced Intermediate in the Biosynthesis of Cocaine

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It has recently been established that the tropane moiety of cocaine (**7**) is derived from ornithine[2] and acetic acid,[3,4] the latter presumably being incorporated via acetoacetate since [1-^{14}C]-acetate afforded cocaine with a preponderance of radioactivity at C-3 and C-9. These results are consistent with a biosynthetic route to cocaine, depicted in Scheme I. A condensation between acetoacetate, perhaps as its coenzyme A ester (**2**) and the *N*-methyl-Δ^1-pyrrolinium salt **1** (derived from ornithine), yields hygrine-1′-carboxylate. It is proposed that this β-keto ester is converted to its methyl ester (**3**) prior to the subsequent reactions which involve dehydrogenation to the iminium salt **5** and cyclization to 2-carbomethoxy-3-tropinone (**4**). A stereospecific reduction of this ketone yields methyl ecgonine (**6**), which on esterification with benzoic acid (derived from phenylalanine[3,5]) yields cocaine.

The intermediacy of **4** in this biosynthetic sequence has now been established by feeding this compound labeled with ^{13}C, ^{14}C, and ^3H to *Erythroxylon coca* plants. Reaction of 3-tropinone with [*carbonyl*-^{13}C,^{14}C,*O-methyl*-^3H]dimethyl carbonate[6] in the

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(1) Contribution 189 from this Laboratory. Part 33 in the series "Chemistry of the Tropane Alkaloids". For Part 32, see: Leete, E. *Phytochemistry* **1983**, *22*, 933. Presented at the 2nd International Conference on the Chemistry and Biotechnology of Biologically Active Natural Products, Budapest, Hungary, Aug 15–19, 1983.

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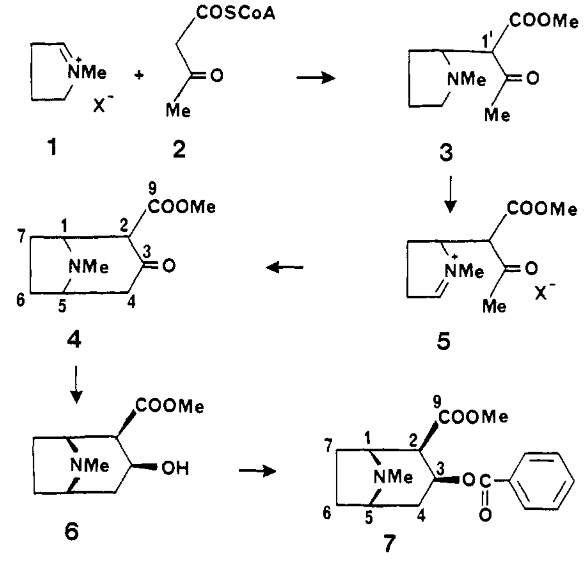
Scheme I. Hypothetical Terminal Steps in the Biosynthesis of Cocaine



presence of sodium hydride yielded [9-^{13}C,^{14}C,*O-methyl*-^{3}H]-2-carbomethoxy-3-tropinone.[8,9] Carbon-13 was introduced into this potential precursor in the hope that its incorporation into cocaine could be established by ^{13}C NMR spectroscopy. A solution of the labeled **4** (0.4 mmol, ^{14}C activity 1.89 × 10^8 dpm/mmol, $^{3}H/^{14}C = 0.29$) in water (40 mL) that contained Tween 80 (0.2 mL) was administered to seven *E. coca* plants (3–10 years old) by painting the solution on the leaves. One week later the leaves (fresh wt 285 g) were harvested and extracted to yield cocaine as previously described,[2] except that the ultimate extraction of cocaine from silica gel TLC plates was carried out with CH_2Cl_2 instead of a mixture of methanol and ethyl acetate (to avoid any exchange of the *O*-methyl group of cocaine with the solvent). The incorporation of radioactivity into the cocaine (387 mg, ^{14}C activity 1.68 × 10^5 dpm/mmol, $^{3}H/^{14}C = 0.27$, absolute incorporation (^{14}C) 0.45%, specific incorporation (^{14}C) 0.09%) was good.[10] However, the specific incorporation was not high enough to detect the presence of excess ^{13}C in the carbomethoxy group of cocaine by ^{13}C NMR spectroscopy. The high retention of tritium strongly suggested that **4** was incorporated intact into cocaine without any hydrolysis of the methyl ester. This was confirmed by chemical degradations of the labeled cocaine which have been previously described.[2,3] The *O*-methyl group of cocaine was found to contain 96% of the tritium, and the C-9 carbonyl group contained 98% of the ^{14}C.

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Note Added in Proof. Radioactive cocaine was also isolated from a second crop of leaves which were harvested (September 12, 1983) 11 weeks after the initial administration of labeled **4**. It had much lower ^{14}C activity (7.77 × 10^3 dpm/mmol) but still retained most of the tritium ($^{3}H/^{14}C = 0.20$).

Registry No. 3-Tropinone, 532-24-1; dimethyl carbonate, 616-38-6; 2-carbomethoxy-3-tropinone, 36127-17-0; cocaine, 50-36-2; barium [^{13}C]carbonate, 51956-33-3; silver nitrate, 7761-88-8; silver [^{13}C]-carbonate, 85323-65-5; [^{3}H]methyl iodide, 72165-55-0; [*carbonyl*-^{13}C,-*O-methyl*-^{3}H]dimethyl carbonate, 87351-10-8.

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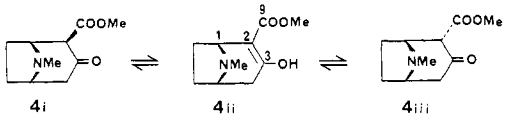
(6) Reaction of barium [^{13}C,^{14}C]carbonate (91% ^{13}C) with aqueous silver nitrate yielded silver [^{13}C,^{14}C]carbonate,[7] which on shaking with an ether solution of [^{3}H]methyl iodide at room temperature yielded [*carbonyl*-^{13}C,^{14}C,*O-methyl*-^{3}H]dimethyl carbonate. The C=O absorption of this ^{13}C-enriched material showed an isotope shift from 1750 to 1710 cm^{-1} in its IR spectrum.

(7) Tsuyuki, T.; Simamura, O. *J. Org. Chem.* **1958**, *23*, 1079. This reference describes the preparation of [*carbonyl*-^{14}C]diethyl carbonate from barium [^{14}C]carbonate and ethyl iodide.

(8) Carroll, F. I.; Coleman, M. L.; Lewin, A. H. *J. Org. Chem.* **1982**, *47*, 13.

(9) The properties of 2-carbomethoxy-3-tropinone have been extensively investigated (Findlay, S. P. *J. Org. Chem.* **1957**, *22*, 13), and it was concluded that this compound exists as an equilibrium mixture of its enol (4ii) and the



4i 4ii 4iii

two keto forms with the carbomethoxy group in the axial (4i) or equatorial (4iii) position. The presence of these three tautomeric forms has been confirmed by ^{13}C NMR spectroscopy, the composition of the mixture being dependent on the solvent. In $CDCl_3$ the intense resonance due to C-9 in the ^{13}C-enriched material appears as three signals (relative intensity) at 171.4 (53.0), 169.3 (32.7), and 169.1 (14.4) ppm. The signal that appears at 102.0 ppm in the unenriched material is assigned to C-2 of the enol isomer 4ii and appears as a triplet ($^{1}J_{2,9} = 74.1$ Hz), due to a one-bond coupling with the enriched C-9.

(10) The previous best absolute incorporations[2,3] of DL-[5-^{14}C]ornithine [1-^{14}C]acetate and DL-[4-^{3}H]phenylalanine into cocaine were 0.039, 0.031, and 0.35%, respectively.

Intramolecular Nitrene C–H Insertions Mediated by Transition-Metal Complexes as Nitrogen Analogues of Cytochrome P-450 Reactions

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We have recently reported[1] that ((tosylimido)iodo)benzene (the tosylimide analogue of iodosobenzene) performs tosylamidation of cyclohexane under catalysis by Fe(III) or Mn(III) tetraphenylporphyrin chloride (TPPCl). The reaction is closely analogous to the hydroxylations by iodosobenzene with metal porphyrin catalysis extensively studied as models for oxidations by the cytochrome P-450 class of enzymes, which contain iron porphyrin.[2-6] Our nitrogen analogue is of special interest, as we pointed out,[1] because the additional valence of nitrogen makes it easy to impose selective geometric control on intramolecular versions of the process. We now wish to describe our study of the first example of such an intramolecular nitrogen functionalization of a saturated carbon.

2,5-Diisopropylbenzenesulfonamide (**1**)[7] was converted to the corresponding (imidoiodo)benzene derivative (**2**) by reaction with phenyliodine diacetate and KOH/MeOH, as in previous preparations of this class of compounds.[1,8] The off-white solid **2**, obtained in 89% yield, decomposed explosively at 100–110 °C and

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(1) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400. Subsequently there has been a report of alkane tosylamidation with ferrous chloride/chloroamine-T, which apparently proceeds by initial radical chlorination: Barton, D. H. R.; Hay-Motherwell, R. S.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 445. Recently aziridines have been synthesized stoichiometrically from alkenes with a nitridomanganese(V) porphyrin complex: Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073.

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