carbon (neopentane, 2,3-dimethylbutane, or cyclohexane) is increased, the viscosity of the inert solvents used (Freon or CCl_4) decreases, and the ratio of competitive rates of geminate cage reaction and diffusion also changes. The reactivity of the hydrocarbon determines the viscosity dependence of polychlorination. The reactivity/molecules of neopentane:2,3-dimethylbutane:cyclohexane is 1:1.6:2.7.[18] The effect of diffusion becomes more important in determining the amount of polychlorination that takes place as the cage walls become less reactive. With the least reactive hydrocarbon, neopentane, over the range of concentrations plotted, 23-65% of the [M]/[P] halogenation ratio is due to changes in viscosity. As the walls of the cage become more reactive, as in the case of DMB, viscosity only affects the ratio 18-55%. In the chlorination reactions of cyclohexane the viscosity affected the amount of [M]/[P] halogenation by a negligible amount, ~5%.

The viscosity of the solution can also affect the isomer distribution of the polychlorination products since the rotation of the caged alkyl halide in viscous media becomes competitive with hydrogen abstraction. The ratio of 1,1-/1,3-dichloroneopentane increases in the viscous solvent, Freon 112, compared to the same ratio produced from the free-encounter chlorination of neopentyl chloride.

Experimental Section

Materials. All reagents except Freon 112 were obtained as reagent grade (2,3-dimethylbutane, cyclohexane, neopentane, Phillips research grade) and were distilled before use. Freon 112 (Matheson) was recrystallized several times before use.

Viscosity Measurements. The viscosities of all the solvent mixtures reported in this work were determined at 23 °C with an Ostwald viscometer, calibrated with the appropriate solvent (e.g., Freon 11, Freon 113, or CCl_4) as a standard.[19]

Solution-Phase Chlorination. A mixture of the hydrocarbon, with or without an internal standard (*p*-dichlorobenzene), and solvent was prepared and its viscosity was measured at 23 °C. In the absence of light, an aliquot of this solution and an aliquot of a chlorine solution (in the same solvent) were added to each ampule. The reaction ampules were degassed by freeze-thaw (three cycles), sealed, thermostated at 23 °C, and irradiated with two 150-W incandescent lamps. After the reactions were completed, the product mixtures were analyzed by GC using a 100-m fused silica capillary column (SE-30). The relative product yields from three or more independent experiments were calculated by comparison of their peak integrations to that of the internal standard and corrected for the FID detector response. The areas were determined with use of a Varian Vista 401 computing integrator interfaced to a Varian 6000 gas chromatograph fitted with an FID detector. The mono- and dichlorinated products of neopentane and 2,3-dimethylbutane were identified by comparison of the retention times, GC-MS, spectra and GC-IR spectra with those of authentic samples.

The structures of the products obtained from the chlorination of cyclohexane were assigned by comparison of their GC retention times (i.e., their order of retention) with those reported by Ingold using the same column.[9a] Under our GC conditions all seven of the isomeric dichlorides could be separated. Their GC-MS spectra confirmed their assignments as dichlorides. As an additional confirmation, the retention times of authentic samples of *trans*-1,2-dichlorocyclohexane and chlorocyclohexane were used to check the retention times of the dichlorides, and to calibrate the correction factors used for the FID response factors for the [M]/[P] ratios.

Gas-Phase Chlorinations. In the absence of light, a weighed amount of the hydrocarbon substrate and an aliquot of a chlorine solution in Freon 113 or Freon 11 were added to a 0.5-L reaction vessel. The mixture was degassed by freeze-thaw (two cycles), sealed, thermostated at 23 °C, and irradiated with two 150-W incandescent lamps. After the reactions were completed, the product mixtures were analyzed in the same manner as was used for the solution-phase reactions.

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(η^6-Arene)chromium Complexes in Organic Synthesis: Synthesis of (±)-Dihydroxyserrulatic Acid

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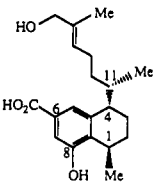
Abstract: The title compound **1** has been synthesized by utilizing some characteristic properties of (η^6-arene)chromium complexes. The synthesis of dihydroxyserrulatic acid (**1**) consists of the following three key steps: (1) nucleophilic addition of a dithianyl group at the meta position to an electron-donating methoxy group, (2) trans arrangement of two benzylic substituents (at C-1 and C-4 positions), and (3) stereocontrol between C-4 and C-11 positions (extracyclic position). These three steps have been realized with high regio- and stereoselectivities by utilizing (arene)chromium complexes.

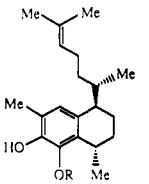
Introduction

Serrulatane class diterpenoids dihydroxyserrulatic acid (**1**),[1] *seco*-pseudopterosins A-D (**2**),[2] pseudopterosins A-D (**3**),[3] and the related compounds[4,5] have been isolated from the leaves of *Eremophila serrulate*, a visid schrub, and marine sea whip *Pseudopterogorgia elisabethae*. Some of these diterpenoids possess the anti-inflammatory and analgesic activity with potencies comparable to that of indomethacin.[6] Moreover, it appears that their mechanism of actions is distinct from that of the cyclooxygenase-inhibiting anti-inflammatory agents, making them particularly fascinating compounds from a biological standpoint.



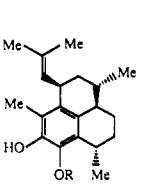
1

Dihydroxyserrulatic acid



2

Seco-pseudopterosins A-D
A; R= arabinose



3

Pseudopterosins A-D
A; R= β-xylose

These compounds have 1,4,6-trisubstituted 8- (or 7,8-di-) hydroxytetralin as a common structural unit and are prenylated

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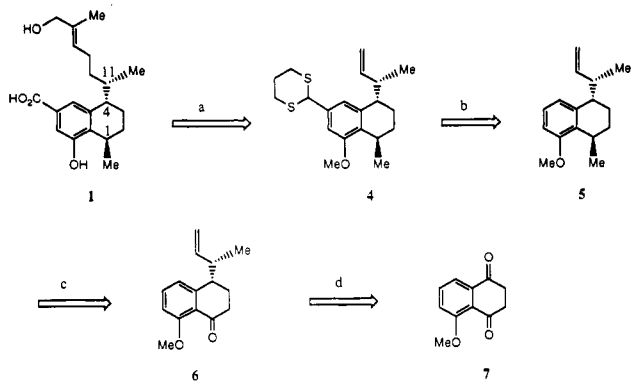
Scheme I. Reterosynthesis of Dihydroserrulatic Acid

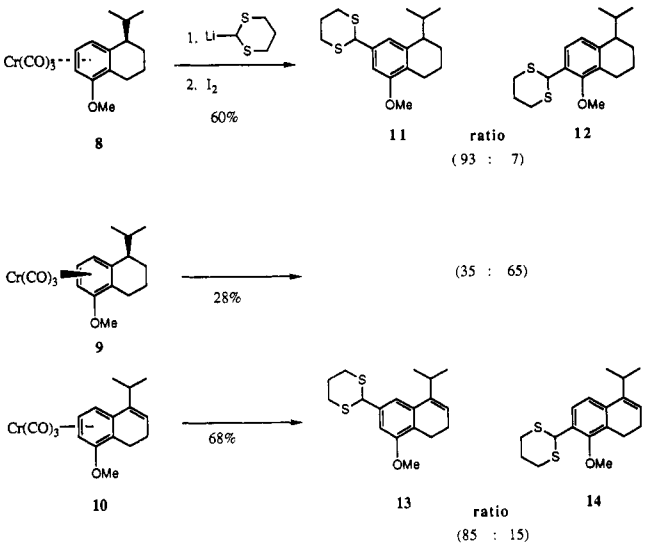


analogues of sesquiterpenoids hydroxycalamenenes.[7,8] For stereo- and regioselective synthesis of these phenolic diterpenoids from the tetralin derivatives, the following three tactical problems are required to be solved: (1) stereocontrol between C-4 and C-11 positions, (2) trans arrangement of two benzylic substituents (at C-1 and C-4), and (3) introduction of a C-1 unit at the 6-position (meta position to electron-donating OH group at C-8). Retrosynthetic analysis of dihydroxyserrulatic acid (**1**) seems to be derived from the methoxytetralin derivative **4** with satisfactory stereochemistry, which is, in turn, led from an easily available dihydrojuglone equivalent (**7**) (Scheme I). Three steps (b, c, and d) in this retrosynthetic scheme are essential for high selective synthesis of **1** and could be sufficiently realized by utilizing some characteristic properties of (arene)chromium complexes. We report herein the first synthesis[9] of (±)-dihydroxyserrulatic acid (**1**) utilizing characteristic properties of (arene)chromium complexes, by a route that should also lend itself to preparation of these types of diterpenoids.

Results and Discussion

1. Regioselectivity on Nucleophilic Addition of (Arene)chromium Complexes. An introduction of proper substituents at the meta position to an electron-donating group is a fundamental step for the synthesis of these diterpenoids (step b in Scheme I) and is not so easy under electrophilic substitution conditions. However, the use of (arene)chromium complexes seems to be effective for the achievement of this problem by following two methods: nucleophilic addition and meta lithiation[10] of (arene)chromium complexes. Of the two methods, we have employed the nucleophilic addition reactions to (arene)chromium complexes in the total synthesis of these diterpenoids owing to easy preparation of the starting material methoxytetralin complexes. An addition of

Scheme II. Nucleophilic Addition of 2-Lithio-1,3-dithane to (Arene)chromium Complexes



carbon nucleophiles to the (arene)chromium complexes and subsequent oxidation developed by Semmelhack have become a useful method for the introduction of substituents at proper positions not accessible by electrophilic substitution reactions.[11] High regioselectivity in the nucleophilic addition is often observed with substituted (arene)chromium complexes. With strong electron-donating substituents, meta substitution is preferred. It is well known that (anisole)$Cr(CO)_3$ is reacted with carbon nucleophiles to give meta-substituted anisole with extremely high regioselectivity after oxidation of intermediate cyclohexadienylchromium anion complexes.[12] This method seems to be profitable for our purpose, but the regioselectivity in the nucleophilic addition is confusing in some cases. Therefore, we have investigated the influence of a configuration of the substituent on the regioselectivity in the nucleophilic addition of a dithianyl group to stereoisomeric (substituted methoxytetralin)$Cr(CO)_3$ complexes as model compounds for the meta functionalization.

(1-*exo*-Isopropyl-5-methoxytetralin)$Cr(CO)_3$ (**8**) was treated with 2-lithio-1,3-dithiane in THF/HMPA at −78 °C followed by an oxidative demetalation with I_2 to produce a meta-dithianylated compound (**11**) with high regioselectivity (Scheme II). High meta selectivity in the exo complex **8** is a result similar to that of (anisole)$Cr(CO)_3$. However, the corresponding *endo*-isopropyl complex **9** afforded predominantly an ortho-substituted compound (**12**) in 28% yield under the same conditions. The results (low yield and preference of the formation of the ortho isomer) in the endo complex **9** are unexpected results, regardless of the presence of a OMe group. With (dihydronaphthalene)chromium complex **10**, a meta-substitution product was still predominant without a formation of addition product to the double bond. The formation of addition product to only the arene ring in the complex **10** is in marked contrast with the results of a chromium complex of 5-methoxy-3,4-dihydronaphthalene without an isopropyl group at the C-1 position, in which nucleophiles attacked always to the double bond as a Michael-type reaction.[13] The regioselectivities

(1) Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Raston, C. L.; White, A. H.; Hall, S. R. *Tetrahedron* **1977**, *33*, 1475. Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Stuart, A. D. *Aust. J. Chem.* **1979**, *32*, 2079. Bunko, J. D.; Ghisalberti, E. L.; Jefferies, P. R. *Ibid.* **1981**, *34*, 2237.

(2) Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363.

(3) Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140. The synthesis of pseudopterosin A has been achieved by the following two groups: Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584. Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472. Idem. *Tetrahedron Lett.* **1990**, *31*, 3857.

(4) Hall, S. R.; Raston, C. L.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1467.

(5) Harris, C. A.; Burch, M. T.; Fenical, W. *Tetrahedron Lett.* **1988**, *29*, 4361.

(6) Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 6238.

(7) Rowe, J. W.; Toda, J. K. *Chem. Ind. (London)* **1969**, 922. Burden, R. S.; Kemp, S. M. *Phytochemistry* **1983**, *22*, 1039. Lindgre, O. B.; Svahn, C. M. *Ibid.* **1968**, *7*, 1407.

(8) Kashman, Y. *Tetrahedron* **1979**, *7*, 1407. Nishizawa, M. Inoue, A.; Sastrapradja, S.; Hayashi, Y. *Phytochemistry* **1983**, *22*, 2083.

(9) A preliminary communication of the synthesis of dihydroxyserrulatic acid: Uemura, M.; Nishimura, H.; Hayashi, Y. *Tetrahedron Lett.* **1990**, *31*, 2319.

(10) Meta lithiation; Masters, N. F.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, 955. Beswick, P. J.; Leach, S. J.; Masters, N. F.; Widdowson, D. A. *Ibid.* **1984**, 46. Clough, J. M.; Mann, I. S.; Widdowson, D. A. *Tetrahedron Lett.* **1987**, *28*, 2645.

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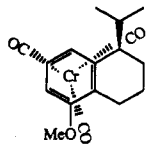
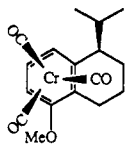
(13) (a) Semmelhack, M. F. Suefert, W.; Keller, L. *J. Am. Chem. Soc.* **1980**, *102*, 6586. (b) Uemura, M.; Minami, T.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1193.

in the nucleophilic addition reactions of 2-lithio-1,3-dithiane to the chromium complexes **8**, **9**, and **10** were not varied significantly by the change of reaction conditions (reaction time, temperature, and solvents). These results indicate that a dissociation of the carbanion from intermediate cyclohexadienylchromium anion complexes would be largely suppressed. In any event, the regioselectivity in nucleophilic reactions to these complexes with 2-lithio-1,3-dithiane is cleanly dependent on a configuration of the isopropyl to the $Cr(CO)_3$ group. However, nitrile- or cyanohydrine-stabilized carbanions instead of 2-lithio-1,3-dithiane changed greatly the regioselectivity in the reaction with *endo*-isopropyl complex **9**. Thus, the endo complex **9** gave predominantly the corresponding meta-substituted compounds in high yields with high selectivities (meta:ortho = 88–95:12–5) by the treatment of 2-lithio-2-methylpropionitrile or a lithio compound of protected acetaldehyde cyanohydrine under the same conditions and subsequent oxidation with I_2. Both exo complex **8** and dihydronaphthalene complex **10** afforded still the corresponding meta-substituted compounds with high regioselectivity under the same reaction conditions.

Usually, the reaction with sulfur-stabilized carbanions is known to be governed by a kinetic control,[14] and the regioselectivity is contributed to the balance of charge control and frontier orbital control.[14,15] The charge control is induced by a preferred conformation of $Cr(CO)_3$ tripod to the arene ring, and the frontier orbital control is based on the magnitude of coefficient in the LUMO of the uncomplexed arenes. The *exo*-isopropyl complex **8** can adopt preferentially a syn-eclipsed conformation (**15**) as



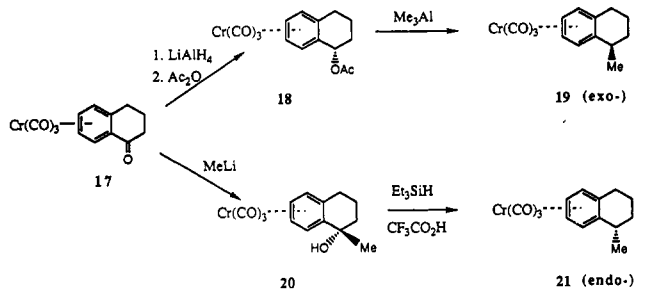
15



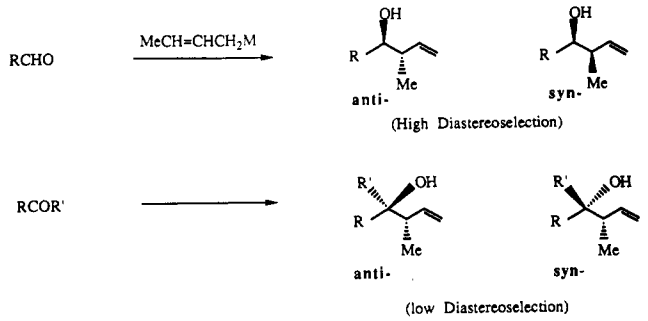
16

well as (anisole)$Cr(CO)_3$,[16] and therefore the *meta*-carbon eclipsed by the other CO ligand is exclusively attacked by nucleophiles, because of cooperation of $Cr(CO)_3$ tripod and an electron-donating OMe group. However, the corresponding *endo*-isopropyl complex **9** exists in a staggered conformation[17] (**16**) to avoid an adverse steric interaction between the endo-oriented isopropyl group and the CO ligand. This staggered conformation in the endo complex **9** would result in lower yield and regioselectivity in the nucleophilic addition reactions. As mentioned above, in the case of *endo*-isopropyl chromium complex **9**, the regioselectivity of the nucleophilic addition reaction with 2-lithio-1,3-dithiane is distinct from the result of reaction with cyanohydrine- or nitrile-stabilized carbanions. Although it is not clear at the present time that the nucleophilic addition reactions of 2-lithio-1,3-dithiane to the complexes **8**, **9**, and **10** are governed by a kinetic or a thermodynamic control, the exo orientation of the C-1 substituent in (5-methoxytetralin)chromium complexes is required for the introduction of a dithianyl group at the meta position with high yield and selectivity.[18]

Scheme III



Scheme IV



2. Stereoselective Synthesis of Both (exo-Substituted Tetralin)- and (endo-Substituted Tetralin)chromium Complexes. It is required that two benzylic substituents (at C-1 and C-4 positions) should be oriented as a trans configuration for the synthesis of these phenolic diterpenoids, and this problem could be easily solved with (arene)chromium complexes. The arene–$Cr(CO)_3$ unit can perform a dual property in stabilization of both carbanions and carbocations at the benzylic position. The formations of benzylic anions and cations are each rendered more facile relative to those in the uncomplexed arenes, and these two contrasting properties have found widespread applications in organic syntheses. The $Cr(CO)_3$ moiety can also function as a useful stereochemical template. Therefore, nucleophilic or electrophilic attack at the reactivc center of an alicyclic ring condensed to an aromatic ring, e.g., indane or tetralin derivatives, always occurs stereoselective in an exo fashion. These interesting properties can be applied for the stereoselective synthesis of both *exo*- and *endo*-alkyl-substituted isomers from a common compound as follows.[19]

(1-*endo*-Acetoxytetralin)$Cr(CO)_3$ (**18**), prepared from (α-tetralone)$Cr(CO)_3$ (**17**), was converted into (1-*exo*-methyltetralin)$Cr(CO)_3$ (**19**) via $Cr(CO)_3$-stabilized carbocation by the treatment with Me_3Al (Scheme III). On the other hand, (1-*exo*-methyl-1-*endo*-tetralol)$Cr(CO)_3$ (**20**), obtained from **1** and MeLi, produced (1-*endo*-methyltetralin)chromium complex **21** by an ionic hydrogenolysis with Et_3SiH and CF_3CO_2H. Thus, both (*exo*-alkyl-substituted tetralin)- and (*endo*-alkyl-substituted tetralin)chromium complexes could be stereoselectively synthesized from a common compound, only by a change of reaction order of nucleophiles. This method could be useful for the stereocontrol at the benzylic positions.

3. Stereocontrol between C-4 and C-11 Positions. For the synthesis of these terpenoids, stereoselective conversion from α-tetralone carbonyl to the isobutenyl group is required (see step d in Scheme I). Since this type of stereoselective construction of the isobutenyl group from carbonyl ketone is not so easy, we have investigated the following three methods using (arene)-chromium complexes.

(a) Addition of Crotylmetals to $Cr(CO)_3$-Complexed Aromatic Ketones. Considerable attention has been focused on the ste-

(14) (a) Kündig, E. P. *Pure Appl. Chem.* **1985**, *57*, 1855. (b) Kündig, E. P.; Desobry, V.; Simmons, D. P.; Wenger, E. *J. Am. Chem. Soc.* **1989**, *111*, 1804.

(15) (a) Solladie-Cavallo, A. *Polyhedron* **1985**, *4*, 901. (b) Ohlsson, B.; Ullenius, C. *J. Organomet. Chem.* **1988**, *350*, 35. (c) M. F. Semmelhack, M. F.; Garcia, J. L.; Cortes, D.; Farina, R.; Hong, R.; Carpenter, B. K. *Organometallics* **1983**, *2*, 467. (d) Albright, T. A.; Carpenter, B. K. *Inorg. Chem.* **1980**, *19*, 3092. (e) Jackson, W. R.; Rae, I. D.; Wong, M. G.; Semmelhack, M. F.; Garcia, J. N. *J. Chem. Soc., Chem. Commun.* **1982**, 1359. (f) Semmelhack, M. F.; Clark, G. R.; Farina, R.; Saeman, M. *J. Am. Chem. Soc.* **1979**, *101*, 217. (g) Rose, E.; Boutonnet, J. C.; Mordenti, L.; Le Matret, O.; Precigoux, G. *J. Organomet. Chem.* **1981**, *221*, 147.

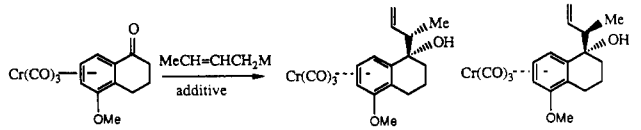
(16) (a) Carter, O. L.; Mcphail, A. T.; Sim, G. A. *J. Chem. Soc. A* **1966**, 288. (b) Huttner, G.; Fischer, E. O.; Carter, O. L.; McPhail, A. T.; Sim, G. A. *J. Organomet. Chem.* **1966**, *6*, 288. (c) Meurs, F.; Konigsveld, H. *Ibid.* **1977**, *131*, 423.

(17) A staggered conformation of the complex **9** was determined by an X-ray diffraction study.

(18) In contrast to 2-lithio-1,3-dithiane, the reaction of cyanohydrine- or nitrile-stabilized carbanions with the endo complex **9** gave meta-substituted products with high regioselectivity: Uemura, M.; Minami, T.; Shinoda, Y.; Nishimura, H.; Shiro, M.; Hayashi, Y. *J. Organomet. Chem.* **1991**, *406*, 371.

(19) Uemura, M.; Isobe, K.; Hayashi, Y. *Tetrahedron Lett.* **1985**, *26*, 767.

Table I. Diastereoselective Addition of Crotylmetals to Chromium Complex **22**



22 23 (anti-) 24 (syn-)

entry	M	additive	**23:24**	yield (%)
1	MgCl	none	50:50	75
2	MgCl	Me_3Al	80:20	75
3	MgCl	Et_3Al	93:7	73
4	MgCl	$(i\text{-}Bu)_3Al$	85:15	65
5	Li	Et_3Al	94:6	60
6	MgCl	Et_3B	28:72	30

reoselective carbon–carbon bond forming process in acyclic and conformationally flexible molecules.[20] Reaction of crotylmetal reagents with the carbonyl group seems to be useful for the synthesis of these terpenoids. Generally, a high degree of diastereoselectivity has been achieved in the reactions with *aldehydes* to form anti- or syn-homoallylic alcohols, respectively (Scheme IV).[21] The stereochemical outcome depends on the geometry of the double bond of crotylmetals, nature of the metal, and reaction conditions. However, much less selectivity[22] is observed in the reaction of *ketones* with the crotyl reagents, because of a smaller difference in the steric size between both groups attached to the ketone carbonyl. Recently, Seebach's and Reetz's groups have independently reported[23] that crotyltitanium reagents reacted with some ketones to yield the anti adducts with high selectivity. However, α-tetralone gave no satisfactory diastereoselectivity with the crotyltitanium reagents. In order to obtain high selectivity in the reaction of crotylmetals with ketones, the aromatic part was modified temporarily by a sterically bulkier group, e.g., the arene transition-metal complexes.[24]

Reaction of (α-tetralone)$Cr(CO)_3$ (**22**) with the crotyltitanium reagents or crotylmagnesium chloride and the related reagents gave no sufficient diastereoselectivity. However, the reaction with crotyl Grignard or lithium reagent in the presence of 1 equiv of trialkylaluminum afforded in sufficiently high selectivity the anti adduct **23** without formation of the regioisomer by α-attack of the crotylmetal group. An addition of Et_3Al showed particularly high anti selectivity. Since α-tetralone itself without $Cr(CO)_3$ complexation gave a mixture of a 2:1 ratio of anti and syn adducts under the same conditions, (Table I) the $Cr(CO)_3$ complexation apparantly increased the anti selectivity in this reaction. Interestingly, (benzaldehyde)$Cr(CO)_3$, in contrast to $Cr(CO)_3$-complexed aromatic ketones, exhibited no selectivity with this aluminum "ate" complex.

This reaction presumably proceeds via a six-membered chair transition state, in which the smaller group on the ketone carbonyl function occupies a pseudoaxial position and the double bond of the ate complex exists as the *E* form. Although the cyclic pentacoordinate transition state of the aluminum ate complex may be curious, a number of other reactions has been proposed via the ate complex mechanism.[25] Interestingly, the combination of Et_3B and crotyl Grignard produced predominantly the syn adduct **24**. An alternative transition state should be considered in this case.

Scheme V

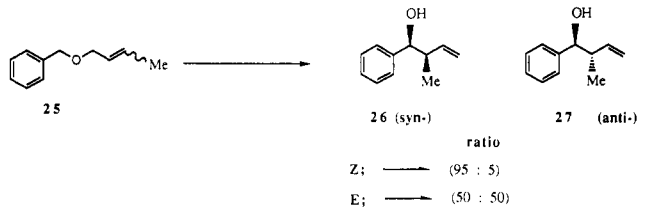
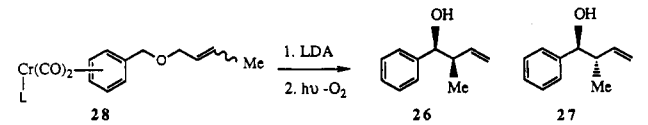


Table II. Sigmatropic Wittig 2,3-Rearrangement of (Benzyl crotyl ether)$Cr(CO)_3$



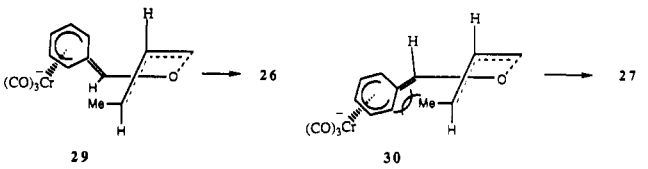
28 26 27

substrates 28	geometry (purity)	**26:27**	yield (%)
L = CO	*E* (96%)	95:5	69
L = PPh_3	*E* (96%)	88:12	95
L = CO	*Z* (88%)	48:52	40

(b) Wittig Sigmatropic 2,3-Rearrangement of $Cr(CO)_3$-Complexed Benzyl Crotyl Ethers. The Wittig sigmatropic 2,3-rearrangement has become an efficient method for an acyclic stereocontrol. It has already been reported that the Wittig 2,3-rearrangement of benzyl (*Z*)-crotyl ether provides extremely high syn stereoselection, whereas the corresponding *E* substrate gives poor stereoselectivity (Scheme V).[26]

The mechanism of stereoselection in the Wittig 2,3-rearrangement has been rationalized in terms of pseudo 1,3-diaxial interaction and gauche interaction in the enveloped five-membered transition state.[26,27] Since the extent of stereoselectivity is influenced by the steric bulkiness and a nature of the substituents, the modification of the aromatic ring to a sterically bulkier group, e.g., chromium complexation, is of interest in the synthetic applications and mechanistic study of the Wittig 2,3-rearrangement.[28]

Treatment of [benzyl (*E*)-crotyl ether]$Cr(CO)_3$ (**28**, L = CO) with LDA in THF at −78 °C for 7 h afforded a diastereomeric mixture of the syn product **26** and the anti product **27** in a ratio of 95:5 after a demetalation by an exposure to sunlight. The high syn selectivity from the *E* substrate in chromium complex is in contrast to the result from the $Cr(CO)_3$-free substrate and can be explained as follows. The coordination of the $Cr(CO)_3$ group to the arene ring would greatly enhance the stability of benzylic carbanions by a delocalization onto the transition metal, and the migration terminus (benzylic position) has high sp^2 character, restricting a rotation about the benzylic carbon–*ipso*-carbon bond. Of the two possible transition states, the severe gauche interaction between Ar(Cr) and methyl groups exists in the transition state **30**. Therefore, the other transition state **29** would be preferred



29 30

for the rearrangement on the exo face away from the $Cr(CO)_3$ to lead to the syn isomer **26**, in which 1,3-diaxial interaction of

(20) Reviews: (a) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (c) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (d) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (e) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (f) Masamune, S.; Choy, W.; Peterson, J. C.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1983**, *24*, 1. (g) Braun, M. *Ibid.* **1987**, *26*, 24.

(21) (a) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (b) Buse, C. T.; Heathcock, C. H. *Ibid.* **1978**, 1685. (c) A review: Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1986; p 176; see also ref 20.

(22) Sjoholm, R. E. *Acta Chem. Scand.* **1990**, *44*, 82.

(23) (a) Seebach, D.; Widler, L. *Helv. Chim. Acta* **1982**, *65*, 1972. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441.

(24) Uemura, M.; Minami, T.; Isobe, K.; Kobayashi, T.; Hayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 967.

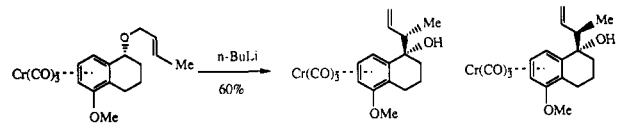
(25) (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969. (b) Reetz, M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259.

(26) Review: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(27) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

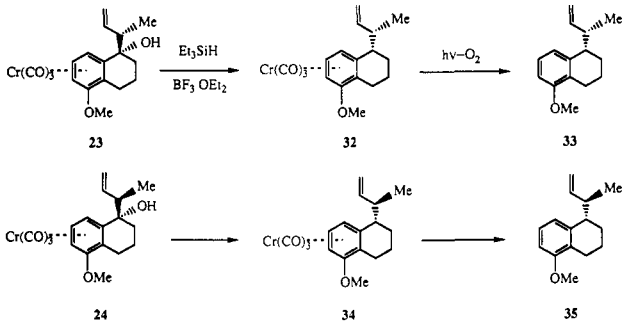
(28) (a) Uemura, M.; Nishimura, H.; Hayashi, Y. *J. Organomet. Chem.* **1989**, *376*, C3. (b) Brocard, J.; Mahmoudi, M.; Pelinski, L.; Maciewski, L. *Tetrahedron Lett.* **1989**, *30*, 2549.

Scheme VI. Sigmatropic Wittig 2,3-Rearrangement



31 23 24

Scheme VII



23 32 33

24 34 35

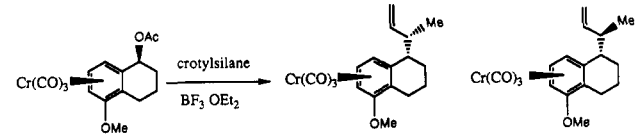
the transition state **29** is reduced due to the formation of the sp^2 carbon. The restricting rotation about the C–C bond would be supported from a result that [ortho-substituted benzyl (*E*)-crotyl ether]$Cr(CO)_3$ gave only one syn-rearranged complex (of two syn- and two anti-rearranged chromium complexes possible) by the Wittig sigmatropic 2,3-rearrangement.[28a] Similarly, it is well known[26] that (*E*)-crotyl ethers of glycolic acid derivatives, such as ester, amide, and oxazoline, resulted in high syn selectivity in the Wittig 2,3-rearrangement.[26] In these cases, the migrating carbons have also sp^2 character due to the formation of enolate anions. On the other hand, the corresponding *Z* substrate chromium complex gave a 1:1 diastereomeric mixture in the Wittig 2,3-rearrangement (Table II).

A high syn stereoselectivity from the *E* compound in the Wittig rearrangement is also evident in the chromium complexes with an alkyl substituent at the benzylic position. [*endo*-1-((*E*)-Crotyloxy)-5-methoxytetralin]$Cr(CO)_3$ (**31**) was treated with *n*-BuLi to afford predominantly the syn-rearranged complex **24**, the ratio being in marked contrast to that obtained from (5-methoxy-1-tetralone)$Cr(CO)_3$ and crotylaluminum ate complex (Table I) as mentioned above (Scheme VI). The corresponding *Z* substrate produced a 1:1 mixture of **23** and **24**. [*exo*-(Crotyloxy)tetralin]chromium complexes gave no rearranged products under the same conditions. In the [*exo*-(crotyloxy)tetralin]chromium complex, the corresponding endo benzylic hydrogen was not removed with base owing to the steric effect. These chromium complexes **23** and **24** were easily converted to compounds **33** and **35**, respectively, by hydrogenolysis and following photooxidation as mentioned in the above methods (Scheme VII). The compound **33**, derived from the tetralone complex **22** by the reaction with crotylaluminum ate complex, has a suitable stereochemistry for the synthesis of dihydroxyserrulatic acid (**1**). On the other hand, the stereochemistry at the extracyclic position in the compound **35** derived by the Wittig 2,3-rearrangement is consistent with that of pseudopterosins and *seco*-pseudopterosins. However, both chromium complexes **32** and **34** have the endo configuration of the isobutenyl groups, and the nucleophilic addition of dithianyl group to these complexes seems to be difficult with respect to both regioselectivity and yield, as mentioned above.

(c) Reaction of Crotylsilanes with (Acetoxytetralin)chromium Complex. In order to prepare the (exo-substituted tetralin)-chromium complex for an easy access of nucleophilic addition reactions, we have examined stereochemical outcomes in the reaction of $Cr(CO)_3$-stabilized benzylic carbocations with stereoisomeric crotylsilanes. With (*E*)-crotyltrimethylsilane,[29] an

(29) (*E*)- and (*Z*)-crotyltrimethylsilanes were prepared by cross-coupling of [(trimethylsilyl)methyl]magnesium chloride with (*E*)- and (*Z*)-bromopropene in the presence of nickel(II) catalyst: Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865.

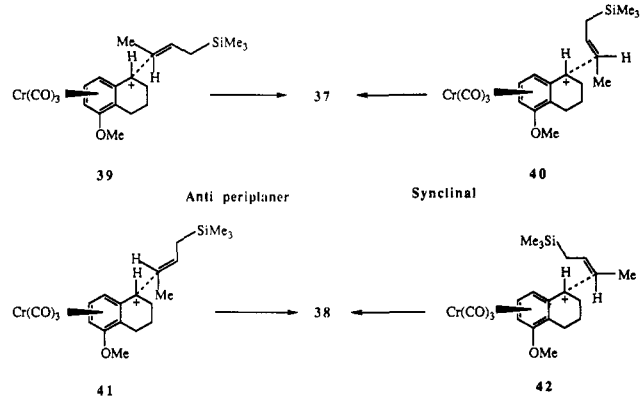
Table III. Reaction of Crotylsilanes with (Arene)chromium Complex



36 37 38

crotylsilanes	37:38	yield (%)
(*E*)-MeCH=CHCH$_2$SiMe$_3$	75:25	92
(*E*)-MeCH=CHCH$_2$SiMePh$_2$	73:27	91
(*Z*)-MeCH=CHCH$_2$SiMe$_3$	50:50	90

Scheme VIII



39 37 40

41 38 42

(*endo*-acetoxytetralin)chromium complex (**36**) gave two (exo-isobutenylated tetralin)chromium complexes **37** and **38** in a ratio of 75:25 (Table III). The stereochemistry at the extracyclic position of the major complex **37** was defined as the anti configuration by the conversion of photooxidized product **33**, whereas the corresponding (*Z*)-crotylsilane gave no selectivity in the reaction with the complex **36** under the same conditions. Thus, the reaction with (*E*)-crotylsilanes provides a simple and convenient method, albeit a moderate diastereoselectivity, for the synthesis of dihydroxyserrulatic acid (**1**).

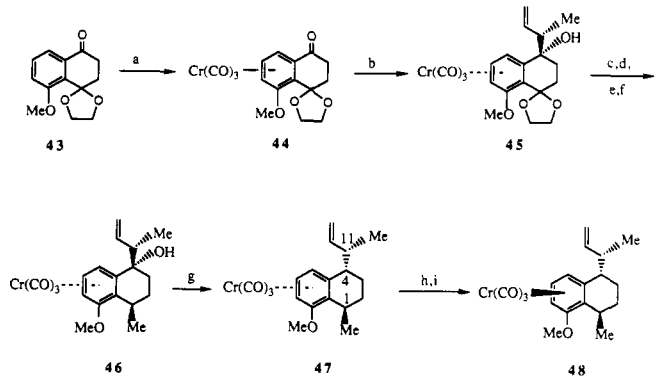
The proclivities of the (*E*)-silanes to give the C-1/11 syn product **37** could be rationalized as follows (Scheme VIII). Four transition-state structures (**39**–**42**) would be considered for an "open" or "extended" mode.[30] Both sinclinal structures **40** and **42** have a significant steric interaction. Of the two anti periplanar transition states, the structure **39** would seem to be the preferred transition state, which produce the syn chromium complex **37**.

4. Synthesis of (±)-Dihydroxyserrulatic Acid via (Arene)-chromium Complexes. Mono(ethylene acetal) of dihydro-1,4-naphthoquinone **43**[31] was converted to the corresponding (arene)chromium complex **44** by thermal conditions with $Cr(CO)_6$. At first, the complex **44** was treated with the crotylaluminum ate complex to afford a stereochemically desirable anti adduct (**45**) (in C-4/C-11 relationship) and a C-11 stereoisomeric compound (ratio of 85–90:15–10) as described by the above-mentioned method. Stereoselective conversion of the acetal group to the *exo*-methyl derivative **46** was achieved in 61% overall yield in four steps as shown in Scheme IX. An ionic hydrogenolysis of the benzylic hydroxyl of the complex **46** produced a C-4 endo-substituted complex (**47**) in 56% yield, along with a dehydration product at the C-3/C-4 position (18% yield). Although the relative configuration at the C-1, C-4, and C-11 positions in the complex **47** is contended with that of dihydroxyserrulatic acid, the isobutenyl substituent at the C-4 position is oriented as the endo configuration. As mentioned above, the reaction of the complex

(30) (a) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (b) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1651. (c) Denmark, S. E.; Weber, E. J.; Wilson, T. M. *Tetrahedron* **1989**, *45*, 1053. (d) Yammamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.

(31) Crouse, D. J.; Wheeler, M. M.; Goemann, M.; Tobin, P. S.; Basu, S. K.; Wheeler, D. M. S. *J. Org. Chem.* **1981**, *46*, 1814.

Scheme IX[a]



[a] Reagents: (a) $Cr(CO)_6$ (80%), (b) $MeCH{=}CHCH_2MgCl/Et_3Al$ (81%), (c) 1 N HCl (90%), (d) $NaBH_4$ (95%), (e) Ac_2O/pyr (95%), (f) Me_3Al (75%), (g) $Et_3SiH/BF_3{\cdot}OEt_2$ (56%), (h) $h\nu$ O_2 (95%), (i) $Cr(CO)_6$ (60%).

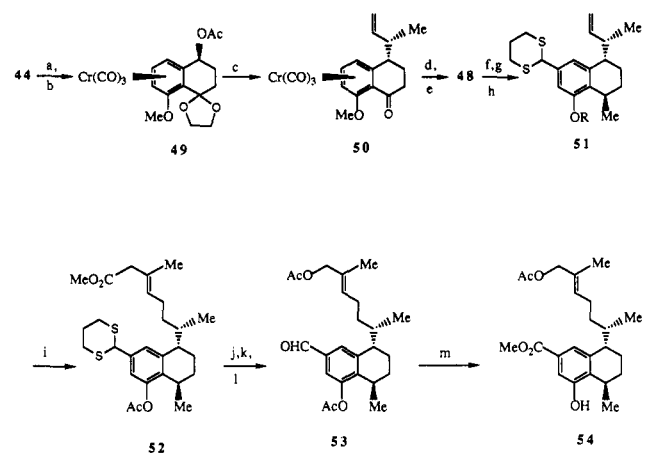
47 with 2-lithio-1,3-dithiane and subsequent demetalation gave a low yield (less than 5%) of nucleophilic addition products, in which the major product is on ortho-substituted compound (ratio of 3:1). In order to achieve the meta nucleophilic addition with high selectivity and yield, the face of chromium complexation in **47** should be inverted to the other face. On oxidative demetalation and subsequent recomplexation with $Cr(CO)_6$, the chromium complex **47** gave the face inverted C-4 exo-substituted complex **48** in 60% yield, but still accompanied by the diastereomer **47** in 20% yield. In this route, $Cr(CO)_6$ has to be used in two times, and many steps are required. Therefore, we turned our efforts to an alternative route for the synthesis of the key chromium complex **48**.

endo-Acetate complex **49** obtained from the complex **44** was reacted with the (*E*)-crotyltrimethylsilane in the presence of BF_3OEt_2 to afford a stereochemically desirable exo-substituted tetralone complex (**50**) in 72% yield, along with a C-11 stereoisomer (24% yield) (Scheme X). Stereoselective introduction of the *endo*-methyl at C-1 was straightforward. Treatment of the complex **50** with MeLi followed by hydrogenolysis of the resulting carbinol produced (1-endo-4-exo-substituted tetralin)chromium complex **48** in 45% overall yield. Nucleophilic addition of the dithianyl carbanion to the complex **48** gave C-6 dithianylated tetralin **51**, as expected, in 50% yield without a detectable amount of regioisomers. The acetate compound **51** (R = Ac) derived from **51** (R = Me) by demethylation and subsequent acetylation was converted to a coupling product (**52**) by the reaction with methyl β-bromomethacrylate in the presence of Pd catalyst after hydroboration with 9-BBN.[32] Reduction of the ester group in **52** followed by acetylation and subsequent hydrolysis of the 1,3-dithianyl group produced an aldehyde compound (**53**). The compound **53** was oxidized[33] to a methyl ester (**54**), which was further converted to (±)-dihydroxyserrulatic acid (**1**) by a basic hydrolysis.

Experimental Section

^1H NMR spectra were measured on a Hitachi R-90 and a JEOL GX-400 spectrometer. All NMR spectra were recorded in $CDCl_3$ solvent with tetramethylsilane as an internal reference. Chemical shifts are recorded in parts per million on the δ scale from tetramethylsilane, and coupling constants are given in hertz. IR spectra were determined on a JASCO A-100 spectrometer. Mass spectra were taken on a JEOL D-300 and a JEOL AX-500 spectrometer. Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyzer. All melting points were determined on a Yanagimoto MPJ-2 micromelting point apparatus and are uncorrected. Ether and THF were dried by distillation from sodium benzophenone ketyl before use, and methylene chloride was distilled from P_2O_5.

Scheme X[a]



[a] Reagents: (a) $LiAlH_4$ (95%), (b) Ac_2O/pyr (98%), (c) (*E*)-$MeCH{=}CHCH_2SiMe_3/BF_3{\cdot}OEt_2$ (72%), (d) MeLi (60%), (e) Et_3SiH/CF_3CO_2H (75%), (f) 2-lithio-1,3-dithiane/THF, then I_2 (50%), (g) EtSH/NaH/DMF (95%), (h) Ac_2O/pyr (96%), (i) 9-BBN, then (*E*)-methyl β-bromomethacrylate/$PdCl_2$(dppf)/K_2CO_3/H_2O (77%), (j) DIBAL-H (90%), (k) Ac_2O/pyr (98%), (l) $HgO/BF_3{\cdot}OEt_2/H_2O$ (69%), (m) $NaCN/MnO_2$/MeOH/AcOH (85%).

Nucleophilic Addition of 2-Lithio-1,3-dithiane to Tricarbonyl(1-*exo*-isopropyl-5-methoxytetralin)chromium (8). *n*-Butyllithium (1.6 M in hexane, 0.36 mL, 0.58 mmol) was added to a solution of 1,3-dithiane (70 mg, 0.58 mmol) in THF (5 mL) at −78 °C under argon, and the reaction mixture was stirred for 20 min at −20 °C. The mixture was again cooled to −78 °C, followed by addition of HMPA (1 mL). Into the above mixture was added a solution of *exo*-isopropyl chromium complex **8** (100 mg, 0.29 mmol) in THF (5 mL) at −78 °C, and the solution was stirred for an additional 30 min before addition of a solution of I_2 (221 mg, 0.87 mmol) in THF (2 mL). After 1 h of stirring, the reaction mixture was poured to an aqueous solution of Na_2SO_3. The mixture was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent produced a crude product (55 mg) as oil. The ratio of regioisomeric products was determined by 400-Mz ^1H NMR of $ArCH(S-)_2$: meta product **11**, 5.13 ppm; ortho product **12**, 5.59 ppm. Physical data of compound **11**: IR ($CHCl_3$) 1600, 1580, 1460, 1280, 1100, 915 cm^{-1}; ^1H NMR δ 0.75 (3 H, d, *J* = 7), 1.01 (3 H, d, *J* = 7), 1.50–3.20 (14 H, m), 3.82 (3 H, s), 5.13 (1 H, s), 6.76 (1 H, d, *J* = 2), 6.94 (1 H, d, *J* = 2); MS *m/e* 322 (M^+), 279, 248, 205. ^1H NMR of ortho isomer **12**: δ 0.80 (3 H, d, *J* = 7), 1.01 (3 H, d, *J* = 7), 1.50–3.20 (14 H, m), 3.80 (3 H, s), 5.59 (1 H, s), 7.02 (1 H, d, *J* = 8), 7.36 (1 H, d, *J* = 8). The addition to the corresponding *endo*-isopropyl complex **9** was carried out under the same conditions: yield 28%, the ratio of **11**:**12** is 35:65.

Nucleophilic Addition of 2-Lithio-1,3-dithiane to Dihydronaphthalene Complex 10. The addition of 1,3-dithiane to dihydronaphthalene complex **10** was conducted in a similar way as described above. The ratio of two regioisomeric products was determined by proton areas of $ArCH(S-)_2$: ortho, 5.57 ppm; meta, 5.08 ppm. Physical data of **13**: IR ($CHCl_3$) 1600, 1570, 1420, 1275, 1130, 1035, 910 cm^{-1}; ^1H NMR δ 1.13 (6 H, d, *J* = 7), 1.80–3.20 (11 H, m), 3.73 (3 H, s), 5.08 (1 H, s), 5.83 (1 H, t, *J* = 5), 6.84 (1 H, d, *J* = 2), 7.00 (1 H, d, *J* = 2); MS *m/e* 320 (M^+), 246, 203.

Tricarbonyl(1-*exo*-methyltetralin)chromium (19). To a solution of tricarbonyl(1-*endo*-acetoxytetralin)chromium (**18**) (100 mg, 0.31 mmol) in dry CH_2Cl_2 (5 mL) was added Me_3Al (1.4 mL, 1.0 M in hexane, 1.4 mmol) at −78 °C under argon. The reaction mixture was stirred for 30 min at the same temperature and warmed to 0 °C over 2 h. After addition of aqueous dilute HCl solution, the mixture was extracted with methylene chloride. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by SiO_2 chromatography with ether/hexane gave 82 mg of **19** as yellow crystals: mp 94 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 1960, 1880, 1450 cm^{-1}; ^1H NMR δ 1.30 (3 H, d, *J* = 7), 1.40–2.18 (4 H, m), 2.48–3.01 (3 H, m), 5.35–5.50 (4 H, m). Anal. Calcd for $C_{14}H_{14}O_3Cr$: C, 59.57; H, 5.00. Found: C, 59.54; H, 5.04.

Tricarbonyl(1-*endo*-methyltetralin)chromium (21). To a solution of chromium complex **20** (200 mg, 0.67 mmol), prepared from **17** with MeLi, and triethylsilane (214 μL, 1.34 mmol) in dry CH_2Cl_2 (1.0 mL) was added trifluoroacetic acid (155 μL, 2.01 mmol) at room temperature under argon. The reaction mixture was stirred at 30–40 °C for 4 h and

(32) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314 and references cited therein.
(33) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

quenched with water. The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration under reduced pressure and purification by SiO_2 chromatography produced 122 mg of endo complex **21**: mp 84 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 1960, 1880, 1460 cm^{-1}; ^1H NMR δ 1.40 (3 H, d, J = 7), 1.48–2.02 (4 H, m), 2.52–2.84 (3 H, m), 5.18 (2 H, t, J = 7), 5.60 (2 H, t, J = 7). Anal. Calcd for $C_{14}H_{14}O_3Cr$: C, 59.57; H, 5.00. Found: C, 59.52; H, 5.02.

Reaction of Tricarbonyl(5-methoxy-1-tetralone)chromium (22) with Crotylmagnesium Chloride in the Presence of Triethylaluminum. To a solution of 1.62 mL of crotylmagnesium chloride (0.26 M in THF, 0.44 mmol) in dry THF (5 mL) was added 0.44 mL of Et_3Al (1 M in hexane, 0.44 mmol) at −78 °C under argon. After stirring for 30 min, a solution of the complex **22** (130 mg, 0.40 mmol) in dry CH_2Cl_2 (4 mL) was injected to the above reaction mixture by a syringe at −78 °C. The reaction mixture was warmed to 0 °C over 3 h and quenched with saturated aqueous ammonium chloride. The mixture was extracted with ether and worked up as usual. SiO_2 chromatography gave a yellow crystalline product (110 mg) as a diastereomeric mixture of anti and syn adducts: The ratio of diastereomers (93:7) was determined by ^1H NMR (0.96 ppm for anti adduct; 1.11 ppm for syn adduct). Physical data of the anti adduct **23**: mp 101 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 2940, 1960, 1880, 1515, 1450, 1415, 1255 cm^{-1}; ^1H NMR δ 0.96 (3 H, d, J = 7), 2.14 (1 H, s), 1.78–2.96 (7 H, m), 3.70 (3 H, s), 4.82–5.42 (5 H, m), 5.94 (1 H, ddd, J = 18, 11, 8). Anal. Calcd for $C_{18}H_{20}O_5Cr$: C, 58.69; H, 5.47. Found: C, 58.76; H, 5.50.

Tricarbonyl[benzyl (*E*)-crotyl ether]chromium (28, L = CO). To a solution of tricarbonyl(benzyl alcohol)chromium (400 mg, 1.6 mmol) and (*E*)-crotyl alcohol (576 mg, 8.0 mmol) in dry CH_2Cl_2 (10 mL) was added zinc chloride (1.1 g, 8.0 mmol) at 0 °C under argon. The mixture was stirred for 3 h and quenched with water. The reaction mixture was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The organic layer was evaporated under reduced pressure and purified by SiO_2 chromatography (eluent ether/hexane) to afford 308 mg of the complex **28** (L = CO); IR ($CHCl_3$) 1970, 1890, 1100 cm^{-1}; ^1H NMR δ 1.74 (3 H, d, J = 7), 4.02 (2 H, d, J = 6), 4.18 (2 H, s), 5.23 (1 H, m), 5.36 (4 H, m), 5.55–5.64 (1 H, m), 5.70–5.82 (1 H, m); MS m/e 298 (M^+), 214.

Sigmatropic Wittig 2,3-Rearrangement of Chromium Complex 28 (L = CO). A solution of LDA in THF was prepared from *n*-BuLi (1.3 mL, 1.6 M in hexane, 2.0 mmol) and diisopropylamine (203 mg, 2.0 mmol) in dry THF (5 mL) by the standard method. To the above mixture was added a solution of the complex **28** (L = CO) (200 mg, 0.67 mmol) in THF (5 mL) at −78 °C under argon, and the reaction mixture was stirred for 7 h and quenched with water. The mixture was extracted with ether, and the extract was exposed to sunlight until a yellow solution was changed to colorless. The precipitate was filtered off, and the organic layer was concentrated under reduced pressure. Purification by SiO_2 chromatography gave 74 mg of the rearranged products **26** (syn) and **27** (anti) as a diastereomeric mixture. The ratio was determined by 400-Mz ^1H NMR (*Me*: 1.01 ppm for **26**; 0.86 ppm for **27**): ^1H NMR δ 1.01 (3 H, d, J = 7), 2.56–2.61 (1 H, m), 4.59 (1 H, d, J = 5), 5.02 (2 H, d, J = 11), 5.72–5.80 (1 H, m), 7.25–7.34 (5 H, m).

Tricarbonyl[benzyl (*Z*)-crotyl ether]chromium (28, L = CO): IR ($CHCl_3$) 1970, 1890, 1210, 1100 cm^{-1}; ^1H NMR δ 1.68 (3 H, d, J = 7), 4.16 (2 H, d, J = 6.5), 4.20 (2 H, s), 5.23–5.28 (1 H, m), 5.37 (4 H, s), 5.54–5.62 (1 H, m), 5.69–5.78 (1 H, m); MS m/e 298 (M^+), 214. This *Z* complex gave a 1:1 diastereomeric mixture by the Wittig rearrangement under the same conditions.

Tricarbonyl[1-*endo*-((*E*)-crotyloxy)-5-methoxytetralin]chromium (31). To a suspended mixture of NaH (60% in oil, 190 mg, 4.7 mmol) in DMF (2 mL) and ether (15 mL) was added a solution of tricarbonyl(5-methoxy-1-*endo*-tetralol)chromium (962 mg, 3.1 mmol) in ether (10 mL) at 0 °C under argon. To the above reaction mixture was added (*E*)-crotyl bromide (840 mg, 6.2 mmol) in ether (5 mL) at the same temperature, and the mixture was stirred for 2 h. The reaction mixture was quenched with water and extracted with ether. The extract was washed with aqueous dilute HCl and brine and dried over $MgSO_4$. Concentration of the organic layer under reduced pressure and purification by SiO_2 by SiO_2 chromatography producing 950 mg of the complex **31**: mp 80 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 1960, 1880, 1460, 1420, 1270 cm^{-1}; ^1H NMR δ 1.73 (3 H, d, J = 6.5), 1.97 (1 H, m), 2.13 (1 H, m), 2.57–2.73 (2 H, m), 3.72 (3 H, s), 4.03 (1 H, m), 4.24 (1 H, m), 4.35 (1 H, m), 5.05 (1 H, d, J = 7), 5.27 (1 H, d, J = 7), 5.33 (1 H, t, J = 7), 5.59–5.68 (1 H, m), 5.82 (1 H, m). Anal. Calcd for $C_{18}H_{20}O_5Cr$: C, 58.69; H, 5.47. Found: C, 58.73; H, 5.49.

Sigmatropic Wittig 2,3-Rearrangement of Complex 31. To a solution of the complex **31** (180 mg, 0.49 mmol) in THF (6 mL) was added 0.46 mL of *n*-BuLi (1.6 M in hexane, 0.74 mmol) at −78 °C under argon, and the reaction mixture was stirred for 5 h. Usual workup gave 108 mg (60%) of the rearranged products *anti*-**23** and *syn*-**24** as a diastereomeric mixture in a ratio of 12:88. Physical data of the syn product **24**: IR ($CHCl_3$) 2940, 1960, 1870, 1520, 1450, 1420, 1260 cm^{-1}; ^1H NMR δ 1.11 (3 H, d, J = 7), 1.70–2.91 (8 H, m), 3.66 (3 H, s), 4.82–5.42 (5, H, m), 5.85–5.90 (1 H, m). MS m/e 368 (M^+), 312, 284, 264, 228, 177. Exact Mass Calcd for $C_{18}H_{20}O_5Cr$: 368.0706. Found: 368.0711.

Preparation of (1*S,11*S**)-1-Isobutenyl-5-methoxytetralin (33) from Complex 23.** To a solution of the complex **23** (60 mg, 0.16 mmol) and triethylsilane (190 mg, 1.63 mmol) in CH_2Cl_2 (15 mL) was added boron trifluoride etherate (0.10 mL, 0.82 mmol) at −78 °C under argon, and the mixture was warmed to 0 °C over 3 h. The mixture was quenched with water and extracted with methylene chloride. The extract was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration in vacuo and purification by SiO_2 chromatography afforded 35 mg of hydrogenolysis exo-butenylated complex **32**: ^1H NMR δ 1.25 (3 H, d, J = 7), 1.60–2.95 (8 H, m), 3.71 (3 H, s), 4.95–5.50 (5 H, m), 5.70–6.18 (1 H, m). Without further purification on the complex **32**, a yellow solution of **32** (30 mg) in ether (5 mL) was exposed to sunlight for 30 min. The precipitate was filtered off, and the organic layer was evaporated. Silica gel chromatography gave 16 mg of **33**: IR ($CHCl_3$) 1580, 1460, 1435, 1255, 1205 cm^{-1}; ^1H NMR δ 1.07 (3 H, d, J = 7), 1.45–2.00 (4 H, m), 2.45–2.94 (4 H, m), 3.65 (3 H, m), 4.75–5.10 (2 H, m), 5.40–5.85 (1 H, m), 6.60 (1 H, d, J = 8), 6.80 (1 H, d, J = 8), 7.05 (1 H, t, J = 8); MS m/e 216 (M^+), 161, 146, 129. Exact Mass Calcd for $C_{15}H_{20}O$: 216.1520. Found: 216.1517.

(1*S,11*R**)-1-Isobutenyl-5-methoxytetralin (35).** The compound **35** was prepared from the complex **24** by the same reaction sequence: ^1H NMR δ 0.84 (3 H, d, J = 7), 1.50–1.95 (4 H, m), 2.40–2.90 (4 H, m), 4.75–5.10 (2 H, m), 5.40–5.85 (1 H, m), 6.61 (1 H, d, J = 8), 6.80 (1 H, d, J = 8), 7.04 (1 H, t, J = 8).

Reaction of Tricarbonyl(1-*endo*-acetoxy-5-methoxytetralin)chromium (36) with Trimethyl-(*E*)-crotylsilane. To a solution of the complex **36** (50 mg, 0.14 mmol) and trimethyl-(*E*)-crotylsilane (36 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (0.055 mL, 0.21 mmol) at −78 °C under argon, and the reaction mixture was stirred for 30 min, then warmed to 0 °C over 1 h, and then quenched with water. The mixture was extracted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Usual workup gave 47 mg of exo-isobutenylated complexes **37** and **38** in a ratio of 75:25. The ratio was determined by the area of the methyl signal (1.08 ppm for **37**; 0.90 ppm for **38**). Physical data of **37**: mp 66 °C; IR ($CHCl_3$) 1960, 1860, 1520, 1210 cm^{-1}; ^1H NMR δ 1.08 (3 H, d, J = 7), 1.20–2.90 (8 H, m), 3.66 (3 H, s), 4.75–5.05 (4 H, m), 5.35 (1 H, t, J = 8), 5.46–5.80 (1 H, m); MS m/e 352 (M^+), 297, 268, 212, 161. Exact Mass Calcd for $C_{18}H_{20}O_4Cr$: 352.0821. Found: 352.0771. The complex **37** was oxidized by an exposure to sunlight under the usual conditions to give the decomplexed product, in which the spectra of ^1H NMR was consistent with that of the compound **33** derived from the complex **23**.

Tricarbonyl[1,4-dihydro-4,4-(ethylenedioxy)-5-methoxy-1-oxonaphthalene]chromium (44). A mixture of 1,4-dihydro-4,4-(ethylenedioxy)-5-methoxy-1-oxo-naphthalene (**43**) (1.0 g, 4.3 mmol) and $Cr(CO)_6$ (1.9 g, 8.5 mmol) in di-*n*-butyl ether (120 mL), heptane (12 mL), and THF (12 mL) was heated at 120–130 °C with stirring under a nitrogen atmosphere for 60 h. After the reaction mixture was cooled to room temperature, solvents and excess of $Cr(CO)_6$ were removed under reduced pressure. The residue was dissolved with ether (50 mL), and the precipitate was filtered off. The red ether solution was evaporated in vacuo, and the residue was purified by SiO_2 chromatography with ether/hexane to give chromium complex **44** (1.8 g, 80%) as red crystals: mp 168 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 1980, 1910, 1690, 1500, 1415 cm^{-1}; ^1H NMR δ 2.05–2.88 (4 H, m), 3.70 (3 H, s), 3.97–4.27 (4 H, m), 5.10 (1 H, t, J = 3.0), 5.57 (2 H, d, J = 6.0). Anal. Calcd for $C_{16}H_{14}O_7Cr$: C, 51.90; H, 3.81. Found: C, 51.86; H, 3.80.

(4*S,11*S**)-Tricarbonyl[1,4-dihydro-1,1-(ethylenedioxy)-4-*endo*-hydroxy-4-*exo*-isobutenyl-8-methoxynaphthalene]chromium (45).** A solution of triethylaluminum in hexane (1.0 M, 1.62 mL, 1.62 mmol) was added dropwise over 5 min to a solution of crotylmagnesium chloride (0.5 M in THF, 3.24 mL, 1.62 mmol) in THF (12 mL) at −78 °C under nitrogen, and the mixture was stirred for 30 min. To the resulting mixture was added a solution of complex **44** (400 mg, 1.08 mmol) in THF (8 mL) at −78 °C, and the reaction mixture was warmed to −20 °C over 3 h. The mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 (30 g) chromatography with ether/hexane to afford chromium complex **45** (420 mg, 90%) as yellow crystals. The chromium complex of the reaction products was determined by the proton area of the methyl group (anti adduct, δ 0.94; syn adduct, δ 1.10): mp 126 °C; IR ($CHCl_3$) 1960, 1890, 1510 cm^{-1}; ^1H NMR δ 0.94 (3 H, d, J = 6.3), 1.95–2.26 (4

H, m), 2.16 (1 H, s), 2.55 (1, H, m), 3.76 (3 H, s), 4.02–4.20 (4 H, m), 4.95–5.13 (4 H, m), 5.60 (1 H, t, J = 6.3), 5.91–6.00 (1 H, m). Anal. Calcd for $C_{20}H_{22}O_7Cr$: C, 56.34; H, 5.20. Found: C, 56.38; H, 5.21.

(4*S,11*S**)-Tricarbonyl(4-*endo*-hydroxy-4-*exo*-isobutenyl-8-methoxy-1-tetralone)chromium.** A solution of the chromium complex **45** (400 mg, 0.94 mmol) in THF (30 mL) and 1 N HCl (10 mL) was stirred at room temperature for 3 h under nitrogen. The reaction mixture was extracted with ether, and the extract was washed with saturated aqueous $NaHCO_3$ solution and brine and dried over $MgSO_4$. The organic layer was evaporated in vacuo, and the residue was purified by SiO_2 (40 g, ether/petroleum ether, 1:3) to afford 323 mg (90%) of a hydrolyzed (ketone)chromium complex as red crystals: mp 172 °C (recrystallization from ether); IR ($CHCl_3$) 1970, 1910, 1680, 1520 cm^{-1}; ^1H NMR δ 1.16 (3 H, d, J = 6.5), 1.86 (1 H, s), 2.20–2.80 (5 H, m), 3.71 (3 H, s), 4.78–5.25 (4 H, m), 5.56–6.00 (2 H, m). Anal. Calcd for $C_{18}H_{18}O_6Cr$: C, 56.55; H, 4.75. Found: C, 56.28; H, 4.76.

(1*S,4*S**,11*S**)-Tricarbonyl(1-*endo*-acetoxy-4-*endo*-hydroxy-4-*exo*-isobutenyl-8-methoxytetralin)chromium.** A solution of the above (ketone)chromium complex (385 mg, 1.01 mmol) in MeOH (140 mL) was added to a solution of $NaBH_4$ (573 mg, 15.16 mmol) in MeOH (50 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min, warmed to room temperature over 1.5 h, and quenched with water (50 mL). Methanol was concentrated under reduced pressure and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by SiO_2 chromatography to give a reduction product. This hydroxy chromium complex was acetylated without further purification. A solution of the hydroxy chromium complex and catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine in acetic anhydride (2 mL) and pyridine (5 mL) was stirred at room temperature under nitrogen. The mixture was stirred for 3 h, poured into cold aqueous 0.5 N HCl (100 mL) solution, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel (30 g, ether/petroleum ether, 1:1) chromatography afforded 400 mg (93%) of an *endo*-acetoxy complex as yellow crystals: mp 118 °C (from ether/hexane): IR ($CHCl_3$) 3200, 1970, 1890, 1720, 1510 cm^{-1}; ^1H NMR δ 1.06 (3 H, d, J = 7.0), 2.00 (1 H, s), 2.19 (3 H, s), 1.75–2.35 (5 H, m), 3.69 (3 H, s), 4.83–5.06 (4 H, m), 5.55 (1 H, t, J = 6.5), 5.68–6.13 (2 H, m). Anal. Calcd for $C_{20}H_{22}O_7Cr$: C, 56.34; H, 5.20. Found: C, 56.52; H, 5.32.

(1*R,4*S**,11*S**)-Tricarbonyl(4-*endo*-hydroxy-4-*exo*-isobutenyl-1-*exo*-methyl-8-methoxytetralin)chromium (46).** To a solution of the above prepared *endo*-acetoxy chromium complex (200 mg, 0.47 mmol) in CH_2Cl_2 (16 mL) was added 1.9 mL of Me_3Al (1.47 M in hexane, 2.8 mmol) at −78 °C under argon. The reaction mixture was warmed to 0 °C over 3 h, quenched with saturated aqueous NH_4Cl solution, and extracted with methylene chloride. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to give an *exo*-methyl complex (**46**) (152 mg, 80%) as a yellow liquid: IR ($CHCl_3$) 1960, 1890, 1410, 1012 cm^{-1}; ^1H NMR δ 0.88 (3 H, d, J = 7), 1.20 (3 H, d, J = 7), 2.26 (1 H, s), 1.11–3.30 (6 H, m), 3.66 (3 H, s), 4.80–5.40 (5 H, m), 5.76–6.14 (1 H, m); MS m/e 382 (M^+), 298 (M^+ − 3CO). Exact Mass Calcd for $C_{19}H_{22}O_5Cr$: 382.0873. Found: 382.0889.

(1*R,4*S**,11*S**)-Tricarbonyl(4-*endo*-isobutenyl-1-*exo*-methyl-8-methoxytetralin)chromium (47).** Boron trifluoride etherate (1.7 mL, 6.5 mmol) was added to a solution of the *exo*-methyl chromium complex **46** (500 mg, 1.3 mmol) and triethylsilane (1.52 g, 13 mmol) in CH_2Cl_2 (20 mL) at −78 °C under argon. The mixture was warmed to −30 °C over 3 h and quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with methylene chloride, and usual workup afforded a complex (**47**) (280 mg, 56%) as yellow crystals: mp 128 °C; IR ($CHCl_3$) 1960, 1870 cm^{-1}; ^1H NMR δ 1.19 (3 H, d, J = 7), 1.24 (3 H, d, J = 7), 1.55–3.20 (7 H, m), 3.73 (3 H, s), 5.10–5.20 (4 H, m), 5.34 (1 H, t, J = 7), 6.00–6.18 (1 H, m). Anal. Calcd for $C_{19}H_{22}O_7Cr$: C, 62.29; H, 6.05. Found: C, 62.41; H, 5.89.

Tricarbonyl[1,4-dihydro-4-*endo*-acetoxy-1,1-(ethylenedioxy)-8-methoxynaphthalene]chromium (49). To a solution of the chromium complex **44** (500 mg, 1.35 mmol) in ether (90 mL) and THF (5 mL) was added a mixture of $LiAlH_4$ (26 mg, 0.68 mmol) in ether (20 mL) at −20 °C under nitrogen. The reaction mixture was stirred for 30 min at the same temperature and quenched with water. A precipitate was filtered and washed with ether. The ether layer was concentrated in vacuo to produce a hydroxy complex, which was acetylated immediately with acetic anhydride (1 mL), 4-(*N*,*N*-dimethylamino)pyridine (small amount) and pyridine (3 mL) at room temperature under nitrogen. Usual workup afforded an *endo*-acetoxy complex (**49**) (495 mg, 92%): mp 199 °C (recrystallization from ether/methylene chloride); IR ($CHCl_3$) 1970, 1890, 1730 cm^{-1}; ^1H NMR δ 1.88 (2 H, m), 2.08 (2 H, m), 2.18 (3 H, s), 3.76 (3 H, s), 4.05–4.23 (4 H, m), 4.79 (1 H, d, J = 7), 4.97 (1 H, d, J = 7), 5.52 (1 H, t, J = 7), 5.84 (1 H, m). Anal. Calcd for $C_{18}H_{18}O_8Cr$: C, 52.18; H, 4.38. Found: C, 52.06; H, 4.37.

(4*S,11*S**)-Tricarbonyl(4-*exo*-isobutenyl-8-methoxy-1-tetralone)chromium (50).** Boron trifluoride etherate (1.14 mL, 4.4 mmol) was added to a solution of the *endo*-acetoxy chromium complex **49** (300 mg, 0.72 mmol) and (*E*)-crotyltrimethylsilane (368 mg, 2.8 mmol) in CH_2Cl_2 (30 mL) at −78 °C under argon. The mixture was stirred at room temperature for 3 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with methylene chloride. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel (40 g, ether/hexane, 1:3) chromatography to afford a chromium complex (**50**) (236 mg, 94%) as red crystals. The ratio of **50** and C-11 stereoisomeric complex (75:25) was determined by ^1H NMR: mp 125 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 1970, 1890, 1680 cm^{-1}; ^1H NMR δ 1.07 (3 H, d, J = 7), 2.00–2.65 (6 H, m), 3.74 (3 H, s), 4.70–5.05 (4 H, m), 5.46–5.72 (2 H, m). Anal. Calcd for $C_{18}H_{18}O_5Cr$: C, 59.02; H, 4.95. Found: C, 58.99; H, 4.99.

(1*R,4*S**,11*S**)-Tricarbonyl(1-*endo*-methyl-4-*exo*-isobutenyl-8-methoxytetralin)chromium (48).** MeLi (1.7 M in ether, 1.64 mL, 2.74 mmol) was added to a solution of the complex **50** (500 mg, 1.37 mmol) in ether (50 mL) and THF (10 mL) at −78 °C under argon. The reaction mixture was warmed to −20 °C over 3 h and quenched with water. The mixture was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Usual workup gave 320 mg (60%) of (1-*exo*-methyl-1-*endo*-tetralol)chromium complex as yellow crystals: mp 140 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 3200, 1970, 1880 cm^{-1}; ^1H NMR δ 1.13 (3 H, d, J = 7), 1.53 (3 H, s), 1.90 (1 H, s), 1.40–3.20 (6 H, m), 3.78 (3 H, s), 4.80–5.15 (4 H, m), 5.53 (1 H, t, J = 7), 5.35–5.78 (1 H, m). Anal. Calcd for $C_{19}H_{22}O_5Cr$: C, 59.68; H, 5.80. Found: C, 59.68; H, 5.84. To a solution of the above methylated chromium complex (320 mg, 0.83 mmol) and triethylsilane (595 mg, 5.12 mmol) in CH_2Cl_2 (30 mL) was added CF_3COOH (0.25 mL, 3.2 mmol) at 0 °C under argon, and the reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with methylene chloride. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with SiO_2 chromatography to give the chromium complex **48** (232 mg, 73%) as yellow crystals: mp 83 °C (recrystallization from ether/hexane); IR ($CHCl_3$) 1960, 1870, 1240 cm^{-1}; ^1H NMR δ 1.16 (3 H, d, J = 7), 1.31 (3 H, d, J = 7), 1.45–2.05 (5 H, m), 2.58 (1 H, m), 2.84 (1 H, m), 3.79 (3 H, s), 4.68 (1 H, d, J = 7), 4.90 (1 H, d, J = 7), 4.65–5.05 (2 H, m), 5.60 (1 H, t, J = 7), 5.50–5.83 (1 H, m). Anal. Calcd for $C_{19}H_{22}O_4Cr$: C, 62.29; H, 6.05. Found: C, 62.30; H, 6.05.

(1*R,4*S**,11*S**)-1-Methyl-4-isobutenyl-6-(1,3-dithian-2-yl)-8-methoxytetralin.** *n*-BuLi (1.6 M in hexane, 0.56 mL, 0.90 mmol) was added to a solution of 1,3-dithiane (118 mg, 0.98 mmol) in THF (4 mL) at −78 °C under argon, and the mixture was stirred at −20 °C for 30 min. HMPA (2.0 mL) was added to the above mixture, and the flask was again cooled to −78 °C. A solution of the chromium complex **48** (150 mg, 0.41 mmol) in THF (6 mL) was added to the above mixture, and the mixture was stirred for 30 min. The reaction mixture was warmed to −20 °C over 30 min and quenched with I_2 (240 mg, 0.94 mmol) in THF (3 mL). After stirring for 1 h, the mixture was poured into an aqueous solution of Na_2SO_3. The mixture was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentrated in vacuo, and the residue was purified with silica gel (12 g, ether/hexane, 1:30) chromatography to produce 70 mg (50%) of dithianylated compound **51** (R = Me) as a liquid: IR ($CHCl_3$) 1560, 1440, 1220, 1080 cm^{-1}; ^1H NMR δ 1.07 (3 H, d, J = 7), 1.11 (3 H, d, J = 7), 1.60–3.10 (13 H, m), 3.83 (3 H, s), 4.87–4.92 (2 H, m), 5.11 (1 H, s), 5.63–5.72 (1 H, m), 6.77 (1 H, s), 6.89 (1 H, s); MS m/e 348 (M^+), 293, 175; exact MS, Calcd for $C_{20}H_{28}OS_2$, 348.1581. Found: 348.1607.

(1*R,4*S**,11*S**)-1-Methyl-4-isobutenyl-6-(1,3-dithan-2-yl)-8-acetoxytetralin (51) (R = Ac).** Ethyl mercaptan (0.60 mL, 7.9 mmol) was added to a suspension of NaH (60% in mineral oil, 316 mg, 7.9 mmol) in DMF (30 mL), and the mixture was stirred at room temperature for 30 min. To the mixture was added a solution of the methoxy compound **51** (R = Me) (274 mg, 0.79 mmol) in DMF (20 mL), and the reaction mixture was refluxed with stirring for 6 h. After cooling to room temperature, the mixture was acidified with 2 M HCl solution. The reaction mixture was extracted with ether, and usual workup gave a demethylated phenolic compound (263 mg, 95%). The above phenolic demethylated compound was acetylated with acetic anhydride (1.5 mL), pyridine (3 mL), and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine under usual conditions. Usual workup and silica gel purification afforded 270 mg (95%) of an acetoxy compound (**51**) (R = Ac): IR ($CHCl_3$) 1740, 1410, 1380, 1180 cm^{-1}; ^1H NMR δ 1.05 (3 H, d, J = 7), 1.09 (3 H, d, J = 7), 1.40–3.18 (13 H, m), 2.33 (3 H, s), 4.70–4.91 (2 H, m), 5.03 (1 H, s), 5.40–5.80 (1 H, m), 6.95 (1 H, d, J = 2), 7.11 (1 H, d, J = 2);

MS m/e 376 (M^+), 321, 279. Exact Mass Calcd for $C_{21}H_{28}O_2S_2$: 376.1529. Found: 376.1538.

Preparation of Compound 52. 9-BBN (0.5 M in THF, 2.9 mL, 1.4 mmol) was added to a solution of **51** (R = OAc) (256 mg, 0.68 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the above solution were added $PdCl_2$(dppf) (31 mg, 0.043 mmol), methyl β-bromomethacrylate (197 mg, 11 mmol), DMF (15 mL), and powdered K_2CO_3 (496 mg, 3.6 mmol) and H_2O (630 mg, 35 mmol) at room temperature. The reaction mixture was heated at 50 °C for 16 h. After the mixture was cooled to room temperature, water was added. The reaction mixture was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Usual workup and silica gel chromatography gave 200 mg (77%) of **52**: IR ($CHCl_3$) 1730, 1700, 1420, 1360, 1260 cm^{-1}; ^1H NMR δ 0.99 (3 H, d, J = 7), 1.12 (3 H, d, J = 7), 1.78 (3 H, s), 2.29 (3 H, s), 1.30–3.10 (17 H, m), 3.71 (3 H, s), 5.09 (1 H, s), 6.70 (1 H, t, J = 6), 6.99 (1 H, br s), 7.17 (1 H, br s); MS m/e 476 (M^+), 416. Exact Mass Calcd for $C_{26}H_{36}O_4S_2$: 476.2053. Found: 476.2068.

Preparation of Compound 53. DIBAL (1 M in CH_2Cl_2, 2.3 mL, 2.3 mmol) was added to a solution of the compound **52** (110 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) at −78 °C under argon. The reaction mixture was warmed to 0 °C over 3 h and quenched with water. The mixture was extracted with methylene chloride, and usual workup produced a dihydroxy compound, which was acetylated with acetic anhydride (0.5 mL), pyridine (1 mL), and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine under usual conditions: yield, 99 mg (87%); IR ($CHCl_3$) 1720, 1360, 1220 cm^{-1}; ^1H NMR δ 0.97 (3 H, d, J = 7), 1.11 (3 H, d, J = 7), 1.60 (3 H, s), 2.05 (3 H, s), 2.28 (3 H, s), 1.30–3.15 (17 H, m), 4.44 (2 H, s), 5.08 (1 H, s), 5.31 (1 H, t, J = 6), 6.98 (1 H, br s), 7.16 (1 H, br s). Exact Mass Calcd for $C_{27}H_{38}O_4S_2$: 490. Found: 490.2200. A solution of the above diacetoxy compound (80 mg, 0.16 mmol) in THF (1 mL) was added a mixture of BF_3OEt_2 (0.08 mL) and HgO (69 mg, 0.32 mmol) in aqueous THF (15% H_2O, 2 mL) at room temperature. The reaction mixture was stirred for 20 min, diluted with ether, and extracted with ether. The extract was washed with brine and dried over $MgSO_4$. Concentration and purification by silica gel chromatography gave the compound **53** (44 mg 69%): IR ($CHCl_3$) 1725, 1690, 1360, 1210, 1110, 900 cm^{-1}; ^1H NMR δ 0.95 (3 H, d, J = 7), 1.13 (3 H, d, J = 7), 1.56 (3 H, s), 2.01 (3 H, s), 2.32 (3 H, s), 1.45–3.20 (11 H, m), 4.37 (2 H, s), 5.29 (1 H, t, J = 6), 7.36 (1 H, br s), 7.53 (1 H, br s), 9.89 (1 H, s); MS m/e 400 (M^+), 358, 330, 298, 189. Exact Mass Calcd for $C_{24}H_{32}O_5$: 400.2250. Found: 400.2255.

Preparation of Methyl Ester 54. A mixture of **53** (44 mg, 0.12 mmol), freshly prepared active MnO_2 (189 mg, 2.3 mmol), acetic acid (11 mg, 0.18 mmol), and sodium cyanide (27 mg, 0.55 mL) in MeOH (3 mL) was stirred at room temperature for 6 h. After filtration and evaporation of methanol in vacuo, water was added to the residue. The residue was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Concentration and purification with silica gel afforded a mixture of acetoxy methyl ester and phenolic methyl ester. The above methyl ester mixture was acetylated under usual conditions to give 40 mg (85%) of methyl ester **54**: IR ($CHCl_3$) 1720, 1710, 1370, 900 cm^{-1}; ^1H NMR δ 0.99 (3 H, d, J = 7), 1.14 (3 H, d, J = 7), 1.60 (3 H, s), 2.06 (3 H, s), 2.34 (3 H, s), 1.22–2.00 (9 H, m), 2.72 (1 H, m), 3.04 (1 H, m), 3.89 (3 H, s), 4.40 (2 H, s), 5.31 (1 H, t, J = 6), 7.53 (1 H, s), 7.75 (1 H, s); MS m/e 430 (M^+), 398, 356, 328, 219. Exact Mass Calcd for $C_{25}H_{34}O_6$: 430.2355. Found: 430.2359.

Dihydroxyserrulatic Acid (1). A mixture of the compound **54** (30 mg, 0.07 mmol) in 1 M aqueous NaOH (2 mL) and MeOH (3 mL) was heated at 70 °C for 5 h. The mixture was acidified with 6 M HCl and concentrated in vacuo. The residue was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. Evaporation in vacuo and chromatography with silica gel gave 13 mg (60%) of (±)-dihydroxyserrulatic acid, which was identified with the ^1H NMR an authentic sample.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the ministry of Japanese Education. We are grateful to Prof. E. L. Ghisalberti, The University of Western Australia, for his generous gift of a natural dihydroxyserrulatic acid.

Cyclophane–Arene Inclusion Complexation in Protic Solvents: Solvent Effects versus Electron Donor–Acceptor Interactions

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Abstract: This paper describes a comprehensive ^1H NMR analysis of the inclusion complexation of neutral 2,6-disubstituted naphthalene and para-disubstituted benzene derivatives by cyclophanes. The major attractive host–guest interactions in these complexes are π–π-stacking and edge-to-face aromatic–aromatic interactions. Individual studies investigate relative binding strength as a function of (i) the electronic properties of the guests, (ii) the nature of the solvent, and (iii) the nature of the cyclophane hosts. For these investigations, two new tetraoxa[*n*.1.*n*.1]cyclophanes with eight methoxy groups ortho to the aryl ether linkages were synthesized. A comparison between different cyclophanes shows that functional groups attached to the aromatic rings increase binding strength if they deepen the cavity without perturbing the apolar character of the binding site. Electron donor–acceptor (EDA) interactions control the relative stability of cyclophane–arene inclusion complexes in CD_3OD and $(CD_3)_2SO$. Generally, electron-deficient guests form the most stable complexes with the electron-rich cyclophanes. Deviations from the EDA model in these solvents are best explained by unfavorable complexation-induced changes in the solvation of the guest functional groups. In water, such solvation effects may dominate, thus masking contributions of EDA interactions to the relative complexation strength. Electronic host–guest complementarity determines the relative association strength in water only if guest functionalities retain their favorable solvation in the complexes formed. In binary aqueous solvent mixtures, overall complexation strength increases with the amount of water added and follows a linear free energy relationship with the empirical solvent polarity parameter $E_T(30)$.

Introduction

The role of aromatic–aromatic interactions, and in particular π-donor–π-acceptor interactions in stabilizing synthetic host–guest complexes has attracted considerable interest in recent theoretical[1] and experimental molecular recognition studies.[2-12] Advances have been made in defining the contributions of individual terms, which include electrostatic interaction, polarization interaction,

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