Total Synthesis of (−)-Macrocarpal C. Stereoselective Coupling Reaction with a Novel Hexasubstituted Benzene $Cr(CO)_3$ Complex as a Biomimetic Chiral Benzyl Cation Equivalent

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Received July 20, 1998

The first total synthesis of (−)-macrocarpal C (**3**) is described. The synthesis features a highly stereoselective coupling reaction of silyldienol ether **6** with biomimetic benzyl cation species (*R*)- and (*S*)-**B**, which were generated from novel hexasubstituted benzene chromium tricarbonyl complexes (*R*)- and (*S*)-**17**. At the final step of the total synthesis, we developed the tris-*O*-demethylation of macrocarpal C trimethyl ether **34** under basic conditions using lithium *p*-thiocresolate. Moreover, spectroscopic evidence shows that the synthetic (−)-**3** is identical to natural macrocarpal G (**4**).

Introduction

A number of novel compounds, arising from the combination of acylphloroglucinol and terpenoid residues, have been identified from the *Eucalyptus* species in recent years.[1] Among them, macrocarpals[2] are structurally characterized by fusion of isopentylphloroglucinol dialdehyde at its benzylic position to various sesquiterpene skeletons. Since the original isolation of macrocarpal A (**1**) from *E. macrocarpa* in 1990,[2a] a number of macrocarpals have been isolated[2b−g] and have been shown to display a wide spectrum of biological activity, i.e., inhibitory activity of HIV reverse transcriptase,[2b] antibacterial activity against cariogenic and periodontopathic bacteria, etc.,[2a,c,e,g] aldose reductase,[2d,e] and glucosyl transferase.[2e,g] Complete structures have been elucidated for macrocarpals A (**1**), B (**2**), and C (**3**) using X-ray diffraction studies and spectral and chemical investigations. The absolute stereochemistries of **1** and **3** have been determined by modified Mosher's method.[2b] Macrocarpal G (**4**),[2c] the structure of which is based solely on spectroscopic evidence, has been assigned the same planar structure as that established for **3**. However, the ^1H and ^{13}C NMR spectral parameters quoted for these two compounds were obtained using different solvents, a discrepancy that renders comparison difficult.[3]

The unique structural and the impressive biological features of macrocarpals prompted us to develop a synthetic method. In this paper, we report the full account of the first efforts to produce a stereocontrolled total synthesis of (−)-macrocarpal C, the identity of which is clarified with respect to macrocarpal G.[4]

Results and Discussion

The simplest biogenetic proposal for the generation of the macrocarpals involves the appropriate benzyl cation (**A**) or a stabilized equivalent, as illustrated in Scheme 1.[2b] This species can replace a proton as the cationic initiator in the cyclization of a sesquiterpene bicyclogermacrene. From the resulting tricyclic carbocationic species (**B**) as a general precursor, it can be seen that hydration or deprotonation derives macrocarpals A−C.

Taking this proposed biosynthetic pathway into consideration, we planned the syntheses of macrocarpal A (**1**), B (**2**), and C (**3**) from the previously discussed tricyclic enone **5**,[5c] as shown in Scheme 2. In connection with the introduction of the isopentylphloroglucinol dialdehyde part to the sesquiterpene moiety **5**, the coupling reaction of cross-conjugated silyldienol ether **6** prepared from **5** with biomimetic benzyl cation species **A′** was first considered. **A′** can be generated from properly functionalized benzyl chloride **7** by the action of Lewis acid. According to our previous studies,[5b,c] the benzyl cation species **A′** would attack from the less-hindered β-side at the C11 position of **6** to afford coupling products **8** and/or **9**. On the basis of previous investigations,[5a,c] catalytic

(1) For a review of bioactive acylphloroglucinol derivatives from *Eucalyptus* species, see: Ghisalberti, E. L. *Phytochemistry* **1996**, *41*, 7.

(2) (a) Murata, M.; Yamakoshi, Y.; Homma, S.; Aida, K.; Hori, K.; Ohashi, Y. *Agric. Biol. Chem.* **1990**, *54*, 3221. (b) Nishizawa, M.; Emura, M.; Kan, Y.; Yamada, H.; Ogawa K.; Hamanaka, N. *Tetrahedron Lett.* **1992**, *33*, 2983. (c) Yamakoshi, Y.; Murata, M.; Shimizu, A.; Homma, S. *Biosci. Biotech. Biochem.* **1992**, *56*, 1570. (d) Murata, M.; Yamakoshi, Y.; Homma, S.; Arai, K.; Nakamura, Y. *Biosci. Biotech. Biochem.* **1992**, *56*, 2062. (e) Osawa, K.; Yasuda, H.; Morita, H.; Takeya, K.; Itokawa, H. *Phytochemistry* **1995**, *40*, 183. (f) Singh, I. P.; Etoh, H. *Biosci. Biotech. Biochem.* **1995**, *59*, 2330. (g) Osawa, K.; Yasuda, H.; Morita, H.; Takeya, K.; Itokawa, H. *J. Nat. Prod.* **1996**, *59*, 823. (h) Satoh, H.; Etoh, H.; Watanabe, N.; Kawagishi, H.; Arai, K.; Ina, K. *Chem. Lett.* **1992**, 1917.

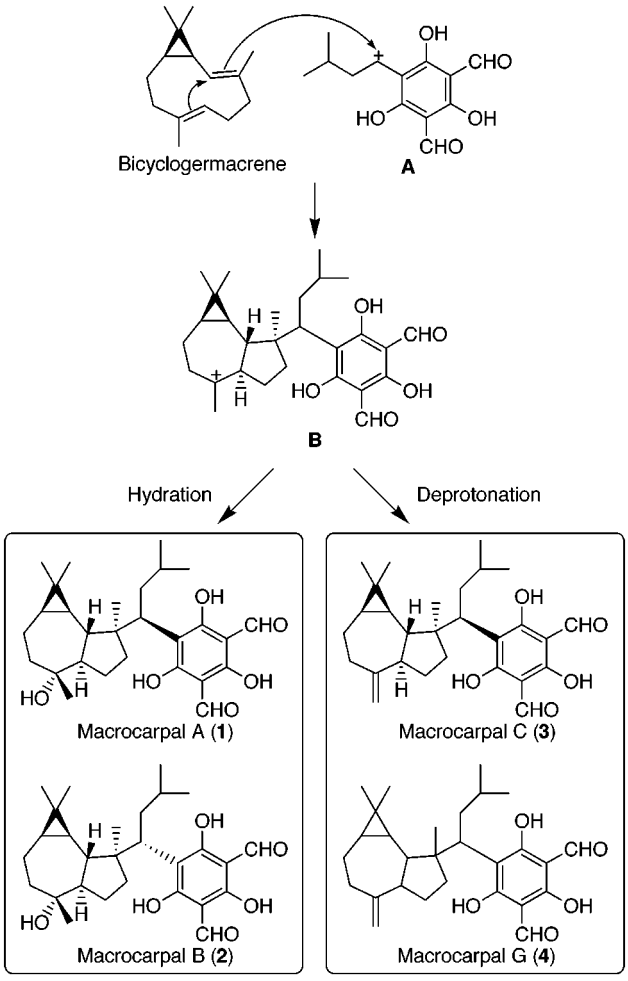
(3) The ^1H and ^{13}C NMR spectra of macrocarpals C **3** and G **4** were measured in different solvents, which made comparison difficult. In ref 1, it has been considered that these were diastereomers due to difference between their physicochemical properties.

(4) Tanaka, T.; Mikamiyama, H.; Maeda, K.; Ishida, T.; In, Y.; Iwata, C. *Chem. Commun.* **1997**, 2401.

(5) (a) Tanaka, T.; Funakoshi, Y.; Uenaka, K.; Maeda, K.; Mikamiyama, H.; Takemoto, Y.; Maezaki, N.; Iwata, C. *Chem. Pharm. Bull.* **1994**, *42*, 300. (b) Tanaka, T.; Funakoshi, Y.; Uenaka, K.; Maeda, K.; Mikamiyama, H.; Iwata C. *Chem. Pharm. Bull.* **1994**, *42*, 1243. (c) Tanaka, T.; Maeda, K.; Mikamiyama, H.; Funakoshi, Y.; Uenaka, K.; Iwata, C. *Tetrahedron* **1996**, *52*, 4257.

10.1021/jo981413+ CCC: $15.00
Published on Web 12/03/1998

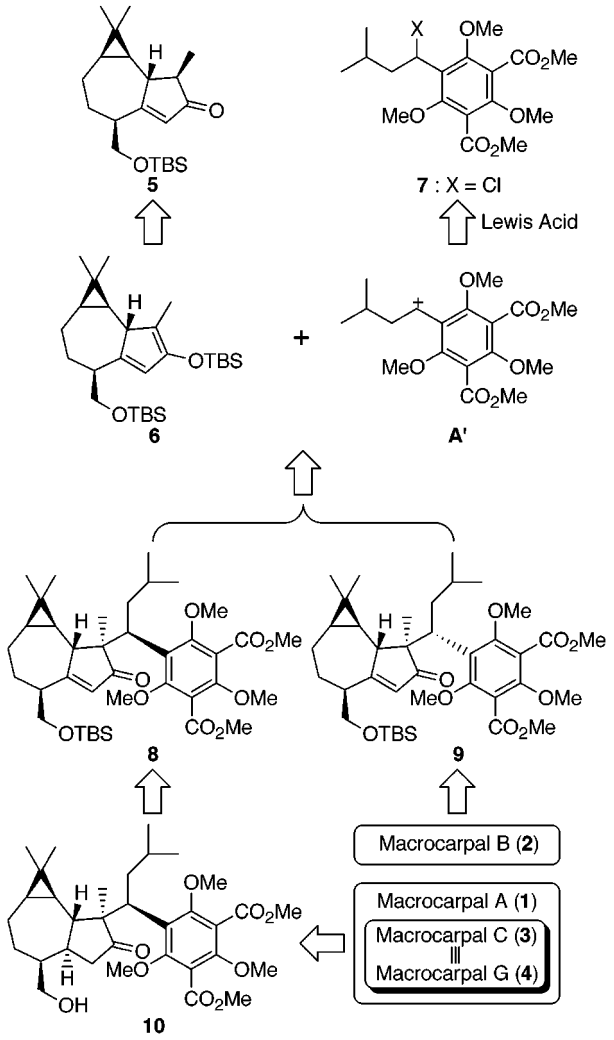
Scheme 1. Hypothetical Scheme for the Biosynthesis of Macrocarpals



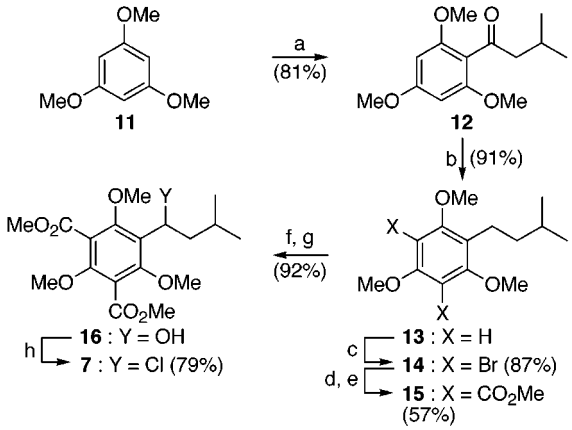
hydrogenation of one enone **8** would lead to *trans*-fused ketone **10**, which would possess the requisite functionalities and desired stereochemistry for the subsequent manipulation toward macrocarpals A (**1**) and C (**3**). In a similar manner, the enone **9** would be converted to macrocarpal B (**2**).

Coupling Reaction of Silyldienol Ether 6 with Biomimetic Benzyl Cation Equivalent. As shown in Scheme 3, we first pursued the synthesis of benzyl chloride **7** as the biomimetic benzyl cation equivalent, which was equipped with three methoxyl groups and two methoxycarbonyl groups onto its aromatic ring corresponding to phloroglucinol dialdehyde. Commercially available 1,3,5-trimethoxybenzene **11** was acylated with isovaleryl chloride and $AlCl_3$ (91% yield),[6] followed by hydrogenolysis of the benzylic ketone[7] afforded compound **13** via ketone **12** (91% yield). Introduction of two methoxycarbonyl groups onto the aromatic ring of **13** was then attempted by employing the protocol reported by Salomon et al.[6] Thus, treatment of **13** with 2 equiv of bromine gave dibromide **14** (87% yield) which was subjected to lithium−bromine exchange with excess *n*-BuLi, followed by sequential treatment with carbon dioxide and diazomethane

Scheme 2. Synthetic Strategy



Scheme 3. Preparation of Simple Aromatic Side-Chain Unit 7



Reagents and conditions: (a) isovaleryl chloride, $AlCl_3$, CH_2Cl_2, 0 °C, 3.5 h; (b) H_2 (5 atm), 10% Pd/C, conc.HCl, MeOH, 44 h; (c) Br_2, CH_2Cl_2, rt, 15 h; (d) *n*-BuLi, THF, –78 °C, 30 min, then CO_2, –78 °C, 15 min; (e) CH_2N_2, Et_2O, rt, 12 h; (f) NBS, AIBN, CCl_4, reflux, 30 min; (g) H_2O:THF (1:1), rt, 3 h; (h) triphosgene, pyridine, THF, rt, 1.5 h.

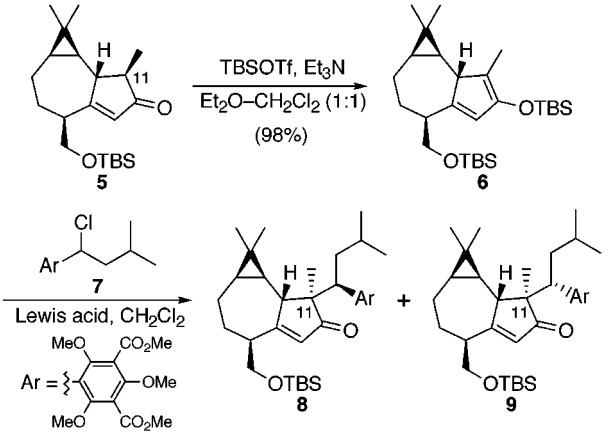
to afford diester **15** (57% overall yield). Radical bromination of **15** with NBS in the presence of AIBN gave rise to labile benzyl bromide, which was then immediately hydrolyzed with H_2O/THF (1:1)[8] to give benzyl alcohol

(6) Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1311. Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Org. Chem.* **1988**, *53*, 3673.

(7) Tanaka, T.; Murakami, K.; Okuda, O.; Kuroda, T.; Inoue, T.; Kamei, K.; Murata, T.; Yoshino, H.; Imanishi, T.; Iwata C. *Chem. Pharm. Bull.* **1994**, *42*, 1756.

(8) Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592.

Table 1. Coupling of Silyldienol Ether 6 with Simple Aromatic Side-Chain Unit 7



Entry	Lewis Acid (eq.)	Conditions	Yields (%)[a] 8	9
1	$ZnCl_2$ (0.1)	rt, 60 min	33 (46)[b]	32 (44)[b]
2	$AgBF_4$ (1.2)	–78°C, 45 min	17 (27)[c]	14 (23)[c]

[a] Isolated yields based on the silyldienol ether **6**.
[b] Yields in parenthesis are considering recovered mixture of enone **5** and its C11 epimer (*ca.* **1** : 5).
[c] Yields in parenthesis are considering recovered C11 epimer of enone **5**.

16 (92% overall yield). Finally, chlorination of the benzyl alcohol **16** with bis(trichloromethyl) carbonate (triphosgene) in the presence of pyridine[9] afforded the targeted benzyl chloride **7** (79%), together with (*E*)-olefin (20%) resulting from the elimination of HCl.

With the benzyl cation equivalent **7** in hand, we next investigated the Lewis acid mediated coupling reaction of cross-conjugated silyldienol ether **6** with **7**[10] (Table 1). The silyldienol ether **6** was regioselectively prepared by treatment of the enone **5**, which can be synthesized from commercially available and inexpensive (+)-3-carene in 12 steps,[5c] with TBSOTf and Et_3N. After various reaction conditions (Lewis acids, solvents, and reaction temperature) were examined, we found that **6** and **7** coupled most smoothly in the presence of a catalytic amount of $ZnCl_2$ in CH_2Cl_2 at room temperature,[11] which gave desired coupling products **8** (33%) and **9** (32%) in a ratio of ca. 1:1 (entry 1). As expected, neither the C11 epimer nor the regioisomer was isolated. Although the coupling reaction was carried out at low temperature (−78 °C) by using $AgBF_4$, which has a closer affinity with chloride ion, little change was observed in the diastereomeric ratio between **8** and **9** (entry 2).

The configurational assignment at the C11 position of **8** and **9** was confirmed by NOE experiments. Furthermore, diagnostically higher field shifts of the methylene protons of the TBS-oxymethylene group of **9** and the

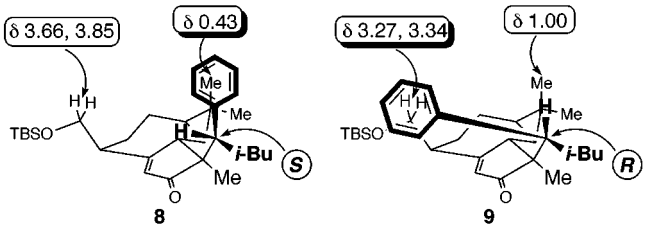


Figure 1. Presumed benzylic configurations of coupling products **8** and **9**.

protons of the *endo*-methyl group on the cyclopropane ring of **8** were observed in the respective ^1H NMR spectra. These shifts are likely due to the shielding effects of the ring current as shown in Figure 1. Accordingly, we presumed the benzylic configurations of **8** (as *S*) and **9** (as *R*) at this stage, since their aromatic rings were considered to be located as illustrated in Figure 1 and the bulkier isobutyl groups were distant from the sesquiterpene moieties, thus avoiding steric interactions. That these presumptions were correct was verified by the X-ray crystallographic analysis of an advanced intermediate **27** derived from **8** (vide infra).

As shown in Table 1, the stereochemistries at the C11 position were completely controlled, but stereoselectivity in generating the benzylic stereocenter was not observed in the coupling reaction of silyldienol ether **6** with the benzyl chloride **7**. It appears that the asymmetry of **6** did not take part in face selectivity in the attack of **6** on the prochiral cationic plane of the benzyl cation species **A′** (see Scheme 2), which was generated from **7**. Likewise, in the coupling reaction of bicyclogermacrene with the biogenetic benzyl cation species **A** (see Scheme 1), asymmetry of bicyclogermacrene was effective in stereocontrol at the C11 position but not at the benzylic position, so that it can be seen that both benzylic diastereomers, macrocarpal A (**1**) and B (**2**), exist in nature. Although the benzylic epimer of macrocarpal C (**3**) has not yet been isolated, it is likely to exist in nature.

Coupling Reaction of Silyldienol Ether 6 with a Chiral Benzyl Cation Equivalent. In an attempt to observe diastereoselectivity in the preceding coupling reaction, we designed a further plan, as shown in Scheme 4. We expected that face selectivity in this reaction would emerge by shielding one side of the aromatic ring of the side-chain unit with the $Cr(CO)_3$ ligand.[12] Lewis acid treatment of chiral (η^6-arene)$Cr(CO)_3$ complex (*S*)- or (*R*)-**17**, which was equipped with a proper leaving group at the benzylic position, would afford $Cr(CO)_3$-stabilized benzyl cation species (*S*)- or (*R*)-**B** by departure of the *exo*-leaving group.[13] Subsequent attack of the nucleophile **6** from the *exo*-face away from the large $Cr(CO)_3$ ligand results in a S_N1-type carbon−carbon bond formation that would proceed with stereochemical retention at the benzylic position; as a result, two diastereomers of the

(9) Goren, Z.; Heeg, M. J.; Mobashery, S. *J. Org. Chem.* **1991**, *56*, 7186. For a review of triphosgene, see: Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. *Synthesis* **1996**, 553.

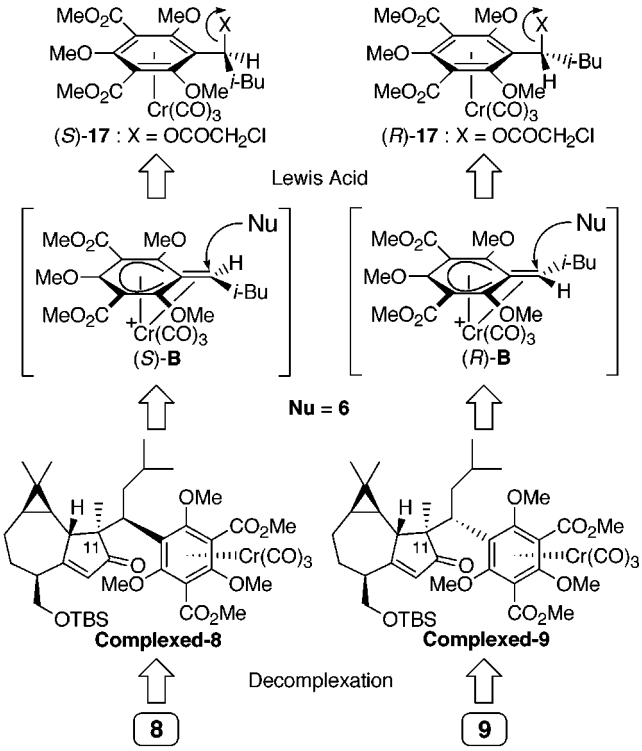
(10) When the corresponding benzyl acetate was used for the coupling reaction, none of the desired product was obtained. For examples for the coupling reaction of benzyl acetates with silylenol ethers, see: Reetz, M. T.; Hüttenhain, S.; Hübner, F. *Synth. Commun.* **1981**, *11*, 217. Grieco, P. A.; Handy, S. T. *Tetrahedron Lett.* **1997**, *38*, 2645.

(11) Paterson, I. *Tetrahedron Lett.* **1979**, 1519. Reetz, M. T.; Hüttenhain, S.; Walz, P.; Löwe, U. *Tetrahedron Lett.* **1979**, *51*, 4971.

(12) For recent reviews of (η^6-arene)$Cr(CO)_3$ complexes, see: Morris, M. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 5, Chapter 8. Davies, S. G.; McCarthy, T. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, Chapter 9.3.

(13) (a) Uemura, M.; Isobe, K.; Hayashi, Y. *Tetrahedron Lett.* **1985**, *26*, 767. Uemura, M.; Kobayashi, T.; Hayashi, Y. *Synthesis* **1986**, 386. Uemura, M.; Kobayashi, T.; Minami, T.; Hayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 2479. Uemura, M.; Kobayashi, T.; Isobe, K.; Minami, T.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 2859. (b) Davies, S. G.; Donohoe, T. J. *Synlett*, **1993**, 323.

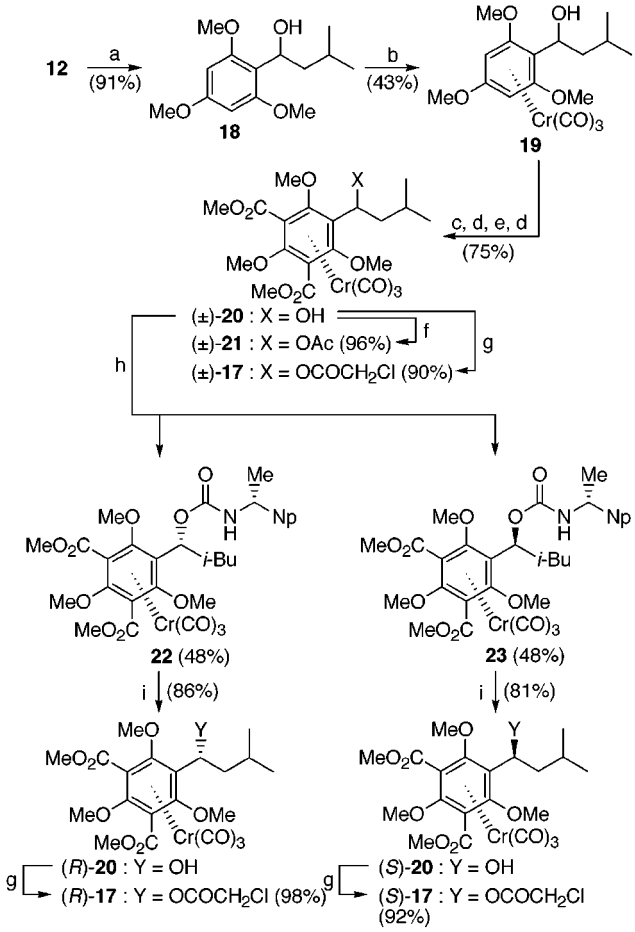
Scheme 4. Strategy for Stereoselective Coupling Reaction



coupling product **8** (from (*S*)-**17**) and **9** (from (*R*)-**17**) would be obtained stereoselectively, after decomplexation.[13a,14]

Scheme 5 outlines the synthesis of the chiral chromium complex (*R*)- or (*S*)-**17** as optically active benzyl cation equivalents. LAH reduction of **12** provided racemic alcohol **18** (91% yield), which, upon heating with $Cr(CO)_6$ in *n*-Bu_2O/1,4-dioxane/*n*-heptane (5:5:1) at 120 °C,[15] led to complexed alcohol **19** (43% yield, 92% based on conversion). Introduction of two methoxycarbonyl groups onto the aromatic ring of complex **19** was accomplished in a stepwise manner via double direct nuclear lithiation,[16] first with *n*-BuLi and then with LDA, followed by sequential treatment with carbon dioxide and TMS-diazomethane[17] to afford complexed diester (±)-**20** (75% overall yield).[18] The resolution of this racemic benzyl alcohol was then examined.[19] Diastereomeric carbamates derived from the CuCl-assisted[23] reaction of (±)-**20** with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate[24a] were separated

Scheme 5. Preparation of Chiral $Cr(CO)_3$ Complexed Aromatic Side-Chain Units (*R*)- and (*S*)-17



Reagents and conditions: (a) $LiAlH_4$, Et_2O, 0 °C, 4 h; (b) $Cr(CO)_6$, *n*-Bu_2O:1,4-dioxane:*n*-heptane (5:5:1), 120°C, 34 h; (c) *n*-BuLi, TMEDA, THF, –78 °C, 2 h, then CO_2, –78 °C, 30 min; (d) $TMSCHN_2$, benzene:MeOH (4:1); (e) LDA, TMEDA, THF, –50 °C, 3 h, then CO_2, –78 °C, 30 min; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 40 min; (g) $(ClCH_2CO)_2O$, pyridine, CH_2Cl_2, 0 °C, 2–3 h; (h) (*R*)-(–)-1-(1-naphthyl)ethyl isocyanate, CuCl, DMF, rt, 3 h, then separation; (i) BF_3•Et_2O, wet.CH_3CN, 0 °C, 2–4 h. Np = 1-naphthyl.

by simple chromatography on silica gel to give **22** (48%) and **23** (48%) (It should be noted that these can be separated visually because of their characteristic yellow color). Initial attempts to remove the chiral auxiliary of carbamates **22** and **23** by the usual procedure (heating with Cl_3SiH and Et_3N in toluene)[24b] met with failure, affording a complicated mixture of products. We presumed this problem to be a result of decomposition of complexed halide generated from **22** or **23**, according to recent reports of Cr-complexed benzyl halide synthesis by treatment of complexed alcohols and ethers with the appropriate boron trihalide.[25] However, treatment of each carbamate with BF_3•Et_2O in hydrous CH_3CN at 0 °C

(14) Reetz, M. T.; Sauerwald, M. *Tetrahedron Lett.* **1983**, *24*, 2837. Reetz, M. T.; Sauerwald, M. *J. Organomet. Chem.* **1990**, *382*, 121.

(15) The reaction should be carried out at 120 ± 5 °C (bath temperature) since **19** decomposes (decomplexes) at 136 °C.

(16) For examples for the direct nuclear lithiation of Cr-complexed benzyl alcohols, see: Uemura, M.; Nishikawa, N.; Hayashi, Y. *Tetrahedron Lett.* **1980**, *21*, 2069. Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 2349. Uemura, M.; Take, K.; Isobe, K.; Minami, T.; Hayashi, Y. *Tetrahedron* **1985**, *41*, 5771.

(17) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

(18) Direct Cr-complexation of the antecedent diester **16** was failed under various conditions.

(19) Attempted enantioselective reduction of the ketone **12** and its chromium complex (which was prepared by oxidation of **19**) with several standard reagents (Brown's *B*-chlorodiisopinocamphenylborane[20a] and its modified method,[20b] or Corey's oxazaborolidine catalyzed borane reductions)[21] provided the unsatisfied results (<50% ee). Recently, it was reported that electron donating substituents in the *para*-position on aromatic rings lead to decreased enantiomeric ratios in the Brown's method.[22]

(20) (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (b) Ramachandran, P. V.; Gong, B.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 2141.

(21) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

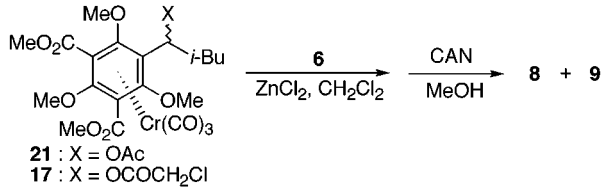
(22) Wiegers, A.; Scharf, H.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 2303.

(23) Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131.

(24) (a) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839. (b) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781.

(25) Gibson, S. E.; Schmid, G. A. *Chem. Commun.* **1997**, 865.

Table 2. Coupling of Silyldienol Ether 6 with $Cr(CO)_3$ Complexed Aromatic Side-Chain Units



21 : X = OAc
17 : X = $OCOCH_2Cl$

		Equiv			Yields (%)[b,c]		
Entry	Complex	**6**	$ZnCl_2$[a]	Conditions	**8**	**9**	de (%)
1	(±)-**21**	1.2	1	rt, 4 h	6 (14)	6 (14)	0
2	(±)-**17**	1.2	1	rt, 2 h	29 (38)	34 (44)	7
3	(*S*)-**17**	2	1.5	rt, 1.5 h	61 (82)	2 (3)	94
4	(*R*)-**17**	2	1.5	rt, 1.5 h	2 (2)	59 (80)	95

[a] 1.0 M solution in Et_2O was used.
[b] Isolated yields after decomplexation based on complexes **17** or **21**.
[c] Yields in parenthesis are considering recovered mixture of enone **5** and its C11 epimer (*ca.* 1 : 5).

successfully provided the optically pure complexed alcohols (*R*)- and (*S*)-**20**.[26] It is conceivable that this reaction followed a mechanism similar to that shown in Scheme 4. That is, the $Cr(CO)_3$-stabilized benzyl cation species (*R*)- or (*S*)-**B**, derived by the action of $BF_3{\cdot}Et_2O$ to the complexed carbamate **22** or **23**, was trapped by H_2O without rotation about the benzylic carbon−arene bond, so that the hydration proceeded with stereochemical retention. It has been reported that, due to allylic strain, the syn conformer of a mono-*ortho*-substituted benzyl cation complex would convert to the more stable anti conformer.[13b] Although allylic strain cannot be avoided in the case of the di-*ortho*-substituted benzyl cation species (*R*)- or (*S*)-**B**, it is considered that the isomerization did not occur, since there is no difference in energy between them. Finally, (*R*)- and (*S*)-**20** were converted to the chloroacetates (*R*)- and (*S*)-**17**, which were expected to have the appropriate reactivity.[28]

Having secured the optically active benzyl cation equivalents (*R*)- and (*S*)-**17**, we subjected them to the crucial coupling reaction. The coupling reaction was demonstrated by treatment of the silyldienol ether **6** and the complexes **17** with a slight excess of $ZnCl_2$ in CH_2Cl_2 at room temperature. Table 2 shows the isolated yields of the coupling products **8** and **9** which were obtained after decomplexation with CAN. Neither the C11 epimer nor the regioisomer was isolated in any of the cases. Initial investigation of the influence of the benzylic leaving group using the racemic complexes led to the finding that the silyldienol ether **6** coupled more smoothly with the complexed chloroacetate (±)-**17** than with acetate (±)-**21** (entries 1 and 2).[28] In addition, at this stage, it was apparent that there was little difference in the reactivity of **6** toward both benzyl cation species (*S*)- and (*R*)-**B**, since the ratio of products **8** and **9** was ca. 1:1. As expected, when the chiral complexes were used, the coupling products **8** and **9** were obtained with high diastereoselectivity (94−95% de) from (*S*)- and (*R*)-**17**, respectively (entries 3, 4).

As described above, we have developed a methodology for stereocontrolling, not only at the C11 position, but also at the benzylic position, which nature does not control. This was achieved by utilizing the novel hexasubstituted benzene $Cr(CO)_3$ complexes[29] (*S*)- and (*R*)-**17** as chiral benzyl cation equivalents. This synthetic methodology is expected to be adaptable for other macrocarpals and euglobals[30] that are adducts of acylphloroglucinol with terpenes. By employing appropriate silyl(di)enol ether, benzylic stereochemistries are controlled in a powerful and beneficial manner.

Conversion of Coupling Product 8 to (−)-Macrocarpal C (Structural Determination of Macrocarpal G). Having developed a stereoselective route to the promising precursors **8** for macrocarpal A and C, and **9** for macrocarpal B, we investigated the following functional manipulations of **8** toward macrocarpal C (**3**) (Scheme 6). Catalytic hydrogenation of enone **8** afforded desilylated saturated ketone **10** with the correct stereochemistry as a single stereoisomer in 88% yield.[5a,c] $NaBH_4$ reduction of keto-alcohol **10** stereoselectively occurred from the less hindered α-side to give diol **24**, which upon acetylation of the primary hydroxyl group, furnished hydroxy-acetate **25** (96% overall yield). Subsequently, we attempted Barton deoxygenation of the C10 position.[31] After examination of the transformation of **25** into radical reduction precursors, only the Nicolaou conditions (excess 1,1′-thiocarbonyldiimidazole (20 equiv), DMAP (20 equiv), THF, 80 °C in a sealed tube)[32] afforded thiocarbamate **26** (66% yield), along with carbamate **27** (25% yield).[33] The complete structure of **27**, including the stereochemistries at the benzylic and C10 positions, was rigorously confirmed by X-ray crystallographic analysis.[34] Unfortunately, all attempted reductions of thiocarbamate **26** failed under various radical conditions. However, since

(26) Their enantiomeric purities were determined to be >98% ee by ^1H NMR analysis of Mosher ester derivatives.[27]

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(30) Sawada, T.; Kozuka, M.; Komiya, T.; Amano, T.; Goto, M. *Chem. Pharm. Bull.* **1980**, *28*, 2546. Kozuka, M.; Sawada, T.; Kasahara, F.; Mizuta, E.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1952. Kozuka, M.; Sawada, T.; Kasahara, F.; Mizuta, E.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1964. Xu, R.-S.; Snyder J. K.; Nakanishi K. *J. Am. Chem. Soc.* **1984**, *106*, 734. Cheng, Q.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 4562. Nakayama, R.; Murata, M.; Homma, S.; Aida, K. *Agric. Biol. Chem.* **1990**, *54*, 231. Takasaki, M.; Konoshima, T.; Shingu, T.; Tokuda, H.; Nishino, H.; Iwashima, A.; Kozuka, M. *Chem. Pharm. Bull.* **1990**, *38*, 1444. Kokumai, M.; Konoshima, T.; Kozuka, M. *J. Nat. Prod.* **1991**, *54*, 1082. Takasaki, M.; Konoshima, T.; Kozuka, M.; Haruna, M.; Ito, K.; Shingu, T. *Chem. Pharm. Bull.* **1994**, *42*, 2591. Takasaki, M.; Konoshima, T.; Kozuka, M.; Yoneyama, K.; Yoshida, S.; Tokuda, H.; Nishino, H.; Iwashima, A. *Biol. Pharm. Bull.* **1995**, *18*, 288.

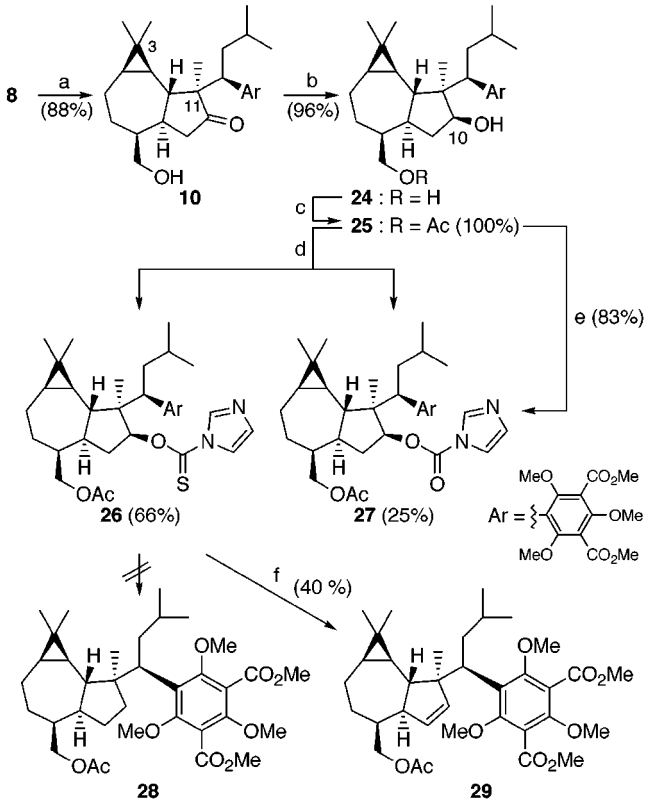
(31) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. For a review on Barton deoxygenation, see: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609. Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. McCombie, S. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Eds.; Pergamon: New York, 1991; Vol. 8, Chapter 4.2.

(32) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624.

(33) It appears that the formation of the byproduct **27** was attributed to more reactive 1,1′-carbonyldiimidazole as contamination of 1,1′-thiocarbonyldiimidazole used in a large excess. In fact, treatment of **25** with 1,1′-carbonyldiimidazole under the same condition afforded only **27** (83% yield).

(34) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre (CCDC 182/601). The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 6. Functional Manipulation of Coupling Product 8

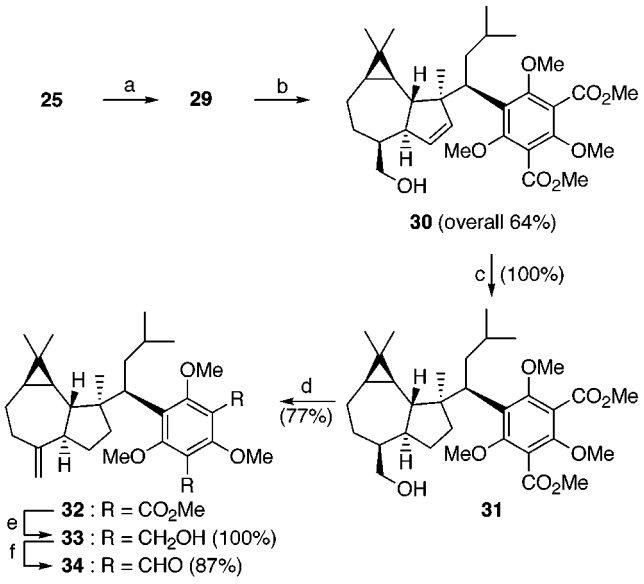


Reagents and conditions: (a) H_2 (5 atm), 10% Pd/C, MeOH, rt, 27 h; (b) $NaBH_4$, MeOH, rt, 1 h; (c) Ac_2O, DMAP, CH_2Cl_2, rt, 1 h; (d) 1,1'-thiocarbonyldiimidazole, DMAP, THF, 80 °C, sealed tube, 14 h; (e) 1,1'-carbonyldiimidazole, DMAP, THF, 80 °C, sealed tube, 20 h; (f) Δ

olefin **29** was obtained in a rather low yield (40%) by the Chugaev type pyrolysis[35] of **26**, we turned our efforts to dehydration of the alcohol **25**.

The C10 position of the β-oriented secondary hydroxyl group of the alcohol **25** is a neopentyl position and is shielded by the aromatic side-chain moiety, so that **25** is unreactive; it was therefore easy to induce a Wagner−Meerwein-type rearrangement. For example, the desired olefin **29** was obtained in a very low yield (14%) even under the reported dehydration conditions, under which it is hard to induce rearrangement (methyltriphenoxyphosphonium iodide, HMPA, 75 °C).[36] After strenuous examination, we applied a severely modified Grieco's protocol.[37] No reaction occurred under the standard conditions, namely treating the alcohol with 2-nitrophenyl selenocyanate and *n*-Bu_3P at room temperature. However, heating it with excess of each reagent (10 equiv) at 75 °C in a sealed tube afforded the olefin **29**, which upon deacetylation using NaOMe led to olefin-alcohol **30** (64% overall yield). Although Grieco's dehydration is the transformation of initially generated selenides into olefins by oxidation, in our case the olefin **29** was already formed before oxidation.[38] Hence, it is conceivable that the reaction occurred via the E2 elimination of an oxo-phosphonium salt intermediate.[39]

Scheme 7. Synthesis of Macrocarpal C Trimethyl Ether 34



Reagents and conditions: (a) 2-NO_2PhSeCN, *n*-Bu_3P, THF, 75 °C, sealed tube, 20 h, then 30% H_2O_2, rt, 3 h; (b) NaOMe, MeOH, rt, 6.5 h; (c) H_2 (5 atm), 10% Pd/C, MeOH, rt, 15 h; (d) 2-NO_2PhSeCN, *n*-Bu_3P, THF, 50 °C, 12 h, then 30% H_2O_2, rt, 30 min; (e) DIBALH, toluene, −78 °C, 1 h; (f) TPAP, NMO, 4Å MS, CH_3CN, rt, 1 h.

We then continued to pursue the transformation from the olefin alcohol **30**. Catalytic hydrogenation of **30** afforded, quantitatively, alcohol **31**, which was then subjected to dehydration under ordinary Grieco's conditions,[37] which furnished *exo*-olefin **32** (77% yield). We thus completed the construction of the sesquiterpene moiety of (−)-macrocarpal C (**3**). The remaining task was to convert the aromatic ring moiety of **32** into phloroglucinol dialdehyde. DIBALH reduction of diester **32** led to crystalline diol **33** in a quantitative yield. Oxidation of **33** with *N*-methylmorpholine *N*-oxide (NMO) in the presence of a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP)[40] furnished macrocarpal C trimethyl ether **34** (87% yield) (Scheme 7).

The tris-*O*-demethylation of aryl methyl ether[41] was considered as the final step to our goal. Since **34** has acid-labile functionalities, a cyclopropane ring and an *exo*-olefin, acidic conditions utilizing Lewis acids such as BBr_3 cannot be applied for this purpose. Tris-*O*-demethylation of trimethoxy aromatic compounds under basic conditions has not been discussed in the previous literature. However, there are some reports on bis-*O*-demethylation using basic reagents.[42] Hansson and Wickberg reported that treatment of 2,3,4-trimethoxybenzaldehyde with

(35) Chugaev reaction: Mundy, B. P.; Ellerd, M. G. *Name Reactions and Reagents in Organic Synthesis*; John Wiley and Sons: New York, 1988; pp. 40−41. Hassner, A.; Stumer C. *Organic Syntheses Based on Name Reactions and Unnamed Reactions*; Pergamon: Oxford, 1994; p 391.

(36) Hutchins, R. O.; Hutchins, M. G.; Milewski, C. A. *J. Org. Chem.* **1972**, *37*, 4190.

(37) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(38) To remove the excess of reagents, we operated the oxidative workup before isolation.

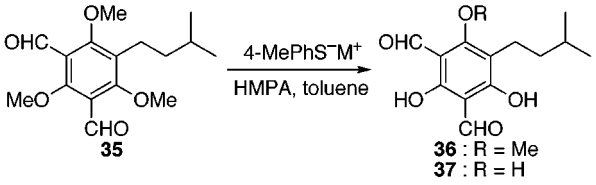
(39) The similar reaction mechanism was reported on the dehydration of secondary alcohols under the Mitsunobu's reaction conditions (Ph_3P−azodicarboxylate): Akita, H.; Yamada, H.; Matsukura, H.; Nakata, T.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38*, 2377. Iimori, T.; Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1991**, *32*, 1209.

(40) For a review on TPAP oxidation, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(41) For a review on cleavage of ethers, see: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.

(42) (a) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191. (b) Hwu, J. R.; Tsay, S.-C. *J. Org. Chem.* **1990**, *55*, 5987. (c) Hwu, J. R.; Wong, F. F.; Huang, J.-J.; Tsay, S.-C. *J. Org. Chem.* **1997**, *62*, 4097. Hwu, J. R.; Tsay, S.-C. *Chem. Commun.* **1998**, 161.

Table 3. Model Study for Tris-*O*-demethylation



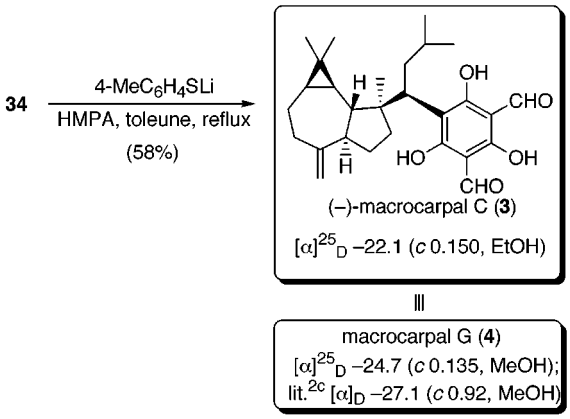
Entry	Equiv Base	Equiv HMPA	Temp.	Yields (%)[a] 36	Yields (%)[a] 37
1	M = Na 8	16	reflux	70	0
2	M = Na 15	30	130°C[b]	44	0
3	M = Li 10	10	reflux	11	50
4	M = Li 10	50	reflux	0	57

[a] Isolated yields. [b] In a sealed tube.

sodium *p*-thiocresolate in the presence of HMPA in toluene at 75 °C allowed bis-*O*-demethylation to occur in the positions *ortho* and *para* to the formyl group.[42a] Accordingly, in the case of **32**, which bears two formyl groups, we expected that three methyl ethers in the *ortho* and *para* positions would be cleaved. We conducted a preliminary study that employed a model compound **35**[43] (Table 3). Contrary to anticipation, only diol **36** was obtained by the use of sodium *p*-thiocresolate, according to Hansson's procedure (entry 1). Even under forcing conditions, the third methyl ether could not be cleaved (entry 2). On the other hand, tris-*O*-demethylation can proceed by utilizing lithium *p*-thiocresolate[44] as a base (entry 3). Finally, all three methyl ethers of **35** were completely cleaved under the conditions shown in entry 4, yielding only a phloroglucinol **37**. The effects of the countercation were as follows: (1) Employment of lithium ion, which has a weaker ionization tendency, as countercation enabled the generation of trianion (delocalization of three negative charges to two formyl groups and the aromatic ring); (2) According to the hard soft acids bases (HSAB) principle,[45] lithium cation is a harder acid and shows greater affinity for phenoxide anion (hard base); thus, the reactivity of *p*-thiocresolate anion was increased.

Macrocarpal C trimethyl ether **34** was then subjected to the same tris-*O*-demethylation conditions to provide (−)-macrocarpal C (**3**) in a 58% yield (Scheme 8). Synthetic **3** displayed ^{1}H and ^{13}C NMR spectra in CD_3OD that were indistinguishable from those reported[2b] for the natural isolate; it had the following optical properties: $[\alpha]^{25}_D$ −22.1 (*c* 0.150, EtOH). A small rotation, $[\alpha]^{24}_D$ −3.0 (*c* 0.92, EtOH), was originally reported for **3** that had been isolated from *E. globulus*.[2b] This rotation, however, is believed to be erroneous due to contamination of the natural sample.[46] Moreover, the synthetic sample **3** exhibited spectroscopic data, including ^{1}H and ^{13}C NMR spectra in pyridine-d_5, identical to those for natural macrocarpal G (**4**). The rotation for synthetic **3**, $[\alpha]^{25}_D$ −24.7 (*c* 0.135, MeOH), corresponded closely to the rotation reported for **4**, $[\alpha]_D$ −27.1 (*c* 0.59, MeOH).[2c]

Scheme 8. Completion of the Total Synthesis



Conclusion

We have accomplished the first total synthesis of (−)-macrocarpal C with high stereoselectivity from the previously discussed tricyclic enone **5**. At the introduction stage of the aromatic side-chain moiety to the enone **5**, the coupling reaction of silyldienol ether **6** with biomimetic benzyl cation species **A′** generated from the benzyl chloride **7** was examined. The formation of the coupling products **8** and **9** in ca. 1:1 ratio is reminiscent of the proposed biosynthetic pathway, where both benzylic stereoisomers, macrocarpals A and B, exist in nature. To synthesize one of the coupling products in a selective manner, we then installed a face chirality to the preceding biomimetic benzyl cation species **A′** by coordination with the $Cr(CO)_3$ ligand. As a result, we succeeded in stereocontrol at a benzylic position that nature does not control, as well as stereocontrol at the C11 position; to accomplish this, we used the novel hexasubstituted benzene $Cr(CO)_3$ complexes (*S*)- and (*R*)-**17**. The final step of the total synthesis was the tris-*O*-demethylation of macrocarpal C trimethyl ether **34**, which was successfully transformed from the coupling product **8**. To accomplish this, employment of lithium *p*-thiocresolate as a nucleophile furnished (−)-macrocarpal C (**3**). Moreover, the synthetic compound obtained in the present study was found to be identical to natural macrocarpal G (**4**). Until recently, laboratory syntheses have generally been less stereoselective than the corresponding biosynthetic pathways. In this context, the total syntheses of several biosynthetically related natural products reported here are unusual because the starategy employed is more stereoselective than the presumed biosyntheses. The results reported here significantly expand the scope and potential of methods for synthesizing various structural types of macrocarpals and euglobals.

Experimental Section

All melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ solution at 500 MHz (^{1}H) and 67.8 MHz (^{13}C), unless otherwise noted. IR absorption spectra (FT: diffuse reflectance spectroscopy) were recorded with KBr powder, and only noteworthy absorptions (cm^{-1}) are listed. Preparative TLC (PTLC) was performed with Merck $60F_{254}$-precoated silica gel plates. Column chromatography was carried out using Merck silica gel 60 (70−230 mesh) and Merck aluminum oxide 90 (70−230 mesh). All air- or moisture-

(43) Compound **35** was prepared from the diester **15** in two steps: (a) DIBALH, toluene, −78 °C; (b) TPAP, NMO, 4 Å MS, CH_3CN.

(44) Lithium *p*-thiocresolate is conveniently prepared in quantitative yield from *p*-thiocresol and *n*-BuLi in toluene at 0 °C. This salt can be stored at room temperature in a desiccator for months.

(45) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. Pearson, R. G. *Science* **1966**, *151*, 172. Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1. Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.

(46) Nishizawa, M., a personal letter on April 15, 1997.

sensitive reactions were carried out in flame-dried glassware under Ar or N_2 atmosphere. All solvents were dried and distilled according to standard procedures. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure.

(−)-(1*S*,2*R*,4*R*,7*S*)-10-(*tert*-Butyldimethylsiloxy)-7-[(*tert*-butyldimethylsiloxy)methyl]-3,3,11-trimethyltricyclo[6.3.0.0^{2,4}]undeca-8,10-diene (6). TBSOTf (0.520 mL, 2.26 mmol) was added to a solution of enone **5** (526 mg, 1.51 mmol) and Et_3N (0.630 mL, 4.52 mmol) in Et_2O/CH_2Cl_2 (1:1, 15 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with H_2O at 0 °C, the mixture was diluted with Et_2O, and the whole was washed with brine, dried, and concentrated. The residue was purified by column chromatography on alumina (*n*-hexane:AcOEt = 40:1) to give silyldienol ether **6** (684 mg, 98%). **6**: colorless oil; $[\alpha]^{28}_D$ −2.9 (*c* 0.535, $CHCl_3$); IR 1649, 1255, 1093, 839; ^{1}H NMR δ 0.00 (3H, s), 0.01 (3H, s), 0.13 (3H, s), 0.14 (3H, s), 0.09 (1H, dd, *J* = 8.8, 9.8 Hz), 0.62 (1H, ddd, *J* = 4.9, 6.1, 8.8 Hz), 0.88 (9H, s), 0.96 (9H, s), 1.06 (3H, s), 1.13 (3H, s), 1.33 (1H, m), 1.58 (1H, m), 1.71 (3H, s), 1.82 (1H, ddd, *J* = 6.1, 7.3, 13.4 Hz), 1.99 (1H, m), 2.45 (1H, d, *J* = 9.8 Hz), 2.86 (1H, m), 3.40 (1H, dd, *J* = 5.5, 9.8 Hz), 3.50 (1H, dd, *J* = 9.2, 9.8 Hz), 5.79 (1H, s); ^{13}C NMR δ −5.5 (q), −5.3 (q), −4.3 (q), −4.2 (q), 9.7 (q), 16.1 (q), 18.1 (s), 18.4 (s), 19.6 (t), 19.8 (s), 25.7 (q × 3), 26.0 (q × 3), 26.2 (t), 26.7 (d), 28.4 (d), 28.8 (q), 43.1 (d), 48.7 (d), 67.2 (t), 120.0 (s), 126.8 (d), 147.0 (s), 150.7 (s); MS (EI) *m*/*z* (relative intensity) 462 (M^+, 86.7), 317 (100); HRMS (EI) Calcd for $C_{27}H_{50}O_2Si_2$: 462.3349. Found: 462.3325 (M^+).

(+)-Dimethyl 5-[(1′*S*)-1′-((1*S*,2*R*,4*R*,7*S*,11*R*)-7-[(*tert*-Butyldimethylsiloxy)methyl]-3,3,11-trimethyl-10-oxotricyclo[6.3.0.0^{2,4}]undec-8-en-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (8) and (+)-Dimethyl 5-[(1′*R*)-1′-((1*S*,2*R*,4*R*,7*S*,11*R*)-7-[(*tert*-Butyldimethylsiloxy)methyl]-3,3,11-trimethyl-10-oxotricyclo[6.3.0.0^{2,4}]undec-8-en-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (9) from Coupling Reaction of 6 with Chloride 7 (Table 1, entry 1). $ZnCl_2$ (26.8 mg, 0.197 mmol) was added to a solution of silyldienol ether **6** (930 mg, 2.01 mmol) and chloride **7** (80% purity, 821 mg, 1.69 mmol) in CH_2Cl_2 (4 mL), and the whole was stirred at room temperature for 1 h. After the reaction was quenched with saturated $NaHCO_3$ (1 mL) at 0 °C, the resulting mixture was extracted with AcOEt. The extract was washed with H_2O and brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 15:1) to give coupling products **8** (469 mg, 33%, 46% considering recovered enones) and **9** (453 mg, 32%, 44% considering recovered enones), together with a 1:5 mixture of enone **5** and its C11 epimer (192 mg, 27%). **8**: colorless syrup; $[\alpha]^{26}_D$ +0.4 (*c* 2.60, $CHCl_3$); IR 1736, 1699, 1610, 1576; ^{1}H NMR δ 0.05 (1H, dd, *J* = 9.8, 10.4 Hz), 0.08 (3H, s), 0.09 (3H, s), 0.43 (3H, s), 0.52 (1H, ddd, *J* = 5.4, 10.4, 10.4 Hz), 0.76 (3H, d, *J* = 6.7 Hz), 0.84 (3H, d, *J* = 6.7 Hz), 0.86 (3H, s), 0.91 (9H, s), 1.03 (3H, s), 1.11−1.29 (2H, m), 1.47−1.60 (2H, m), 1.72 (1H, m), 2.02 (1H, m), 2.07 (1H, m), 2.39 (1H, d, *J* = 10.4 Hz), 3.05 (1H, m), 3.21 (1H, dd, *J* = 4.9, 10.4 Hz), 3.66 (1H, dd, *J* = 5.5, 10.4 Hz), 3.73 (3H, s), 3.77 (3H, s), 3.81 (3H, s), 3.82−3.88 (1H, m), 3.90 (3H, s), 3.93 (3H, s), 5.78 (1H, s); ^{13}C NMR δ −5.2 (q), −5.1 (q), 14.4 (q), 15.0 (q), 18.2 (s), 18.9 (t), 20.9 (s), 21.8 (q), 23.8 (q), 25.9 (q × 3), 26.7 (d), 27.2 (t), 28.1 (q), 28.3 (d), 28.8 (d), 37.1 (t), 42.3 (d), 45.1 (d), 48.9 (d), 52.6 (q), 52.7 (q), 57.7 (s), 60.2 (q), 62.2 (q), 63.9 (q), 64.4 (t), 116.8 (s), 117.1 (s), 123.5 (s), 127.1 (d), 155.4 (s), 158.7 (s), 160.0 (s), 166.2 (s), 166.6 (s), 184.0 (s), 213.7 (s); MS (EI) *m*/*z* (relative intensity) 700 (M^+, 0.51), 297 (100). Anal. Calcd for $C_{39}H_{60}O_9Si$: C, 66.82; H, 8.63. Found: C, 66.44; H, 8.36. **9**: colorless syrup; $[\alpha]^{30}_D$ +6.7 (*c* 0.600, $CHCl_3$); IR 1736, 1699, 1608, 1572; ^{1}H NMR δ 0.01 (6H, s), 0.12 (1H, dd, *J* = 9.8, 9.8 Hz), 0.59 (1H, m), 0.76 (3H, d, *J* = 6.1 Hz), 0.82 (3H, d, *J* = 6.1 Hz), 0.88 (9H, s), 0.96 (3H, s), 1.00 (3H, s), 1.02−1.10 (1H, m), 1.10 (3H, s), 1.23−1.33 (2H, m), 1.50 (1H, m), 1.77 (1H, m), 1.89 (1H, m), 2.05 (1H, m), 2.67 (1H, d, *J* = 10.4 Hz), 2.96 (1H, ddd, *J* = 4.3, 10.4, 10.4 Hz), 3.27 (1H, dd, *J* = 4.9, 9.8 Hz), 3.34 (1H, dd, *J* = 10.4, 10.4 Hz), 3.40 (1H, dd, *J* = 4.3, 11.6 Hz), 3.71 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 5.77 (1H, s); ^{13}C NMR δ −5.5 (q), −5.4 (q), 15.7 (q), 18.2 (s), 18.2 (q), 18.8 (t), 21.2 (s), 21.4 (q), 24.0 (q), 25.8 (q × 3), 26.4 (d), 26.5 (t), 28.1 (d), 28.3 (q), 30.2 (d), 37.3 (t), 44.0 (d), 44.4 (d), 47.6 (d), 52.5 (q), 52.5 (q), 56.3 (s), 59.5 (q), 61.1 (q), 63.1 (t), 64.4 (q), 115.3 (s), 115.6 (s), 121.7 (s), 128.9 (d), 155.8 (s), 159.0 (s), 159.3 (s), 166.5 (s × 2), 182.9 (s), 213.1 (s); MS (EI) *m*/*z* (relative intensity) 700 (M^+, 0.67), 297 (100). Anal. Calcd for $C_{39}H_{60}O_9Si$: C, 66.82; H, 8.63. Found: C, 66.76; H, 8.56.

(±)-3-Methyl-1-(2,4,6-trimethoxyphenyl)butanol (18). A solution of ketone **12**[6] (1.03 g, 4.09 mmol) in Et_2O (5 mL) was added to a suspension of $LiAlH_4$ (126 mg, 3.33 mmol) in Et_2O (25 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h. After successive careful addition of H_2O (0.125 mL), 1 N aqueous NaOH (0.125 mL), and H_2O (0.375 mL) at 0 °C, the resulting precipitates were filtered off through Celite. The filtrate was dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 2:1) to give alcohol **18** (949 mg, 91%). **18**: colorless crystals; mp 46.5−48.5 °C (*n*-hexane); IR 3564, 1610, 1593, 1216, 1205, 1151, 1126; ^{1}H NMR δ 0.91 (3H, d, *J* = 6.7 Hz), 0.94 (3H, d, *J* = 6.1 Hz), 1.51 (1H, quintet, *J* = 6.7 Hz), 1.66 (1H, m), 1.80 (1H, ddd, *J* = 6.1, 7.9, 14.0 Hz), 3.42 (1H, d, *J* = 11.6 Hz), 3.80 (3H, s), 3.81 (6H, s), 5.14 (1H, ddd, *J* = 6.1, 8.5, 11.6 Hz), 6.13 (2H, s); ^{13}C NMR δ 22.4 (q), 23.2 (q), 25.1 (d), 47.0 (t), 55.3 (q), 55.6 (q × 2), 65.9 (d), 91.0 (d × 2), 113.3 (s), 158.3 (s × 2), 160.0 (s); MS (EI) *m*/*z* (relative intensity) 254 (M^+, 0.4), 197 (100). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.12; H, 8.52.

(±)-Tricarbonyl[3-methyl-1-(2,4,6-trimethoxyphenyl)-butanol]chromium (19). A mixture of alcohol **18** (143 mg, 0.561 mmol) and $Cr(CO)_6$ (307 mg, 1.40 mmol) in degassed 1,4-dioxane/*n*-Bu_2O/*n*-heptane (5:5:1, 22 mL) was heated in the dark at 120 °C for 34 h.[15] After cooling, the mixture was filtered, and the filtrate was concentrated and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 2:1, column wrapped with aluminum foil to exclude light) to give alcohol **18** (75.2 mg, 53%) and complexed alcohol **19** (95.1 mg, 91% based on 47% conversion). **19**: pale yellow powder; mp 135.5−136.5 °C (decomposition, Et_2O−*n*-hexane); IR 3575, 1952, 1871, 1859, 1545, 1524, 1219, 1205, 1155, 1101; ^{1}H NMR δ 0.93 (3H, d, *J* = 4.9 Hz), 0.94 (3H, d, *J* = 6.1 Hz), 1.45 (1H, m), 1.82 (1H, m), 1.89 (1H, m), 2.56 (1H, d, *J* = 10.4 Hz), 3.77 (3H, s), 3.82 (3H, s), 3.82 (3H, s), 4.83 (1H, s), 4.85 (1H, m), 4.87 (1H, s); ^{13}C NMR δ 21.6 (q), 23.4 (q), 25.3 (d), 47.2 (t), 55.7 (q), 56.1 (q × 2), 60.2 (d), 60.6 (d), 65.2 (d), 92.3 (s), 140.6 (s), 141.0 (s), 141.7 (s), 233.9 (s × 3); MS (EI) *m*/*z* (relative intensity) 390 (M^+, 10.0), 237 (100). Anal. Calcd for $C_{17}H_{22}CrO_7$: C, 52.31; H, 5.68. Found: C, 52.06; H, 5.55.

(±)-Tricarbonyl[dimethyl 5-(1-hydroxy-3-methylbutyl)-2,4,6-trimethoxyisophthalate]chromium (20). To a solution of complexed alcohol **19** (603 mg, 1.54 mmol) and TMEDA (0.950 mL, 6.29 mmol) in THF (15 mL) was added dropwise *n*-BuLi (1.58 M in *n*-hexane, 2.50 mL, 3.95 mmol) at −78 °C, and the whole was stirred at −78 °C for 2 h. Dry CO_2 was bubbled at −78 °C for 30 min through the reaction mixture, which was allowed to warm slowly to 0 °C, acidified with 5% aqueous HCl, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated The residue was dissolved in benzene/MeOH (4:1, 20 mL) and treated with $TMSCHN_2$ (2.0 M in hexanes, 3.85 mL, 7.70 mmol) and stirred at room temperature for 2 h. The mixture was concentrated and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 1:1, column wrapped with aluminum foil to exclude light) to give a separable 2:1 mixture of monoester (719 mg), which was taken to the next step without further purification. To a solution of the previous monoester (719 mg) and TMEDA (0.950 mL, 6.29 mmol) in THF (30 mL) was added LDA (0.5 M in *n*-hexane/THF, 9.65 mL, 4.83 mmol) dropwise at −78 °C, and the whole was stirred at −50 °C for 3 h. Dry CO_2 was bubbled at −78 °C for 30 min through the reaction mixture, which was allowed to warm slowly to 0 °C, acidified with 5% aqueous HCl, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated The residue was dissolved in benzene/MeOH (4:1, 20 mL), treated with

$TMSCHN_2$ (2.0 M in hexanes, 4.80 mL, 9.60 mmol), and stirred at room temperature for 2 h. The reaction mixture was concentrated and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 2:1, column wrapped with aluminum foil to exclude light) to give complexed diester (±)-**20** (588 mg, 75% from **19**). (±)-**20**: yellow needles; mp 156−157 °C (decomposition, *n*-hexane-AcOEt); IR 3552, 1981, 1911, 1732, 1581, 1240; ^{1}H NMR δ 1.00 (6H, d, J = 6.7 Hz), 1.51 (1H, ddd, J = 2.4, 9.8, 16.5 Hz), 2.02 (1H, ddd, J = 3.7, 9.8, 14.0 Hz), 2.46 (1H, d, J = 9.2 Hz), 3.85 (3H, s), 3.88 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 3.94 (3H, s), 6.11 (1H, d, J = 9.2 Hz); ^{13}C NMR δ 21.2 (q), 23.6 (q), 25.6 (d), 47.7 (t), 53.9 (q × 2), 62.8 (q), 63.0 (q), 63.5 (q), 66.0 (d), 85.1 (s), 85.2 (s), 96.4 (s), 135.6 (s), 136.8 (s), 137.4 (s), 164.4 (s), 164.5 (s), 230.2 (s × 3); MS (EI) *m*/*z* (relative intensity) 506 (M^+, 67.6), 422 (100). Anal. Calcd for $C_{21}H_{26}CrO_{11}$: C, 49.81; H, 5.17. Found: C, 49.69; H, 5.11.

(±)-Tricarbonyl[dimethyl 5-(1-acetoxy-3-methylbutyl)-2,4,6-trimethoxyisophthalate]chromium (21). To a solution of (±)-**20** (34.9 mg, 0.0689 mmol), Et_3N (0.145 mL; 1.04 mmol), and DMAP (26.6 mg, 0.218 mmol) in CH_2Cl_2 (1.5 mL) was added Ac_2O (0.0325 mL, 0.344 mmol), and the whole was stirred at room temperature for 40 min. The mixture was diluted with AcOEt, and the whole was washed with H_2O and brine. The organic layer was dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 1:1) to give complexed acetate (±)-**21** (36.4 mg, 96%). (±)-**21**: yellow oil; IR 1983, 1915, 1732, 1236; ^{1}H NMR δ 0.96 (3H, d, J = 6.7 Hz), 0.98 (3H, d, J = 6.1 Hz), 1.52 (1H, m), 1.64 (1H, m), 2.11 (3H,s), 2.29 (1H, ddd, J = 4.3, 10.4, 14.6 Hz), 3.88 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 3.93 (3H, s), 6.15 (1H, dd, J = 3.1, 10.4 Hz); ^{13}C NMR δ 21.1 (q), 21.5 (q), 23.2 (q), 25.4 (d), 45.5 (t), 53.9 (q), 53.9 (q), 63.2 (q), 63.7 (q), 63.7 (q), 66.3 (d), 85.6 (s), 86.2 (s), 92.9 (s), 135.8 (s), 137.3 (s), 138.6 (s), 164.4 (s), 164.4 (s), 170.0 (s), 229.9 (s × 3); MS (EI) *m*/*z* (relative intensity) 548 (M^+, 4.0), 417 (100); HRMS (EI) Calcd for $C_{23}H_{28}CrO_{12}$: 548.0985. Found: 548.0978 (M^+).

(±)-Tricarbonyl[dimethyl 5-(1-chloracetoxy-3-methylbutyl)-2,4,6-trimethoxyisophthalate]chromium (17). To a solution of complexed diester (±)-**20** (10.8 mg, 0.0213 mmol) and pyridine (0.0172 mL, 0.213 mmol) in CH_2Cl_2 (1 mL) was added $(ClCH_2CO)_2O$ (1.0 M in CH_2Cl_2, 0.0533 mL, 0.0533 mmol) at 0 °C, and the whole was stirred at 0 °C for 3 h. The reaction was quenched with H_2O at 0 °C, and the mixture was extracted with CH_2Cl_2. The extract was dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:CH_2Cl_2:AcOEt = 6:3:1) to give complexed chloroacetate (±)-**17** (11.2 mg, 90%). (±)-**17**: yellow oil; IR 1983, 1915, 1732, 1240; ^{1}H NMR δ 0.97 (3H, d, J = 6.7 Hz), 0.98 (3H, d, J = 7.9 Hz), 1.59 (1H, m), 1.66 (1H, m), 2.34 (1H, ddd, J = 4.3, 10.4, 14.0 Hz), 3.88 (3H, s), 3.90 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 3.93 (3H, s), 4.12 (1H, s), 4.13 (1H, s), 6.22 (1H, dd, J = 3.7, 10.4 Hz); ^{13}C NMR δ 21.4 (q), 23.1 (q), 25.3 (d), 40.8 (t), 45.1 (t), 53.9 (q × 2), 63.0 (q), 63.6 (q), 63.8 (q), 68.7 (d), 85.4 (s), 85.8 (s), 91.4 (s), 135.9 (s), 137.2 (s), 138.5 (s), 164.3 (s × 2), 166.5 (s), 229.7 (s × 3); MS (EI) *m*/*z* (relative intensity) 582 (M^+, 4.2), 321 (100); HRMS (EI) Calcd for $C_{23}H_{27}ClCrO_{12}$: 582.0588. Found: 582.0595 (M^+).

(+)-Tricarbonyl[dimethyl 5-[(1*R*)-3-methyl-1-(((1′*R*)-1′-(1-naphthyl)ethyl)aminocarbonyloxy)butyl]-2,4,6-trimethoxyisophthalate]chromium (22) and (−)-Tricarbonyl[dimethyl 5-[(1*S*)-3-methyl-1-(((1′*R*)-1′-(1-naphthyl)ethyl)aminocarbonyloxy)butyl]-2,4,6-trimethoxyisophthalate]chromium (23). Following the general procedure of Duggan,[23] to a mixture of complexed diester (±)-**20** (219 mg, 0.433 mmol) and CuCl (99.9%, 43.0 mg, 0.434 mmol) in DMF (4.5 mL) was added (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.151 mL, 0.867 mmol), and the whole was stirred in the dark at room temperature for 3 h. After dilution with Et_2O, H_2O (5 mL) was added to the mixture at 0 °C. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with H_2O (10 mL) and brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 3:1, column wrapped with aluminum foil to exclude light) to give a 1:1 mixture of complexed carbamates **22** and **23** (302 mg). This mixture was subjected to column chromatography on silica gel (100 g, degassed benzene:AcOEt:*i*-PrOH = 100:2:1, column wrapped with aluminum foil to exclude light) to afford **22** (147 mg, 48%) and **23** (147 mg, 48%). **22**: yellow foam; $[\alpha]^{28}_D$ +17.1 (*c* 0.315, $CHCl_3$); IR 1975, 1919, 1911, 1728; ^{1}H NMR δ 0.90 (3H, d, J = 6.1 Hz), 1.01 (3H, d, J = 6.7 Hz), 1.46 (1H, m), 1.63 (1H, m), 1.67 (3H, d, J = 6.1 Hz), 2.22 (1H, m), 3.89 (3H, s), 3.89 (3H, s), 3.93 (3H, s), 3.93 (3H, s), 3.93 (3H, s), 4.98 (1H, d, J = 7.9 Hz), 5.67 (1H, m), 6.11 (1H, d, J = 9.2 Hz), 7.45 (1H, dd, J = 7.3, 7.9 Hz), 7.52 (3H, m), 7.80 (1H, d, J = 7.9 Hz), 7.88 (1H, d, J = 7.3 Hz), 8.11 (1H, d, J = 7.3 Hz); ^{13}C NMR δ 21.6 (q), 22.0 (q), 23.8 (q), 25.9 (d), 46.0 (t), 47.2 (d), 54.3 (q × 2), 63.5 (q), 64.1 (q), 64.2 (q), 67.3 (d), 86.0 (s), 86.3 (s), 94.3 (s), 122.8 (d), 123.9 (d), 125.7 (d), 126.3 (d), 126.8 (d), 128.8 (d), 129.3 (d), 131.5 (s), 134.4 (s), 136.4 (s), 138.0 (s), 138.8 (s), 139.2 (s), 155.3 (s), 165.0 (s × 2), 230.5 (s × 3); MS (FAB) *m*/*z* 726 ($M + Na^+$); HRMS (FAB) Calcd for $C_{34}H_{37}CrO_{12}NNa$: 726.1619. Found: 726.1604 ($M + Na^+$). **23**: yellow foam; $[\alpha]^{28}_D$ −46.1 (*c* 0.160, $CHCl_3$); IR 1983, 1915, 1728; ^{1}H NMR δ 0.98 (3H, d, J = 6.1 Hz), 1.03 (3H, d, J = 5.5 Hz), 1.45−1.87 (2H, m), 1.68 (3H, d, J = 6.1 Hz), 2.25 (1H, m), 3.73 (3H, s), 3.88 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 4.99 (1H, d, J = 7.9 Hz), 5.66 (1H, m), 6.02 (1H, d, J = 9.2 Hz), 7.39−7.56 (4H, m), 7.77 (1H, d, J = 7.9 Hz), 7.85 (1H, m), 8.06 (1H, m); ^{13}C NMR δ 21.5 (q), 21.6 (q), 23.2 (q), 25.4 (d), 46.1 (t), 46.7 (d), 53.8 (q × 3), 63.3 (q), 63.7 (q), 67.5 (d), 77.2 (s), 85.9 (s), 93.2 (s), 122.1 (d), 123.2 (d), 125.2 (d), 125.8 (d), 126.3 (d), 128.2 (d), 128.8 (d), 130.8 (s), 133.9 (s), 135.7 (s), 137.4 (s), 138.4 (s), 138.8 (s), 154.9 (s), 164.4 (s × 2), 229.9 (s × 3); MS (FAB) *m*/*z* 726 ($M + Na^+$); HRMS (FAB) Calcd for $C_{34}H_{37}CrO_{12}NNa$: 726.1619. Found: 726.1623 ($M + Na^+$).

(+)-Tricarbonyl[dimethyl 5-((*R*)-1-hydroxy-3-methylbutyl)-2,4,6-trimethoxyisophthalate]chromium ((*R*)-20). To a solution of less polar carbamate **22** (98.0 mg, 0.139 mmol) and H_2O (0.0700 mL, 3.88 mmol) in CH_3CN (7 mL) was added $BF_3{\cdot}Et_2O$ (0.175 mL, 1.38 mmol) at 0 °C, and the whole was stirred at 0 °C for 4 h. After the reaction was quenched with saturated $NaHCO_3$ (3.5 mL) at 0 °C, the resulting mixture was extracted with $CHCl_3$. The extract was washed with brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 2:1) to give complexed alcohol (*R*)-**20** (60.7 mg, 86%, >98% ee by Mosher ester analysis[27]). (*R*)-**20**: yellow needles; mp 158−159 °C (decomposition, *n*-hexane-AcOEt); $[\alpha]^{28}_D$ +21.9 (*c* 0.270, $CHCl_3$).

(−)-Tricarbonyl[dimethyl 5-((*S*)-1-hydroxy-3-methylbutyl)-2,4,6-trimethoxyisophthalate]chromium ((*S*)-20). Complexed alcohol (*S*)-**20** was prepared in a manner similar to that described for (*R*)-**20** from polar carbamate **23** (43.9 mg, 0.0624 mmol). Column chromatography on silica gel (*n*-hexane:AcOEt = 2:1) gave complexed alcohol (*S*)-**20** (25.5 mg, 81%, >98% ee by Mosher ester analysis[27]). (*S*)-**20**: yellow needles; mp 158−159 °C (decomposition, *n*-hexane-AcOEt); $[\alpha]^{26}_D$ −21.9 (*c* 0.160, $CHCl_3$).

(+)-Tricarbonyl[dimethyl 5-((*R*)-1-chloracetoxy-3-methylbutyl)-2,4,6-trimethoxyisophthalate]chromium ((*R*)-17). Complexed chloroacetate (*R*)-**17** was prepared in a manner similar to that described for (±)-**17** from complexed alcohol (*R*)-**20** (27.8 mg, 0.0549 mmol). Column chromatography on silica gel (*n*-hexane:CH_2Cl_2:AcOEt = 6:3:1) gave complexed chloroacetate (*R*)-**17** (31.2 mg, 98%). (*R*)-**17**: yellow oil; $[\alpha]^{28}_D$ +63.4 (*c* 0.295, $CHCl_3$).

(−)-Tricarbonyl[dimethyl 5-((*S*)-1-chloracetoxy-3-methylbutyl)-2,4,6-trimethoxyisophthalate]chromium ((*S*)-17). Complexed chloroacetate (*S*)-**17** was prepared in a manner similar to that described for (±)-**17** from complexed alcohol (*S*)-**20** (23.5 mg, 0.0464 mmol). Column chromatography on silica gel (*n*-hexane:CH_2Cl_2:AcOEt = 6:3:1) gave complexed chloroacetate (*S*)-**17** (24.8 mg, 92%). (*S*)-**17**: yellow oil; $[\alpha]^{26}_D$ −62.6 (*c* 0.295, $CHCl_3$).

Diastereoselective Synthesis of Coupling Product 8 from coupling Reaction of 6 with Complexed Chloroacetate (*S*)-17 (Table 2, entry 3). $ZnCl_2$ solution (1.0 m in Et_2O, 0.0572 mL, 0.0572 mmol) was added to a solution of silyldienol ether **6** (35.3 mg, 0.0763 mmol) and complexed chloroacetate (*S*)-**17** (22.2 mg, 0.0381 mmol) in CH_2Cl_2 (1 mL),

and the whole was stirred in the dark at room temperature for 1.5 h. After the reaction was quenched with saturated $NaHCO_3$ (0.2 mL) at 0 °C, the resulting mixture was extracted with AcOEt. The extract was washed with H_2O and brine, dried, and concentrated The residue was dissolved in MeOH (1.5 mL), CAN (32.2 mg, 0.0587 mmol) was added to the mixture at 0 °C, and the whole was stirred at 0 °C for 30 min. After addition of H_2O at 0 °C, the resulting mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 5:1) to give coupling products **8** (16.4 mg, 61% based on (*S*)-**17**, 82% considering enones) and **9** (0.5 mg, 2% based on (*S*)-**17**, 3% considering recovered enones), together with a 1:5 mixture of enone **5** and its C11 epimer (16.6 mg, 62%).

Diastereoselective Synthesis of Coupling Product 9 from Coupling Reaction of 6 with Complexed Chloroacetate (*R*)-17. Coupling product **9** was prepared in a manner similar to that described for **8** from silyldienol ether **6** (44.6 mg, 0.0964 mmol) and complexed chloroacetate (*R*)-**17** (28.1 mg, 0.0482 mmol). Column chromatography on silica gel (*n*-hexane:AcOEt = 5:1) gave coupling products **9** (19.9 mg, 59% based on (*R*)-**17**, 80% considering recovered enones) and **8** (0.5 mg, 2% based on (*R*)-**17**, 2% considering recovered enones), together with a 1:5 mixture of enone **5** and its C11 epimer (21.2 mg, 63%).

(−)-Dimethyl 5-[(1′*S*)-1′-((1*R*,2*R*,4*R*,7*S*,8*R*,11*S*)-7-(Hydroxymethyl)-3,3,11-trimethyl-10-oxotricyclo-[6.3.0.0^{2,4}]undec-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (10). A mixture of enone **8** (119 mg, 0.170 mmol) and 10% Pd/C (13.2 mg) in MeOH (1.7 mL) was stirred under 5 atm of H_2 atmosphere at room temperature for 27 h. The reaction mixture was filtered, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 1:1) to give keto-alcohol **10** (88.3 mg, 88%). **10**: colorless foam; $[\alpha]^{30}_D$ −1.3 (*c* 1.69, $CHCl_3$); IR 3564, 1732, 1570; ^{1}H NMR δ 0.57 (1H, dd, *J* = 9.4, 9.4 Hz), 0.61 (1H, m), 0.86 (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.8 Hz), 0.97 (3H, s), 1.04 (3H, s), 1.11 (3H, s), 1.12−1.28 (2H, m), 1.33 (1H, ddd, *J* = 3.4, 10.3, 13.7 Hz), 1.48 (1H, ddd, *J* = 3.4, 12.8, 13.7 Hz), 1.77 (1H, m), 1.93−2.12 (5H, m), 2.39 (1H, ddd, *J* = 2.6, 15.4, 15.4 Hz), 2.60 (1H, dd, *J* = 9.4, 10.3 Hz), 3.51 (1H, dd, *J* = 3.4, 12.0 Hz), 3.69 (1H, dd, *J* = 6.0, 11.1 Hz), 3.74 (3H, s), 3.79 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 3.96 (1H, dd, *J* = 6.0, 11.1 Hz); ^{13}C NMR δ 17.1 (q), 20.1 (t), 21.0 (q), 21.4 (s), 21.6 (q), 24.3 (q), 26.2 (d), 27.3 (d), 28.9 (q), 30.7 (d), 31.5 (t), 36.5 (t), 39.4 (d), 40.6 (d), 42.6 (d), 43.6 (d), 44.0 (t), 52.7 (q), 52.9 (q), 57.4 (s), 60.9 (q), 61.5 (t), 61.9 (q), 63.9 (q), 116.2 (s), 116.4 (s), 122.9 (s), 155.6 (s), 159.4 (s), 159.7 (s), 166.5 (s), 166.9 (s), 220.8 (s); MS (EI) *m*/*z* (relative intensity) 588 (M^+, 1.0), 297 (100); HRMS (EI) Calcd for $C_{33}H_{48}O_9$: 588.3297. Found: 588.3297 (M^+).

(+)-Dimethyl 5-[(1′*S*)-1′-((1*R*,2*R*,4*R*,7*S*,8*R*,10*S*,11*S*)-10-Hydroxy-7-(hydroxymethyl)-3,3,11-trimethyltricyclo[6.3.0.0^{2,4}]undec-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (24). $NaBH_4$ (43.5 mg, 1.15 mmol) was added to a solution of keto-alcohol **10** (54.2 mg, 0.0921 mmol) in MeOH (2 mL) at 0 °C, and the whole was stirred at room temperature for 1 h. After the reaction was quenched with saturated NH_4Cl at 0 °C, the resulting mixture was extracted with AcOEt. The extract was washed with H_2O and brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 1:1) to give diol **24** (52.2 mg, 96%). **24**: colorless foam; $[\alpha]^{29}_D$ +2.6 (*c* 1.06, MeOH); IR 3568, 3410, 1732, 1578, 1572; ^{1}H NMR δ 0.57 (3H, s), 0.57−0.62 (2H, m), 0.66 (3H, d, *J* = 6.9 Hz), 0.90 (3H, d, *J* = 6.9 Hz), 1.06−1.20 (1H, m), 1.09 (3H, s), 1.15 (3H, s), 1.33 (1H, m), 1.50 (1H, m), 1.67 (1H, m), 1.72 (1H, dd, *J* = 3.4, 14.5 Hz), 1.76 (1H, m), 1.87 (1H, ddd, *J* = 6.4, 12.8, 13.7 Hz), 1.93 (1H, ddd, *J* = 3.4, 6.0, 13.7 Hz), 2.06 (1H, m), 2.18 (1H, m), 2.25 (1H, m), 2.39 (1H, m), 3.27 (1H, brs), 3.50−3.61 (2H, m), 3.80−3.90 (1H, m), 3.83 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 3.93 (3H, s), 3.93 (3H, s), 4.14 (1H, dd, *J* = 9.4, 12.0 Hz); ^{13}C NMR δ 17.7 (q), 20.9 (q), 21.0 (t), 21.5 (s), 23.2 (q), 23.9 (q), 26.7 (d), 27.9 (d), 29.4 (q), 29.5 (d), 32.5 (t), 36.0 (t), 37.1 (t), 38.5 (d), 41.2 (d), 42.5 (d), 45.7 (d), 52.7 (q), 52.8 (q), 54.3 (s), 60.8 (q), 61.4 (q), 64.2 (t), 64.2 (q), 85.2 (d), 116.1 (s), 116.8 (s), 124.8 (s), 155.3 (s), 158.3 (s), 158.5 (s), 166.5 (s), 166.6 (s); MS (EI) *m*/*z* (relative intensity) 590 (M^+, 0.06), 297 (100); HRMS (EI) Calcd for $C_{33}H_{50}O_9$: 590.3452. Found: 590.3441 (M^+).

(+)-Dimethyl 5-[(1′*S*)-1′-((1*R*,2*R*,4*R*,7*S*,8*R*,10*S*,11*S*)-7-(Acetoxymethyl)-10-hydroxy-3,3,11-trimethyltricyclo[6.3.0.0^{2,4}]undec-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (25). Ac_2O (0.0815 mL, 0.863 mmol) was added to a solution of diol **24** (170 mg, 0.288 mmol) and DMAP (158 mg, 1.29 mmol) in CH_2Cl_2 (6 mL) at 0 °C, and the whole was stirred at room temperature for 1 h. After the reaction was quenched with H_2O at 0 °C, the resulting mixture was extracted with AcOEt. The extract was washed with H_2O and brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 1.5:1) to give monoacetate **25** (182 mg, 100%). **25**: colorless foam; $[\alpha]^{32}_D$ +10.8 (*c* 0.665, $CHCl_3$); IR 3618, 1732, 1574, 1236; ^{1}H NMR δ 0.51 (3H, s), 0.54 (1H, dd, *J* = 9.4, 10.3 Hz), 0.62 (1H, m), 0.64 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.9 Hz), 1.09 (3H, s), 1.14 (3H, s), 1.24−1.38 (3H, m), 1.45 (1H, ddd, *J* = 3.4, 12.8, 13.7 Hz), 1.75−1.91 (4H, m), 2.02−2.14 (3H, m), 2.04 (3H, s), 2.20 (1H, m), 2.76 (1H, brs), 3.49 (1H, dd, *J* = 4.3, 12.0 Hz), 3.78 (1H, m), 3.82 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 3.92 (3H, s), 4.24 (1H, dd, *J* = 10.3, 11.1 Hz), 4.49 (1H, dd, *J* = 2.6, 11.1 Hz); ^{13}C NMR δ 17.6 (q), 20.0 (t), 20.0 (q), 21.2 (q), 21.3 (s), 23.2 (q), 23.9 (q), 26.7 (d), 27.4 (d), 29.3 (q), 29.5 (t), 29.5 (d), 36.6 (t), 36.9 (t), 39.3 (d), 40.2 (d), 41.0 (d), 45.8 (d), 52.7 (q), 52.8 (q), 54.6 (s), 60.7 (q), 61.4 (q), 63.0 (t), 64.2 (q), 80.9 (d), 116.0 (s), 116.6 (s), 125.0 (s), 155.2 (s), 158.4 (s), 158.5 (s), 166.5 (s), 166.6 (s), 171.2 (s); MS (EI) *m*/*z* (relative intensity) 632 (M^+, 0.05), 297 (100). Anal. Calcd for $C_{35}H_{52}O_{10}$: C, 66.43; H, 8.28. Found: C, 66.46; H, 8.20.

(−)-Dimethyl 5-[(1′*R*)-1′-((1*R*,2*R*,4*R*,7*S*,8*R*,11*S*)-7-(Hydroxymethyl)-3,3,11-trimethyltricyclo[6.3.0.0^{2,4}]undec-9-en-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (30). To a mixture of monoacetate **25** (269 mg, 0.425 mmol) and 2-nitrophenyl selenocyanate (965 mg, 4.25 mmol) in THF (8.5 mL) was added *n*-Bu_3P (1.06 mL, 4.25 mmol) at room temperature, and the whole was stirred at 75 °C in a sealed tube for 20 h. After cooling, 30% aqueous H_2O_2 (1.20 mL, 10.6 mmol) was added at 0 °C to the reaction mixture, and the whole was stirred at room temperature for 3 h. After addition of H_2O, the resulting mixture was extracted with $CHCl_3$. The extract was washed with brine, dried, concentrated, and purified by column chromatography on silica gel (CCl_4:AcOEt = 50:1) to give olefinic acetate **29** which contained inseparable side products. This mixture was treated at 0 °C with NaOMe (0.1 M in MeOH, 8.30 mL, 0.830 mmol) and stirred at room temperature for 6.5 h. After the reaction was quenched with saturated NH_4Cl at 0 °C, the resulting mixture was extracted with AcOEt. The extract was washed with H_2O and brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) to give olefinic alcohol **30** (157 mg, 64% from **25**). **30**: colorless foam; $[\alpha]^{29}_D$ −11.0 (*c* 0.580, $CHCl_3$); IR 3564, 1732, 1579, 1570, 1234; ^{1}H NMR δ 0.63 (1H, m), 0.63 (3H, s), 0.70 (1H, dd, *J* = 10.3, 10.3 Hz), 0.80 (3H, d, *J* = 6.0 Hz), 0.80 (3H, d, *J* = 6.9 Hz), 1.08 (3H, s), 1.10−1.25 (3H, m), 1.16 (3H, s), 1.51 (1H, ddd, *J* = 3.4, 13.7, 13.7 Hz), 1.74−1.84 (1H, m), 1.77 (1H, dd, *J* = 9.5, 10.3 Hz), 1.84 (1H, dd, *J* = 10.3, 12.9 Hz), 1.92 (1H, dddd, *J* = 2.6, 3.4, 3.4, 14.1 Hz), 2.25 (1H, m), 2.74 (1H, m), 3.34 (1H, dd, *J* = 3.4, 12.9 Hz), 3.59 (1H, m), 3.76−3.86 (1H, m), 3.78 (3H, s), 3.85 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 3.92 (3H, s), 5.46 (1H, d, *J* = 6.0 Hz), 6.06 (1H, dd, *J* = 2.6, 6.0 Hz); ^{13}C NMR δ 17.3 (q), 19.7 (t), 21.6 (s), 22.1 (q), 22.1 (q), 24.4 (q), 26.6 (d), 27.3 (d), 27.5 (d), 28.9 (t), 29.0 (q), 38.2 (t), 40.2 (d), 41.8 (d), 44.2 (d), 52.6 (q), 52.7 (q), 53.5 (d), 54.3 (s), 60.0 (q), 61.7 (q), 61.9 (t), 64.1 (q), 116.0 (s × 2), 124.6 (s), 131.9 (d), 141.0 (d), 155.0 (s), 158.9 (s), 159.1 (s), 166.9 (s × 2); MS (EI) *m*/*z* (relative intensity) 572 (M^+, 0.21), 297 (100); HRMS (EI) Calcd for $C_{33}H_{48}O_8$: 572.3346. Found: 572.3346 (M^+).

(−)-Dimethyl 5-[(1′*R*)-1′-((1*R*,2*R*,4*R*,7*S*,8*R*,11*S*)-7-(Hydroxymethyl)-3,3,11-trimethyltricyclo[6.3.0.0^{2,4}]undec-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (31).

A mixture of olefinic alcohol **30** (21.8 mg, 0.0381 mmol) and 10% Pd/C (1.5 mg) in MeOH (1.5 mL) was stirred under 5 atm of H_2 atmosphere at room temperature for 15 h. The reaction mixture was filtered, and the filtrate was concentrated and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 2:1) to give alcohol **31** (21.9 mg, 100%). **31**: colorless foam; $[\alpha]^{32}_D$ −10.4 (*c* 0.585, $CHCl_3$); IR 3537, 1732, 1579, 1570, 1234; ^{1}H NMR δ 0.49 (1H, dd, *J* = 9.4, 10.3 Hz), 0.55 (1H, ddd, *J* = 6.0, 6.9, 10.3 Hz), 0.58 (3H, s), 0.74 (3H, d, *J* = 5.1 Hz), 0.82 (3H, d, *J* = 5.1 Hz), 1.08 (3H, s), 1.09 (3H, s), 1.09−1.29 (4H, m), 1.32−1.47 (4H, m), 1.66−1.88 (3H, m), 1.90−2.02 (3H, m), 2.14 (1H, m), 3.43 (1H, dd, *J* = 3.5, 12.8 Hz), 3.65−3.78 (2H, m), 3.73 (3H, s), 3.83 (3H, s), 3.83 (3H, s), 3.90 (3H, s), 3.91 (3H, s); ^{13}C NMR δ 17.6 (q), 19.6 (t), 21.1 (q), 21.5 (s), 22.7 (q), 24.4 (q), 26.7 (d), 27.1 (d), 28.1 (t), 28.3 (d), 28.7 (t), 29.3 (q), 35.2 (t), 35.8 (t), 38.7 (d), 43.5 (d), 44.4 (d), 46.6 (d), 49.1 (s), 52.6 (q × 2), 59.5 (q), 60.3 (t), 61.6 (q), 64.1 (q), 115.5 (s), 115.6 (s), 124.9 (s), 154.9 (s), 158.8 (s), 159.2 (s), 167.0 (s), 167.0 (s); MS (EI) *m*/*z* (relative intensity) 574 (M^+, 0.34), 297 (100); HRMS (EI) Calcd for $C_{33}H_{50}O_8$: 574.3503. Found: 574.3480 (M^+).

(+)-Dimethyl 5-[(1′*R*)-1′-((1*R*,2*R*,4*R*,8*R*,11*S*)-3,3,11-Trimethyl-7-methylenetricyclo[6.3.0.0^{2,4}]undec-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalate (32). To a solution of alcohol **31** (73.9 mg, 0.129 mmol) and 2-nitrophenyl selenocyanate (74.8 mg, 0.329 mmol) in THF (5 mL) was added *n*-Bu_3P (0.0801 mL, 0.321 mmol) at room temperature, and the whole was stirred at 50 °C for 12 h. After cooling, 30% aqueous H_2O_2 (0.0729 mL, 0.643 mmol) was added at 0 °C to the reaction mixture, and the whole was stirred at room temperature for 30 min. The resulting mixture was diluted with AcOEt, and the whole was washed with H_2O and brine, dried, concentrated, and purified by column chromatography on silica gel (*n*-hexane:AcOEt = 4:1) to give *exo*-olefin **32** (54.8 mg, 77%). **32**: colorless oil; $[\alpha]^{24}_D$ +3.9 (*c* 0.635, $CHCl_3$); IR 1734, 1633, 1570, 1232; ^{1}H NMR δ 0.62 (1H, dd, *J* = 9.4, 10.3 Hz), 0.66 (1H, m), 0.70 (3H, s), 0.76 (3H, d, *J* = 6.8 Hz), 0.76 (3H, d, *J* = 6.0 Hz), 0.85 (1H, m), 0.97 (3H, s), 1.09 (3H, s), 1.18 (1H, m), 1.26 (1H, m), 1.35 (1H, dd, *J* = 9.4, 10.3 Hz), 1.37 (1H, m), 1.69 (1H, m), 1.75 (1H, m), 1.95−2.12 (4H, m), 2.33−2.43 (2H, m), 3.40 (1H, dd, *J* = 3.4, 12.9 Hz), 3.75 (3H, s), 3.82 (3H, s), 3.83 (3H, s), 3.91 (3H, s), 3.91 (3H, s), 4.67 (1H, s), 4.72 (1H, s); ^{13}C NMR δ 16.9 (q), 19.8 (s), 22.3 (q), 22.8 (q), 24.3 (q), 25.6 (t), 26.8 (t), 26.9 (d), 27.2 (d), 27.9 (d), 29.1 (q), 35.3 (t), 35.5 (t), 39.4 (d), 39.5 (t), 49.3 (s), 50.5 (d), 50.6 (d), 52.5 (q), 52.6 (q), 59.6 (q), 61.4 (q), 64.1 (q), 105.3 (t), 115.5 (s), 115.5 (s), 124.8 (s), 154.8 (s), 155.7 (s), 158.9 (s), 159.3 (s), 166.9 (s), 167.0 (s); MS (EI) *m*/*z* (relative intensity) 556 (M^+, 0.54), 297 (100); HRMS (EI) Calcd for $C_{33}H_{48}O_7$: 556.3400. Found: 556.3401 (M^+).

(+)-5-[(1′*R*)-1′-((1*R*,2*R*,4*R*,8*R*,11*S*)-3,3,11-Trimethyl-7-methylenetricyclo[6.3.0.0^{2,4}]undec-11-yl)-3′-methylbutyl]-2,4,6-trimethoxybenzene-1,3-dimethanol (33). DIBALH (1.01 M in toluene, 0.455 mL, 0.460 mmol) was added to a solution of diester **32** (32.0 mg, 0.0575 mmol) in toluene (3 mL) at −78 °C, and the whole was stirred at − 78 °C for 1 h. The reaction was quenched with saturated sodium potassium tartrate at −78 °C, and the whole was diluted with AcOEt and stirred at room temperature until the layers separated. The aqueous layer was extracted with AcOEt and the combined organic layers were washed with H_2O and brine, dried, concentrated, and purified by PTLC (*n*-hexane:AcOEt = 1:1) to give diol **33** (28.8 mg, 100%). **33**: colorless crystals; mp 152−153 °C (*n*-hexane-AcOEt); $[\alpha]^{27}_D$ +2.6 (*c* 0.925, $CHCl_3$); IR 3425, 1633, 1578, 1095; ^{1}H NMR δ 0.58−0.72 (2H, m), 0.67 (3H, s), 0.80 (3H, d, *J* = 6.0 Hz), 0.88 (1H, m), 0.91 (3H, d, *J* = 6.0 Hz), 0.95 (3H, s), 1.09 (3H, s), 1.26 (1H, m), 1.30−1.44 (3H, m), 1.65 (1H, m), 1.72 (1H, m), 1.96−2.06 (3H, m), 2.13 (1H, ddd, *J* = 6.9, 8.6, 13.7 Hz), 2.34 (1H, dd, *J* = 8.6, 18.0 Hz), 2.40 (1H, dd, *J* = 6.0, 12.8 Hz), 2.45 (1H, dd, *J* = 5.2, 6.9 Hz), 2.51 (1H, dd, *J* = 6.0, 6.0 Hz), 3.32 (1H, dd, *J* = 3.4, 12.8 Hz), 3.85 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 4.67 (1H, s), 4.72 (1H, s), 4.67−4.78 (4H, m); ^{13}C NMR δ 16.9 (q), 19.9 (s), 22.7 (q), 23.3 (q), 24.4 (q), 25.6 (t), 27.0 (d), 27.1 (d), 27.3 (t), 28.6 (d), 29.1 (q), 36.0 (t), 36.4 (t), 39.5 (t), 40.7 (d), 49.6 (s), 50.3 (d), 51.4 (d), 56.4 (t), 56.5 (t), 62.3 (q), 62.6 (q), 63.0 (q), 105.4 (t), 122.7 (s), 123.4 (s), 127.0 (s), 155.6 (s), 157.5 (s), 159.7 (s), 159.9 (s); MS (EI) *m*/*z* (relative intensity) 500 (M^+, 0.33), 279 (100). Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.20; H, 9.50.

(+)-5-[(1′*R*)-1′-((1*R*,2*R*,4*R*,8*R*,11*S*)-3,3,11-Trimethyl-7-methylenetricyclo[6.3.0.0^{2,4}]undec-11-yl)-3′-methylbutyl]-2,4,6-trimethoxyisophthalaldehyde (34). To a mixture of diol **33** (22.2 mg, 0.0443 mmol), NMO (26.9 mg, 0.229 mmol), and 4-Å molecular sieves (22.5 mg) in CH_3CN (0.9 mL) was added TPAP (3.7 mg, 0.010 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was added directly to the top of a silica gel column eluting with AcOEt. The filtrate was concentrated and purified by PTLC (*n*-hexane:AcOEt = 2:1) to give macrocarpal C trimethyl ether **34** (19.2 mg, 87%). **34**: colorless oil; $[\alpha]^{24}_D$ +2.2 (*c* 0.645, $CHCl_3$); IR 1687, 1633, 1556, 1136; ^{1}H NMR δ 0.62 (1H, dd, *J* = 9.4, 10.3 Hz), 0.68 (3H, s), 0.70 (1H, m), 0.76 (3H, d, *J* = 6.9 Hz), 0.83 (3H, d, *J* = 6.9 Hz), 0.96 (1H, m), 1.02 (3H, s), 1.12 (1H, m), 1.13 (3H, s), 1.31 (1H, ddd, *J* = 4.3, 9.4, 13.7 Hz), 1.38 (1H, dd, *J* = 10.3, 10.3 Hz), 1.41 (1H, m), 1.71 (1H, m), 1.77 (1H, m), 1.97−2.08 (3H, m), 2.12 (1H, ddd, *J* = 8.6, 8.6, 12.9 Hz), 2.39 (2H, m), 3.52 (1H, dd, *J* = 4.3, 12.0 Hz), 3.89 (3H, s), 3.95 (3H, s), 4.04 (3H, s), 4.68 (1H, s), 4.74 (1H, s), 10.28 (1H, s), 10.29 (1H, s); ^{13}C NMR δ 17.1 (q), 19.9 (s), 22.4 (q), 23.3 (q), 24.3 (q), 25.8 (t), 26.9 (t), 27.1 (d), 27.2 (d), 27.8 (d), 29.2 (q), 35.5 (t × 2), 39.2 (d), 39.5 (t), 49.1 (s), 50.4 (d), 50.8 (d), 63.6 (q), 64.6 (q), 66.3 (q), 105.7 (t), 117.1 (s), 117.6 (s), 127.1 (s), 155.6 (s), 166.9 (s), 167.4 (s), 168.1 (s), 187.3 (d), 187.4 (d); MS (EI) *m*/*z* (relative intensity) 496 (M^+, 0.89), 203 (100); HRMS (EI) Calcd for $C_{31}H_{44}O_5$: 496.3189. Found: 496.3200 (M^+).

(−)-Macrocarpal C (3).[2b] A mixture of macrocarpal C trimethyl ether **34** (15.2 mg, 0.0306 mmol), lithium *p*-thiocresolate[44] (40.6 mg, 0.312 mmol; prepared from *p*-thiocresol and *n*- BuLi), and HMPA (0.270 mL, 1.55 mmol) in toluene (0.65 mL) was heated at reflux for 5 h. After the reaction mixture was diluted with CH_2Cl_2 (5 mL), the mixutre was extracted with 1 N aqueous NaOH (5 × 1 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 2.5 mL) to remove HMPA and was then acidified with 10% aqueous HCl to pH 1 at 0 °C, and the whole was extracted with Et_2O (10 × 5 mL). The extract was washed with brine (2 × 1 mL), dried, concentrated, and purified by PTLC ($CHCl_3$:AcOH = 200:1) to give (−)-macrocarpal C **3** (8.1 mg, 58%). **3**: yellowish amorphous solid; $[\alpha]^{25}_D$ −22.1 (*c* 0.150, EtOH) {lit.[2b] (−)-macrocarpal C $[\alpha]^{24}_D$ −3.0 (*c* 0.150, EtOH)}, $[\alpha]^{25}_D$ −24.7 (*c* 0.135, MeOH) {lit.[2c] (−)-macrocarpal G $[\alpha]_D$ −27.1 (*c* 0.92, MeOH)}; IR 3084, 1631, 1311; ^{1}H NMR (C_5D_5N) δ 0.70 (1H, m), 0.74 (1H, dd, *J* = 9.8, 9.8 Hz), 0.93 (3H, d, *J* = 6.7 Hz), 0.98 (3H, d, *J* = 6.1 Hz), 1.04 (3H, s), 1.08 (1H, m), 1.18 (3H, s), 1.20 (3H, s), 1.38 (1H, ddd, *J* = 4.3, 9.8, 12.8 Hz), 1.54 (1H, m), 1.56 (1H, dd, *J* = 6.7, 12.8 Hz), 1.61 (1H, dd, *J* = 9.8, 11.0 Hz), 1.80 (1H, m), 1.98 (1H, m), 2.05 (1H, m), 2.08 (1H, ddd, *J* = 12.2, 12.2, 12.8 Hz), 2.44 (1H, m), 2.48 (1H, m), 2.54 (1H, ddd, *J* = 7.3, 7.9, 12.8 Hz), 2.62 (1H, ddd, *J* = 3.7, 12.8, 12.8 Hz), 3.66 (1H, dd, *J* = 4.3, 12.8 Hz), 4.82 (1H, s), 4.93 (1H, s), 10.51 (1H, s), 10.54 (1H, s); ^{1}H NMR (CD_3OD) δ 0.67 (1H, m), 0.68 (1H, m), 0.78 (3H, d, *J* = 6.7 Hz), 0.81 (3H, d, *J* = 6.1 Hz), 0.82 (3H, s), 0.96 (1H, m), 1.01 (3H, s), 1.09 (3H, s), 1.15 (1H, m), 1.18 (1H, m), 1.34 (1H, ddd, *J* = 6.8, 7.3, 12.8 Hz), 1.39 (1H, dd, *J* = 9.8, 10.4 Hz), 1.65 (1H, m), 1.78 (1H, m), 2.01 (1H, m), 2.01 (1H, m), 2.26 (1H, m), 2.30 (1H, m), 2.33 (1H, m), 2.41 (1H, m), 3.38 (1H, dd, *J* = 3.7, 12.8 Hz), 4.64 (1H, s), 4.70 (1H, s), 10.08 (1H, s), 10.08 (1H, s); ^{13}C NMR (C_5D_5N) δ 17.3, 20.3, 22.3, 23.8, 24.9, 26.1, 27.5, 27.6, 28.1, 28.3, 29.1, 35.2, 36.6, 37.5, 39.9, 49.2, 50.8, 51.3, 106.3, 106.8, 107.0, 108.3, 155.5, 171.2, 171.7, 192.0, 192.2; ^{13}C NMR (CD_3OD) δ 18.3, 21.8, 23.3, 24.8, 25.7, 27.6, 29.0, 29.3, 29.5, 30.2, 30.4, 36.9, 38.3, 39.5, 41.4, 50.7, 52.5, 53.4, 107.0, 107.3, 107.5, 111.1, 157.3, 171.2, 171.7, 172.3, 193.6, 193.8; MS (EI) *m*/*z* (relative intensity) 454 (M^+, 8.6), 195 (100); HRMS (EI) Calcd for $C_{28}H_{38}O_5$: 454.2719. Found: 454.2734 (M^+).

Acknowledgment. We thank Professor Mugio Nishizawa (Tokushima Bunri University) for provision of

natural macrocarpal C (**3**), copies of its spectra, and other useful information. We also thank Professor Seiichi Homma (Ochanomizu University) for copies of the spectra for natural macrocarpal G (**4**) and Professor Chisato Mukai (Kanazawa University) for helpful information regarding the preparation of the arene−chromium complexes. This research was supported in part by a grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (No. 08672425).

Supporting Information Available: Experimental procedures and characterization data for compounds **7**, **13**−**16**, **26**, **27**, **36**, **37**; ^{1}H and ^{13}C NMR spectra in C_5D_5N and CD_3OD and the IR spectrum for synthetic (−)-**3**; comparison of ^{1}H and ^{13}C NMR data in C_5D_5N and CD_3OD for synthetic and natural (−)-**3** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981413+