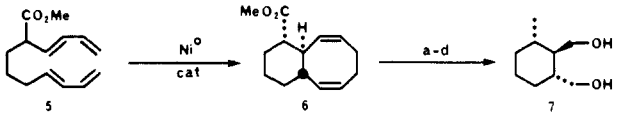
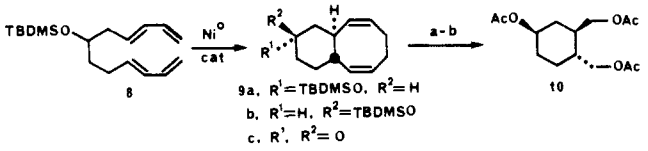
**Scheme I**[a]




[a](a) LAH, THF, quantitative; (b) TsCl, pyr, 0 °C, 59%; (c) $LiEt_3BH$, THF, 0 °C to room temperature, quantitative; (d) $O_3$, $CH_2Cl_2$/MeOH, -78 °C; $NaBH_4$, -78 °C to room temperature, 55%.

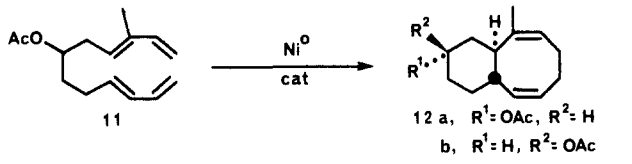
**Scheme II**[a]




[a](a) HOAc/THF/$H_2O$ (3:1:1), 77%, (b) $O_3$, $CH_2Cl_2$/MeOH, -78 °C; NaBH; -78 °C to room temperature; $Ac_2O$, pyr, DMAP, 18%.

prepared via a stereochemically unambiguous sequence (Scheme II).[14]

While diene substitution has been reported[3] to retard intermolecular cyclizations, the above studies involving monosubstituted dienes show that this is not a serious problem in the intramolecular reaction. Further substitution of the diene gave similar results. Thus, cyclization of **11**[15] proceeded with a rate comparable to that found for **8** and again provided trans-fused products (**12a,b**; 1:2.2)[16] in high yield (82%).




Several synthetically and mechanistically important conclusions follow from these studies. First, as with the intermolecular reactions,[1] catalyst variations influence the efficiency and product-type selectivity for these intramolecular reactions. Second, dienes connected by a three-atom tether selectively give cis-fused products whereas those connected by a four-atom chain are converted with comparably high but complementary selectivity to trans-fused products. Both results are in accord with a mechanism involving preferential formation and reaction of the more stable tetraene–nickel and bis-$\pi$-allyl complexes. Third, the remarkably high stereoinduction (99:1) observed in the reaction of tetraene **5** suggests that the ester group directs chemoselective and facial selective coordination of the catalyst to the proximate diene or that this selectivity arises through thermodynamically controlled formation of the bis-$\pi$-allyl or related complexes.[1,3] Finally, intramolecular reaction is favored over intermolecular oligomerization even in the case of the less reactive 1,2-disubstituted dienes. The above reactions serve as model studies for fundamentally new approaches to several structural classes including taxanes, ophiobolins, and fusicoccins. Further studies on the synthetic utility and origins of selectivities of this new reaction class are in progress.

**Acknowledgment.** Support for this work was provided by the National Science Foundation (CHE 83-19020). NMR spectra were obtained by using instruments provided by the National Science Foundation (CHE 81-09064 and CHE 84-14329).

**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR data for **2a,b**, **6**, **9a,b**, and **12a,b** (3 pages). Ordering information is given on any current masthead page.

## Synthesis of a Chiral Rhodium Alkyl via Metal Insertion into an Unstrained C–C Bond and Use of the Rate of Racemization at Carbon To Obtain a Rhodium–Carbon Bond Dissociation Energy

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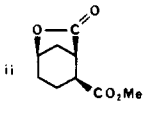
We have found that directed insertion of a Rh(I) complex into an unstrained carbon–carbon bond, where one of the carbons is a chiral center, provides a new route to rhodium–chiral alkyl complexes. The substrate for C–C activation was (*S*)-8-quinolinyl $\alpha$-methoxybenzyl ketone (**1**) $[\alpha]_D$ -117°. As with all other 8-quinolinyl alkyl ketones,[1] it reacted with $[(C_2H_4)_2RhCl]_2$, in this case at 25 °C for 1 h, to give a yellow, chlorine-bridged polymer, **2** (98.6%), that was solubilized by pyridine to give the acylrhodium(III) alkyl **3**, the product of C–C cleavage (Scheme I). Ligand-promoted reductive elimination with $P(OMe)_3$ regenerated **1**.[2] Chromatographic isolation of **1** (71%) gave material with $[\alpha]_D$ -111°. The near identity between the rotation of starting and recovered **1** means either that both the C–C bond breaking and forming steps proceed with retention or both steps proceed with inversion at carbon. Since in other systems C–C bond-forming reductive eliminations proceed with retention,[3] we believe such is also the case here. Therefore, the first step in this cycle, the C–C bond breaking step, must proceed with retention as well.

If complex **3** was heated at 90 °C for 1 h, benzaldehyde formed. Several $CH_3$-derived molecules were produced, including ethane. Carrying out the thermolysis in the presence of $CCl_4$ gave $CH_3Cl$ in addition to PhCHO (>80%). Since $\alpha$-alkoxy radicals are known to fragment to carbonyl compounds and alkyl radicals,[4] these results indicate that the Rh–$CHPh(OCH_3)$ bond in **3** undergoes homolysis at 90 °C and the resulting $^{\bullet}CHPh(OCH_3)$ radical fragments to PhCHO and $^{\bullet}CH_3$. No heterolysis of the C–$OCH_3$ bond was detected when **3** was heated with excess $CD_3OD$, since the $OCD_3$ group was not incorporated into **3**.

At lower temperatures Rh–C bond homolysis also occurred, but due to the stability of the radicals formed, no new products were observed by $^1H$ NMR. However, cage escape products could be detected in a crossover experiment. When the rhodium complexes **3** and **4** were combined and heated (45 °C, 2 h) and then the ligand was regenerated with $P(OMe)_3$, the crossover ligands **6** and **7** were obtained (ca. 20% yield) in addition to the starting ligands **1** and **5**. A control experiment in which a mixture of **3** and **4** was immediately subjected to $P(OMe)_3$ gave no crossover ligands.

Heating **3** at temperature up to 60 °C cleanly racemized the carbon center, which from the above results must arise by homolysis of the Rh–C bond and recombination of the Rh and C radicals. The rate of racemization at carbon was first order in **3** and independent of the pyridine/rhodium ratio over the range

(14) Ester ii (Yadav, J.; Corey, P.; Hsu, C.-T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, *22*, 811) was epimerized (LDA, THF, -78 to -10 °C; aqueous $NH_4Cl$, 32%) and the epimer reduced to provide a triol which upon acetylation (LAH, THF; $Ac_2O$, pyr, DMAP, 64%) gave **10**, found to be identical with material derived from **9b**.




(15) Addition of (3-methylpentadienyl)lithium to hepta-4,6-dienal, alkoxide-accelerated rearrangement (see ref 12), and acetylation ($Ac_2O$, pyr, DMAP) provided **11** (38% overall yield).

(16) Stereochemical assignments in **12a,b** are based on $^1H$ NMR comparison with **9a,b** and the independent conversion of **12a,b**, via saponification and oxidation, to the same ketone.

(1) Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054.
(2) Suggs, J. W.; Wovkulich, M. J.; Cox, S. D. *Organometallics* **1985**, *4*, 1101.
(3) Flood, T. C. *Top. Stereochem.* **1981**, *12*, 37.
(4) Steenken, S.; Schushmann, H.-P.; vonSonntag, C. *J. Phys. Chem.* **1975**, 79, 763.

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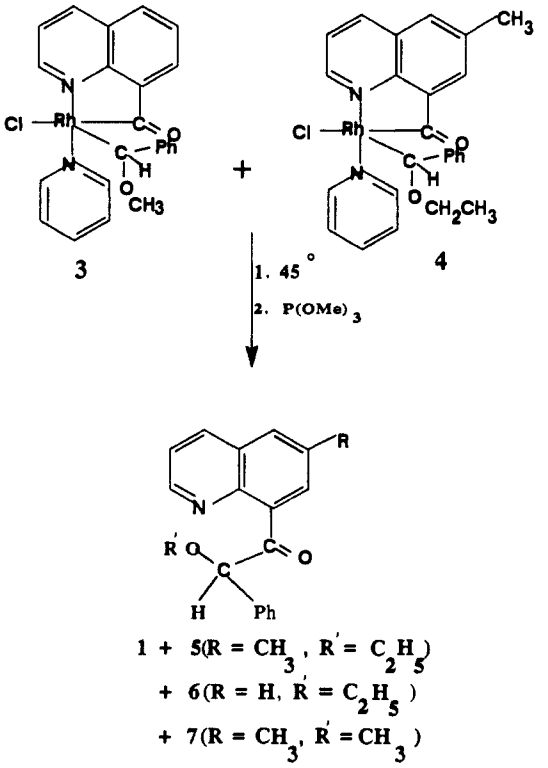
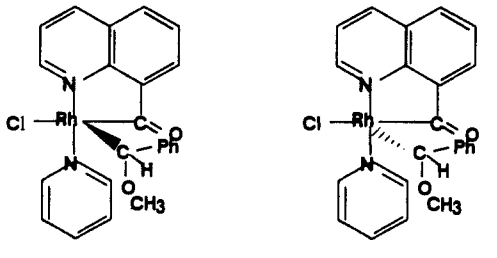



1-3. Table I gives the racemization rate constants at carbon for **3** over the temperature range 37-52 °C. These values lead to $\Delta H^{\ddagger}$(racemization) of 32.5 ± 1.5 kcal/mol and $\Delta S^{\ddagger}$ 22 ± 4 cal/(deg mol).[5] Since the carbon radical formed upon homolysis of the Rh-C bond in **3** should have a very low racemization barrier,[6] $\Delta H^{\ddagger}$(racemization) is the activation enthalpy for homolysis of the Rh-CHPh($OCH_3$) bond. Recombinations in analogous $Co^{II}$-alkyl radical systems have very low barriers, ca. 2 kcal/mol.[7] Assuming a 2 kcal/mol barrier to recombination for the $Rh^{II}$·CHPh($OCH_3$) radical pair results in a Rh-C bond dissociation energy in **3** of 31 kcal/mol.[8] Comparing this number to the Co-C BDE in [($C_6H_5N$)(dimethylglyoxine)$_2$CoCHPh($CH_3$)] of 19.9 kcal/mol[9] supports the expectation that M-C bonds are stronger for second-row metals than for first-row metals.[10]

In addition to providing a new substrate for measuring M-C BDEs, C-C activation of a chiral ligand in this case produced a new route to complexes chiral at the metal. **3** is formed as a single diastereomer. As yet we cannot say if **3** is the diastereomer shown or its enantiomer at Rh, **3a**, with the alkyl group below the plane




(5) Part of the reasons for the high $\Delta S^{\ddagger}$ is that in **3** there is hindered rotation of the phenyl group of the α-methoxybenzyl ligand seen by broad phenyl resonances at 25 °C which sharpen at 50 °C.

(6) Greene, F. D. *J. Am. Chem. Soc.* **1959**, *81*, 2688.

(7) Ng, F. T. T.; Rempel, G. L.; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 621. Finke, R. G.; Hay, B. P. *Inorg. Chem.* **1984**, *23*, 3041.

(8) There may be a slight preference for radical recombination in the solvent cage to give retention (Kopecky, F. R.; Gillan, T. *Can. J. Chem.* **1969**, *47*, 2371). However, the difference in recombination barrier heights for retention vs. inversion should not be significant.

(9) Halpern, J. *Acc. Chem. Res.* **1982**, *15*, 238.

(10) Skinner, H. A.; Connor, J. A. *Pure Appl. Chem.* **1985**, *57*, 79. Collman, J. P.; McElwee-White, L.; Brothers, P. J.; Rose, E. *J. Am. Chem. Soc.* **1986**, *108*, 1332.

**Scheme I**

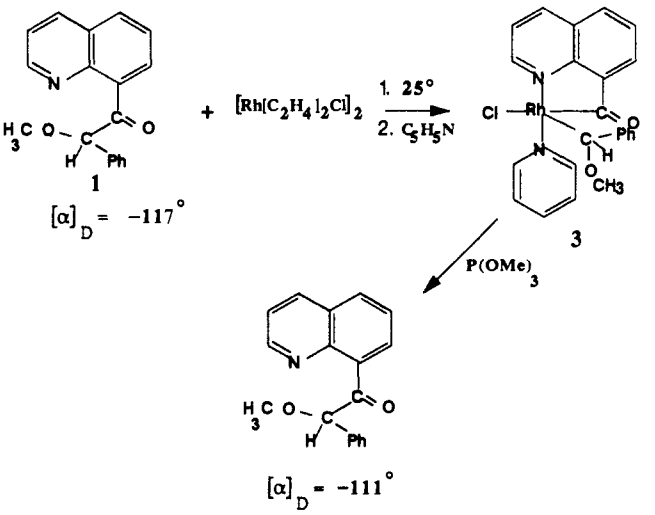


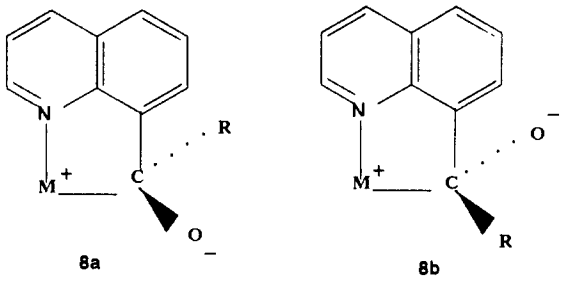

**Table I.** First-Order Rate Constants, $k_{rac}$, for Racemization at Carbon of **3**[a]

| temp, °C | half-life × $10^{-3}$, s | $k_{rac}$, $s^{-1}$ |
|---|---|---|
| 37 | 108.0 | $6.4 \times 10^{-6}$ |
| 40 | 25.2 | $2.7 \times 10^{-5}$ |
| 44.5 | 18.0 | $3.8 \times 10^{-5}$ |
| 47 | 10.8 | $6.4 \times 10^{-5}$ |
| 49 | 13.2 | $5.3 \times 10^{-5}$ |
| 52 | 5.7 | $1.2 \times 10^{-4}$ |

[a] Measured in $CHCl_3$ at 6-12 mM concentrations of **3**. Ligand-promoted reductive elimination by $P(OMe)_3$ of **3** gave **1** which was purified to constant $[\alpha]_D$ by column chromatography.

of the other ligands. Racemization at rhodium takes place at a comparable rate to racemization at carbon and can be followed by $^1H$ NMR.

We propose that chiral induction at Rh arises from collapse of a tetrahedral intermediate (**8a** or **8b**) which is on the path to




C-C cleavage in these chelating ketones. Such a mechanism is similar to mechanisms of known organic reactions, such as the Baeyer-Villiger reaction.[11] Observation of cleavage of RCO-R bonds to quaternary carbons[12] and of oxygen atom transfer from quinolinyl ketone carbonyl oxygens to CO[13] makes this tetrahedral intermediate mechanism more likely. Chiral induction at the Rh center would then arise by having only one of the diastereomers **8a** or **8b** collapse to products. If a tetrahedral intermediate is involved in α-ketone C-C bond activation, then there is a mechanistic basis for expecting to find other systems that could activate RCO-C bonds in the presence of other types of C-C and C-H bonds.

**Acknowledgment.** This work was supported by the NSF (CHE 8207269) and in part by the donors of the Petroleum Research

(11) Gutsche, C. D. *Org. React.* **1954**, *8*, 364.

(12) Suggs, J. W.; Jun, C.-H. *J. Chem. Soc., Chem. Commun.* **1985**, 92.

(13) Suggs, J. W.; Wovkulich, M. J.; Lee, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 5546. The transfer of oxygen from a tetrahedral intermediate to a coordinated CO is similar to the oxygen atom exchange between $CO_2^-$ and CO seen in an iron complex.[14]

(14) Lee, G. R.; Cooper, N. J. *Organometallics* **1985**, *4*, 794.

Fund, administered by the American Chemical Society. J.W.S. is a Research Career Development Awardee of the National Cancer Institute (CA-00947).

**Supplementary Material Available:** Synthesis and spectral data for **1**, **3**, and **3a** (1 page). Ordering information is given on any current masthead page.

## Biosynthesis of Coronatine, a Novel Polyketide

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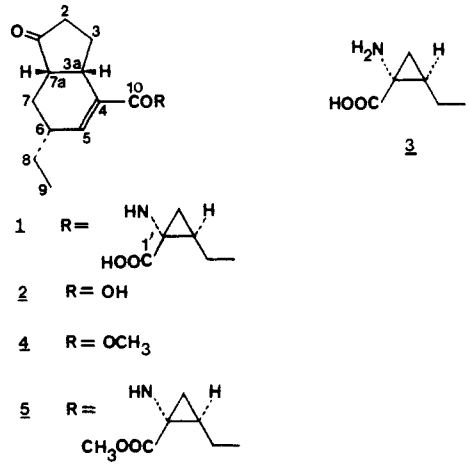
Coronatine (**1**) is a novel phytotoxin isolated from liquid cultures of the plant pathogens *Pseudomonas syringae* pv. *atropurpurea*,[1,3] which infects Italian ryegrass, and *Ps. syringae* pv. *glycinea*,[2,3] which infects soybean plants. Infection of the host plants by these bacteria induces chlorosis on the leaves due to the production of coronatine.[1,2] The importance of coronatine and its unique structure have prompted us to carry out the biosynthetic investigations reported here.

The structure of coronatine (**1**) poses two major biosynthetic problems. One concerns the formation of coronafacic acid (**2**),







3

while the other involves the formation of coronamic acid (**3**). We have examined both of these problems by administration of labeled precursors to liquid cultures of *Ps. syringae* pv. *glycinea* PDDCC 4182.[3] Investigations of coronafacic acid **2** were conducted by isolation of **2** from the culture broth as its methyl ester (**4**) after treatment with diazomethane. The complete assignment of the $^{13}C$ NMR spectrum of **4** (Table I) was accomplished by using several techniques. Treatment of **4** with $D_2O$/DCl led to the disappearance of the $^{13}C$ NMR signal of C-2 from the noise-decoupled spectrum. Reduction of **4** with lithium tri-*tert*-butoxyaluminum hydride yielded a single alcohol,[4] in which the $^{13}C$ NMR signals for C-2 and C-7a were shifted upfield to 31.05 and 42.28 ppm, respectively.

Biosynthetic studies also proved an invaluable aid to assignment. The structure of coronafacic acid suggested that the molecule might be a polyketide. Accordingly, sodium (1-$^{13}C$)- and (2-$^{13}C$)acetate were administered to *Ps. syringae* cultures. The results of these experiments (Table II, experiments 1, 2) clearly indicated that five molecules of acetate are incorporated into **4**. The positions of the labels and their connectivities were unequivocally

**Table I.** Carbon-13 Chemical Shifts for Methyl Coronafacate (**4**)

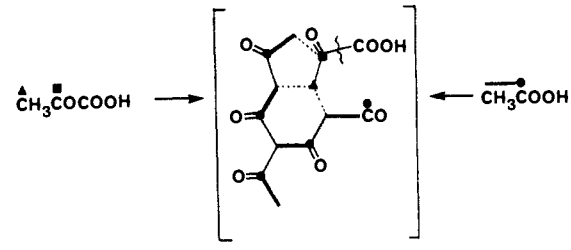
| carbon atom | $\delta^a$ | carbon atom | $\delta^a$ |
|---|---|---|---|
| 1 | 220.5 | 7 | 25.8 |
| 2 | 38.1 | 7a | 46.6 |
| 3 | 28.1 | 8 | 27.8 |
| 3a | 36.2 | 9 | 11.2 |
| 4 | 131.3 | 10 | 167.3 |
| 5 | 144.2 | 11 | 51.7 |
| 6 | 37.7 | | |

[a] Shifts were measured in deuteriochloroform at 75.47 MHz.

**Table II.** Administration of Labeled Precursors to *Ps. syringae*

| expt | precursor | compd isolated | labeling pattern |
|---|---|---|---|
| 1 | sodium (1-$^{13}C$)acetate | 4 | C-1, C-5, C-7, C-8, C-10 |
| 2 | sodium (2-$^{13}C$)acetate | 4 | C-2, C-4, C-6, C-7a, C-9 |
| 3 | sodium (1,2-$^{13}C_2$)acetate | 4 | connectivities between C-1, C-2; C-4, C-10; C-5, C-6; C-7, C-7a; C-8, C-9 |
| 4 | sodium (1-$^{13}C$)butyrate | 4 | no enrichment |
| 5 | (1-$^{13}C$)glycine | 4 | no enrichment |
| 6 | (2-$^{13}C$)glycine | 4 | no enrichment |
| 7 | (1,3-$^{13}C_2$)glycerol | 4 | all carbons except $OCH_3$ enriched |
| 8 | sodium (1-$^{13}C$)pyruvate | 4 | no enrichment |
| 9 | sodium (2-$^{13}C$)pyruvate | 4 | C-3; C-1, C-5, C-7 C-8, C-10 |
| 10 | sodium (3-$^{13}C$)pyruvate | 4 | C-3a; C-2, C-4, C-6, C-7a, C-9 |
| 11 | sodium (2,3-$^{13}C_2$)pyruvate | 4 | connectivities between C-3, C-3a; C-1, C-2; C-4, C-10; C-5, C-6; C-7, C-7a; C-8, C-9 |
| 12 | (1-$^{13}C$)-DL-isoleucine plus (1-$^{13}C$)-DL-alloisoleucine | 5 | C-1′ |

**Scheme I**




2

established by administration of sodium (1,2-$^{13}C_2$)acetate followed by analysis of the resulting ester by using a COSYX ($^{13}C$ COSY) experiment (Table II, experiment 3).[5,6] The presence of an ethyl group in **2** suggested that butyrate might also be a specific precusor. However, administration of (1-$^{13}C$)butyrate yielded unlabeled ester (experiment 4).

The incorporation experiments with labeled acetate demonstrated that two carbon atoms of coronafacic acid, C-3 and C-3a, are *not* acetate derived. It therefore appeared that **2** is a polyketide with a novel starter unit. A number of compounds were evaluated as potential starter units. These included glycine (experiments 5, 6) and glycerol (experiment 7). However, neither of these substances were specific precursors. Pyruvic acid was then evaluated. Administration of pyruvate labeled with $^{13}C$ at C-1, C-2, and C-3 revealed the surprising fact that C-3 and C-3a of coronafacate are derived from C-2 and C-3 of pyruvate, respectively (experiments 8-10). In these experiments, the remaining

(1) Ichihara, A.; Shiraishi, K.; Sata, H.; Sakamura, S.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636.
(2) Mitchell, R. E.; Young, H. *Phytochemistry* **1978**, *17*, 2028.
(3) Mitchell, R. E. *Physiol Plant Pathol.* **1982**, *20*, 83.
(4) The hydroxy group in the reduction product is presumed to be trans to the ethyl group due to approach of the reagent from the less-hindered side.
(5) Aue, W. P.; Bartholdt, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229. Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.
(6) Spectra were taken in deuteriochloroform on an IBM AF300 spectrometer.

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