73 (100), 70 (6.2), 59 (7.5), 55 (20.8), 43 (28.2), 41 (26.3), 39 (11.4), 31 (15.7), 29 (19.9), 27 (13.3). Anal. Calcd for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.70; H, 12.15.

***erythro*/*threo*-2-Ethyl-3-ethoxybutan-1-ol (10e)**: 87% yield; bp 100 °C (18 Torr); ^{1}H NMR 4.2-3.0 (m, 5 H), 1.8 (s, 1 H), 1.6-0.6 (m, 12 H); ^{13}C NMR (79.81, 78.86), (64.50, 64.24), (63.75, 63.72), (47.77, 45.26), (21.37, 19.80), 17.60, (15.40, 14.56), (12.26, 11.63); MS, *m/z* 146 (M^+, 0.1), 73 (100), 55 (14.4), 45 (87.8), 43 (16.0), 41 (14.5), 31 (16.0). Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.80; H, 12.40.

3-Methyl-4-ethoxypentan-2-ol (10f): 86% yield; bp 71 °C (18 Torr); IR 3440, 2980, 2940, 2880, 1450, 1370, 1165, 1110, 1090, 990, 940, 930, 870; ^{1}H NMR 4.2-3.5 (m, 2 H), 3.5-3.0 (m, 2 H), 2.7 (s, 1 H), 1.8-1.4 (m, 1 H), 1.4-0.8 (m, 12 H); MS, *m/z* 147 (M^+ + 1, 0.5), 91 (14.9), 73 (46.9), 56 (48.7), 45 (100), 43 (25.2), 41 (21.7). Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found C, 65.65; H, 12.35.

***erythro*/*threo*-2-Methyl-3-(benzyloxy)pentan-1-ol (10h)**: 87% yield; bp 120 °C (9 Torr); IR 3400, 3090, 3060, 3030, 2970, 2940, 2880, 1670, 1500, 1455, 1380, 1350, 1255, 1210, 1090, 1070, 1050, 1030, 950, 735, 700; ^{1}H NMR 7.2 (s, 5 H), 4.7-4.2 (m, 3 H), 3.6-3.1 (m, 2 H), 3.0-2.6 (m, 1 H), 2.1-1.2 (m, 3 H), 1.1-0.7 (m, 6 H); ^{13}C NMR (138.85, 138.52), (128.34, 127.77), (127.67, 127.60), 127.48, (83.99, 82.76), (71.95, 71.58), (65.99, 65.50), 37.49, (23.33, 22.94), (13.62, 11.56), (10.49, 8.78); MS, *m/z* 131 (30.5), 99 (26.7), 77 (2.9), 71 (100), 59 (12.0), 55 (11.6), 46 (13.6), 45 (11.0), 41 (33.0), 39 (13.4), 29 (27.1), 28 (12.0). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.84; H, 9.76.

2-Methylpentane-1,3-diol (15). A mixture of **10h** (1.43 g, 6.9 mmol), cyclohexene (30 mL), and Pd/C (10%) (0.25 g) in methanol (15 mL) was stirred (10 h), at room temperature. The catalyst was filtered off, and distillation gave chemically pure (SE 30) **15** (0.63 g, 88%) having bp 97 °C (0.3 Torr): IR 3350, 2960, 2940, 2880, 1460, 1380, 1135, 1105, 1030, 970, 870, 820; ^{1}H NMR 4.4 (s, 2 H), 3.8-3.2 (m, 3 H), 2.0-1.1 (m, 3 H), 1.5 (t, 3 H), 0.9 (d, 3 H); ^{13}C NMR (78.17, 75.54), (67.39, 66.68), (39.40, 38.85), (27.83, 26.89), (13.84, 10.67), (10.04, 9.49); MS, *m/z* 118 (M^+, 6.8), 100 (M^+ - 18, 5.1). Anal. Calcd for $C_6H_{14}O_2$: C, 60.98; H, 11.94. Found C, 61.05; H, 11.73.

Acknowledgment. This work was supported in part by the Ministero della Pubblica Istruzione Roma. We thank Prof. G. Valentini for generous supplies of $H_2Ru(PPh_3)_4$.

Registry No. **5**, 22408-41-9; (*E*)-**6a**, 80060-26-0; (*Z*)-**6a**, 80060-25-9; (*E*)-**6b**, 80060-32-8; (*Z*)-**6b**, 80060-31-7; (*E*)-**6c**, 111160-15-7; (*Z*)-**6c**, 111160-16-8; (*E*)-**6d**, 62322-65-0; (*Z*)-**6d**, 62322-41-2; (*E*)-**6e**, 80060-30-6; (*Z*)-**6e**, 80060-29-3; (*E*)-**6f**, 82477-76-7; (*Z*)-**6f**, 82477-75-6; (*E*)-**6g**, 111160-17-9; (*Z*)-**6g**, 111160-18-0; **7**, 17739-45-6; **8**, 38786-79-7; **9a**, 22092-24-6; **9b**, 80060-21-5; **9c**, 111160-13-5; **9d**, 62322-46-7; **9d** (enol ether), 6380-95-6; **9e**, 80060-20-4; **9f**, 87384-21-2; **9g**, 20615-52-5; *erythro*-**10a**, 86335-64-0; *threo*-**10a**, 86335-63-9; *erythro*-**10b**, 111160-19-1; *threo*-**10b**, 86335-65-1; *erythro*-**10c**, 111160-20-4; *threo*-**10c**, 111160-21-5; **10d**, 58330-06-6; *erythro*-**10e**, 111160-22-6; *threo*-**10e**, 111160-23-7; **10f**, 111160-24-8; *erythro*-**10h**, 111160-25-9; *threo*-**10h**, 111160-26-0; (*E*)-**11**, 84736-38-9; (*Z*)-**11**, 84736-39-0; **12**, 14593-43-2; **13**, 15895-87-1; **14**, 111160-14-6; **15**, 149-31-5; $Et(OEt)C{=}CH_2$, 4181-12-8; $HOCH_2CH{=}CH_2$, 107-18-6; $Br(CH_2)_2OH$, 540-51-2; $CH_2{=}C(Me)OEt$, 926-66-9; PhCHO, 100-52-7; $CH(OEt)_3$, 122-51-0; $PhCH(OEt)_2$, 774-48-1; $MeCH(OEt)_2$, 105-57-7; $PhCH{=}CHCH_2OH$, 104-54-1; $PhCH_2OH{\cdot}Na$, 20194-18-7; $CH_2{=}CHCH_2Cl$, 107-05-1; $MeCH{=}CHCH_2OH$, 6117-91-5; $CH_2{=}CHCH(Me)OH$, 598-32-3; $Al(Bu\text{-}i)_3$, 100-99-2; 2,3-dihydropyran, 110-87-2.

A Synthetic Approach to (-)-Quassimarin Based on Intramolecular Diels-Alder Strategy

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A novel approach to the tetracyclic precursor **32** for the total synthesis of (-)-quassimarin based on an intramolecular Diels-Alder strategy is described. The key tricyclic species **22** was constructed from the triene **6** via a highly endo-selective intramolecular Diels-Alder reaction followed by hydrolysis. The dihydrofuranone moiety in **6** was assembled via a magnesium ion controlled diastereoselective addition of α-lithio-α-methoxyallene to an appropriate α-alkoxy ketone. Oxidation of **22** followed by chemo- and stereoselective reduction with lithium triethylborohydride provided the inverted alcohol. The resulting acetate **25** gave **31** by an intramolecular Claisen condensation.

The quassinoids[1] comprise one of the most widely distributed groups of naturally occurring terpenoids. Of the many quassinoids, quassimarin **1** and bruceantin **2** (Figure 1), isolated from *Quassia amara*[2] and *Brucea antidysenterica*,[3] respectively, by Kupchan, display promising biological profiles[4] as well as complex molecular architecture and as such are intriguing candidates for synthetic investigation. Thus, in the past decade many stimulating synthetic efforts[5] have been focused on both of the quassinoids. To date, however, no total syntheses have yet been achieved.

In connection with our project aimed at the total synthesis of the quassinoids,[6] we have undertaken the de-

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(4) Wall, M. E.; Wan, M. C. *J. Med. Chem.* **1978**, *21*, 1186.

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(6) (a) Shishido, K.; Saitoh, T.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2139. (b) Shishido, K.; Takahaski, K.; Oshio, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1986**, *27*, 1339.

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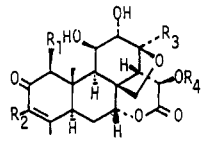
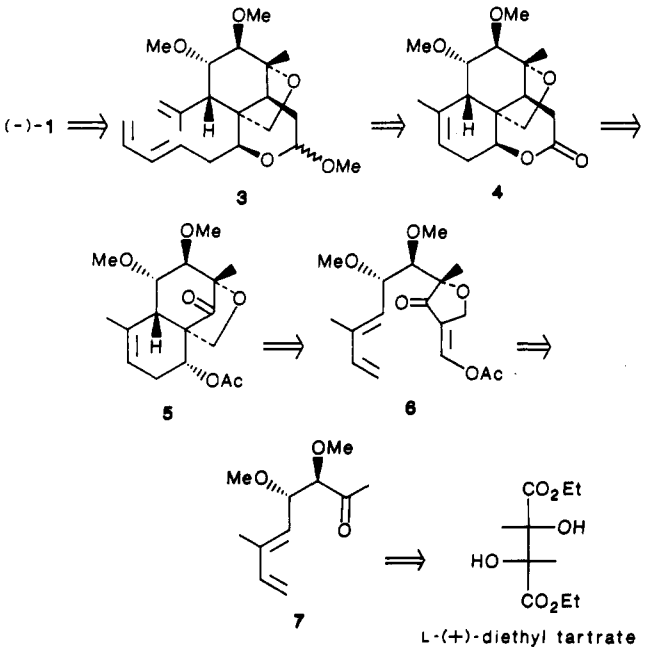


1, R_1=OH, R_2=H, R_3=Me, R_4=COC(OAc)(Me)Et
2, R_1=H, R_2=OH, R_3=CO_2Me, R_4=COCHC(Me)^{i}Pr

Figure 1.

Scheme I



velopment of an enantioselective synthetic route to quassimarin. Recently, we communicated[6b] a new approach to the construction of a tricyclic chiral synthon **22** for (−)-**1** via a highly endo-selective intramolecular Diels–Alder reaction as a key step. In this paper, we present full experimental details of this synthetic approach.

Results and Discussion

Scheme I outlines the key features of our synthetic strategy for the approach to (−)-quassimarin, an enantiomer of the natural product. The pivotal step in this approach is the intramolecular Diels–Alder reaction[7] of the triene **6**. This process would be predicted to afford the tricycle **5**, which, after assembling the D ring, could then be transformed to the triene **3**. This in turn might be converted to (−)-**1** via the another intramolecular cycloaddition. Diastereoselective construction of the quaternary carbon present in the dihydrofuranone moiety was accomplished from methyl ketone **7**, which was easily prepared from L-(+)-diethyl tartrate by a combination of several well-established standard procedures.

Construction of the Diene 17. The diene **17** was prepared in a straightforward manner as outlined in Scheme II. The diol moiety in L-(+)-diethyl tartrate was protected as the bis methyl ether according to the procedure of Felner[8] to provide **8**. After reduction of **8** with lithium aluminum hydride, the resulting diol **9** was monobenzylated with 1 equiv of sodium hydride and benzyl

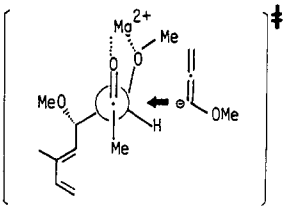


Figure 2.

bromide to yield **10** in 73% yield from **8**. The alcohol was silylated by using the standard method, and the resulting benzyl ether **11** was converted in 90% yield to the alcohol **12** upon treatment with lithium in liquid ammonia. Swern oxidation of **12** followed by a condensation of the resulting aldehyde with (α-carbethoxyethylidene)triphenylphosphorane gave an inseparable mixture of *E* and *Z* isomeric conjugated esters **13**. The mixture of esters was then reduced with lithium aluminum hydride to yield the (*E*)-allylic alcohol **14** and *Z* isomer **15** in a ratio of 20:1 in 83% yield from **12**. The minor alcohol **15** was shown to have the *Z* double bond geometry by nuclear Overhauser effect difference spectroscopy. For example, irradiation of the olefinic methyl group of **15** gave a 10.7% enhancement of the olefinic methine proton, whereas in the major alcohol **14** no enhancement could be observed. Conversion of **14** to the dienol **17** was readily accomplished by oxidation with manganese oxide to yield the corresponding aldehyde. This was immediately condensed with methylenetriphenylphosphorane followed by desilylation of the resulting **16**, providing 83% yield of **17**.

Diastereoselective Synthesis of the Triene 6. The substrate for an intramolecular Diels–Alder reaction was prepared as outlined in Scheme III. The plan for the construction of the triene **6** centered around a diastereoselective addition of α-methoxyallene[9] to α-alkoxy ketone. Swern oxidation of **17** followed by treatment with methylmagnesium bromide provided a mixture of the diastereomeric alcohol **18**, which was immediately oxidized by the conditions of Swern to produce the methyl ketone **7**. With **7** in hand the stage was set to carry out the key addition reaction. Encouraged by a previous example[10] of cyclic-Cram diastereoselective addition of α-lithio-α-methoxyallene to an α-amino ketone, we investigated the illustrated sequence. Sequential treatment of **7** with 4 equiv of α-lithio-α-methoxyallene, generated in situ from α-methoxyallene and *n*-butyllithium, with potassium *tert*-butoxide in *tert*-butyl alcohol in the presence of catalytic 18-crown-6 and hydrochloric acid yielded a 50% yield of an inseparable mixture of the diastereomeric dihydrofuranones **20**[11] in a 1:1 ratio. From this observation, it appeared that a tighter metal ion mediated binding between the oxygens of the alkoxy and carbonyl groups would be helpful. Thus, treatment of α-lithio-α-methoxyallene with anhydrous magnesium bromide,[12] generated in situ from magnesium and dibromoethane, at −78 °C followed by exposure of the metal-exchanged species to **7** at the same temperature provided the allenyl alcohol **19**, which was immediately treated as described above to yield the dihydrofuranone **20** in 46% yield from **17**. This substance exhibited a single ^{1}H NMR resonance and a single set of ^{13}C NMR signals. Although the exact absolute configuration of a newly formed chiral center in **20** could

(7) During the course of our study, a similar approach to the BCE ring system of (+)-quassimarin **1** has been reported, see: Schlessinger, R. H.; Wong, J.-W.; Poss, M. A.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 3950.
(8) Felner, I.; Schenker, K. *Helv. Chim. Acta* **1970**, *53*, 754.
(9) Hoff, S.; Brandsma, L.; Allens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916.
(10) Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 5360.
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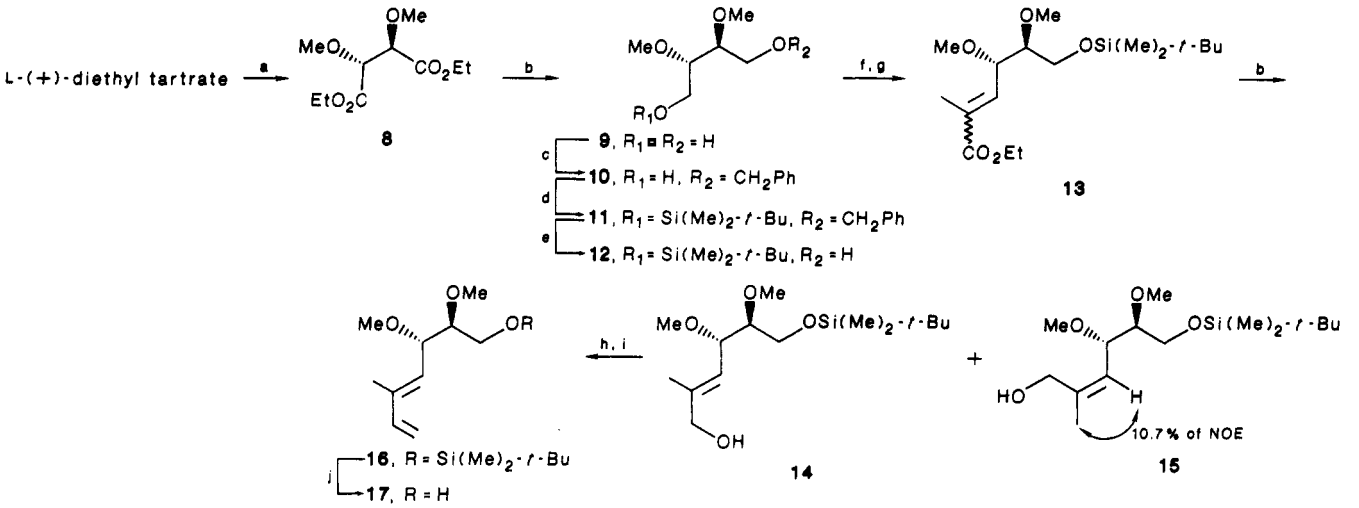
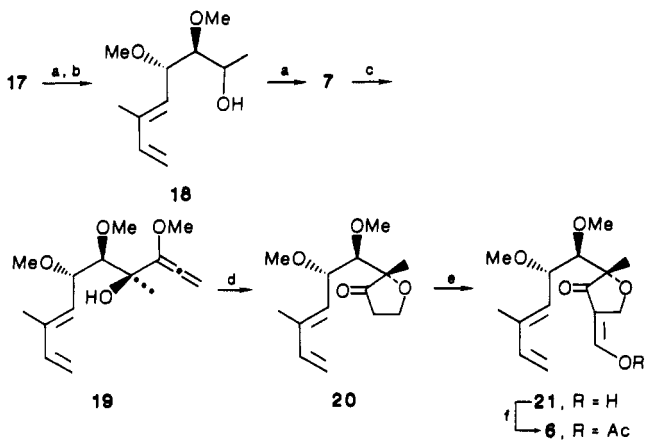
Scheme II[a]



[a] Reagents: (a) MeI, NaH, Et_2O; (b) $LiAlH_4$, THF; (c) $PhCH_2Br$, NaH, DMF; (d) $ClSi(Me)_2$-*t*-Bu, imidazole, 4-DMAP, CH_2Cl_2; (e) Li, liquid NH_3, EtOH; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (g) $Ph_3P{=}C(Me)CO_2Et$, benzene; (h) MnO_2, CH_2Cl_2; (i) $Ph_3P{=}CH_2$, THF; (j) *n*-Bu_4NF, THF.

Scheme III[a]



[a] Reagents: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (b) MeMgBr, Et_2O; (c) $(MeO)CH{=}C{=}CH_2$, *n*-BuLi, $MgBr_2$, THF; (d) *t*-BuOK, 18-crown-6, *t*-BuOH and then 3 N HCl; (e) HCO_2Et, NaH, DME; (f) Ac_2O, pyridine, 4-DMAP, CH_2Cl_2.

not be determined from the spectral properties at this stage, it was suggested that α-alkoxy ketone underwent reaction with magnesium reagents with extremely high diastereoselectivity for the product predicted by the chelation controlled mode of addition mechanism[13] shown in Figure 2.

Introduction of the dienophile moiety[14] could easily be achieved by sequential formylation of **20** with sodium hydride and ethyl formate and acetylation of the resulting vinylogous carboxylic acid **21** with standard conditions providing the triene **6** in 93% yield. The structure of **6** was assigned on the basis of its ^1H NMR spectra. A characteristic triplet (J = 3 Hz) at δ 8.07 for the olefinic methine proton on the acetoxymethylene group substantiated the *E* geometry.[14]

The Intramolecular Diels–Alder Reaction of 6. With successful preparation of the triene **6** behind us, we were ready to effect the crucial cycloaddition step. On refluxing a solution of **6** in toluene for 3 h, the reaction

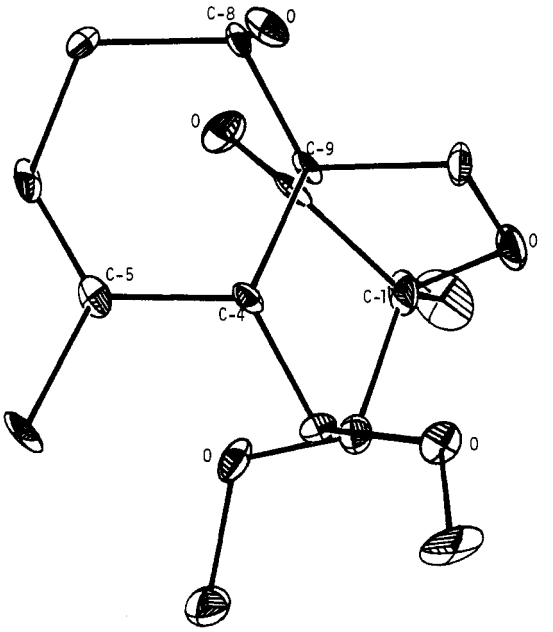
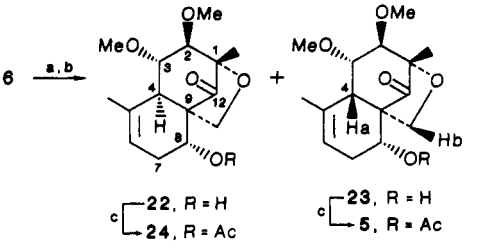


Figure 3. The X-ray structure of compound **22**.

proceeded smoothly, and the resulting mixture of diastereomeric cycloadducts was hydrolyzed with lithium hydroxide to produce a mixture of the diastereomeric alcohols **22** and **23** in a ratio of 30:1 in 83% yield. The structure of the alcohols was determined from the corresponding acetates **24** and **5** on the basis of their 400-MHz ^1H NMR decoupling experiments. A characteristic W-type long range coupling with J = 1 Hz between Ha (δ 2.79) and Hb (δ 4.12) in **5** indicated that the minor isomer might have the desired configuration at C-4 (eq 1). The structure of



(1)

reagents: (a) toluene, reflux; (b) LiOH, MeOH, H_2O, CH_2Cl_2; (c) Ac_2O, pyridine, 4-DMAP

(13) (a) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, 1031. (b) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.

(14) Shishido, K.; Hiroya, K.; Ueno, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *J. Chem. Soc., Perkin Trans 1* **1986**, 829.

Table I. The Intramolecular Diels–Alder Reaction of 21

entry	solvent	temp, °C	time, h	additive	product	% yield
1	xylene	150	9	methylene blue (cat.)[14,27]	**25**	12
2	*o*-dichlorobenzene	180	9		dec	
3	CH_2Cl_2	−78 → 0	2	Me_3Al	dec	
4	H_2O	80	8		**24**	17
5	H_2O/*t*-BuOH (2:1)	80	14	*n*-Bu_4NHSO_4 (cat.)	**24** + **25** (1:1)[a]	31
6	*t*-BuOH[b]	120	8		dec	

[a] Determined from ^1H NMR. [b] Conducted in a sealed tube.

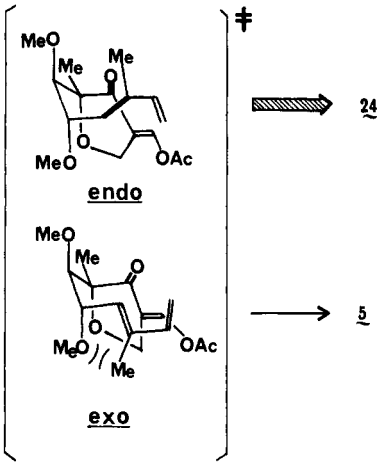


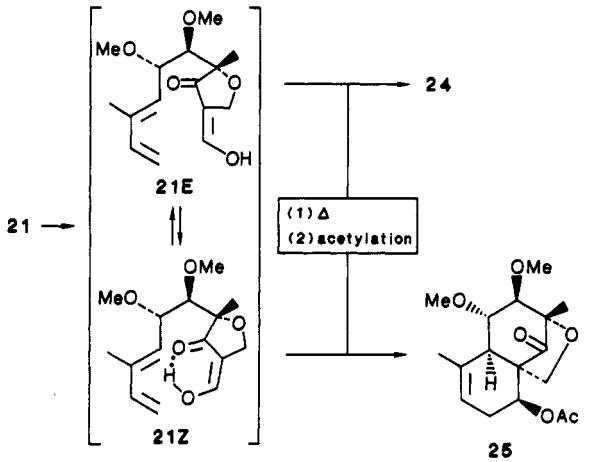
Figure 4. The transition states of intramolecular Diels–Alder reaction of 6.

the major alcohol **22** was established by single-crystal X-ray analysis as shown in Figure 3. It was confirmed that the stereochemistry at C-4 in **24** was opposite to that desired. Therefore, the acetate **24** requires two stereochemical inversions at C-4 and C-8 for the total synthesis of (−)-**1**.

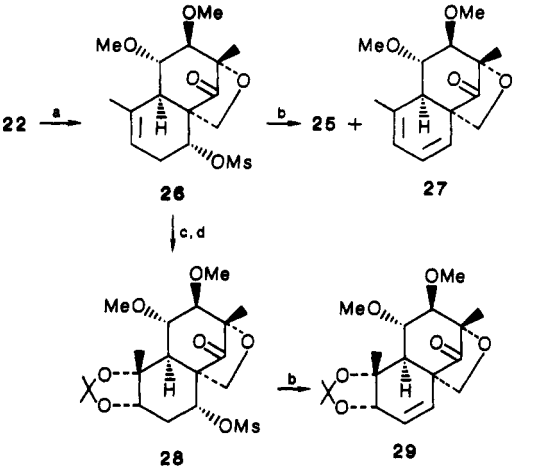
At this point, the configuration of quaternary carbon in the dihydrofuranone **20** could firmly be established as *S*, and part of our presumption could be substantiated. It was also found that the intramolecular Diels–Alder reaction of **6** proceeded in a highly endo-selective manner, completely contrary to our expectation and the results of Schlessinger[7] but easily rationalized by considering the transition state. Thus, in the exo-transition state, severe $A^{1,3}$ strain develops between the olefinic methyl group and a methoxy function, whereas less severe $A^{1,4}$ strain is present in the endo-transition state (Figure 4).

The Intramolecular Diels–Alder Reaction of 21. With a viable method in hand for assembling the BCE ring system with promising fuctionalities at appropriate positions, our attention turned to the introduction of C-8 oxygen function with the desired *S* configuration during the course of cycloaddition. We reasoned that when the intramolecular Diels–Alder reaction of **21** was conducted under the conditions causing greater contribution of *Z* form (hydrogen bonded form) of the vinylogous carboxylic acid moiety, we might be able to get preferentially the cycloadduct with 8*S* configuration (Scheme IV). The cycloaddition of crude **21** was attempted under various conditions, and the results are shown in Table I. In a nonpolar solvent (entry 1),[15] the product, after acetylation, was the desired acetate **25**, whereas in a polar media (entry 4), the 7*R* isomer, which was completely identical with authentic sample of **24** prepared above, could be obtained. However, because of the low yields of product, this transformation was not further investigated in any detail.

Scheme IV



Scheme V[a]



[a] Reagents: (a) $MeSO_2Cl$, NEt_3, 4-DMAP, CH_2Cl_2; (b) CsOAc, 18-crown-6, toluene; (c) NMO, OsO_4, *t*-BuOH, acetone, H_2O; (d) $(MeO)_2CMe_2$, *p*-TsOH, DMF.

Construction of the D Ring and Further Transformation. Initial attempts to construct the lactone ring from **22** by using our previous successful transformations,[6a] namely, sequential Horner–Emmons condensation with (diethylphosphinyl)acetate, conjugate reduction, and lactonization with inversion at C-8, were disappointing due, presumably, to severe steric congestion around the carbonyl carbon. Therefore, our attention was focused on a sequence that consisted of initial inversion of the configuration at C-8 followed by lactonization. Thus, treatment of the mesylate **26**, prepared from **22** by a standard method, with the conditions of Ikegami[16] provided the inverted acetate **25** and the diene **27** in 48% and 52% yield, respectively (Scheme V). To supress the formation of E2 elimination product, we attempted the inversion of the

(15) When the reaction was conducted without a catalytic amount of methylene blue, a mixture of diastereomeric acetates **24** and **26** could be obtained in less than 5% yield.

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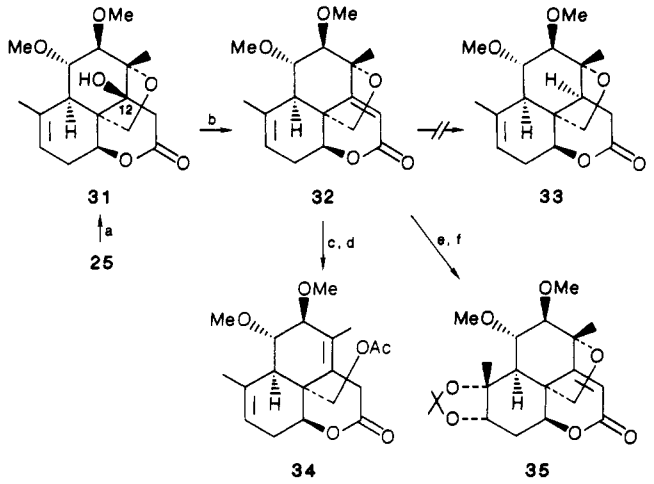
Table II. Oxidation of 22 with Various Reagents

entry	reagent	solvent	temp,[a] °C	% yield of 30
1	PCC	CH_2Cl_2	rt	15
2	PDC	CH_2Cl_2	rt	27
3	$(COCl)_2$, DMSO, NEt_3	CH_2Cl_2	−78	19
4	CrO_3	H_2SO_4, acetone, H_2O	0	23
5	NCS, Me_2S, NEt_3	toluene	−25	62
6	$(CF_3CO)_2O$, DMSO, NEt_3[20]	CH_2Cl_2	−78	100

[a] rt = room temperature.

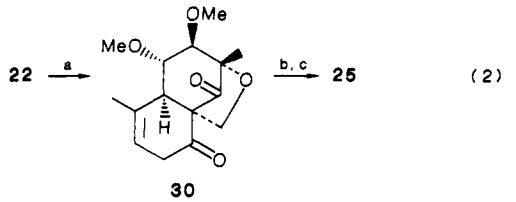
Scheme VI[a]



[a] Reagents: (a) LDA, THF; (b) $SOCl_2$, pyridine; (c) Ca, liquid NH_3, *t*-BuOH; (d) Ac_2O, pyridine, 4-DMAP; (e) NMO, OsO_4, *t*-BuOH, acetone, H_2O; (f) $(MeO)_2CMe_2$, PPTS, DMF.

mesylate **28**,[17] in which C-7 was changed to nonallylic carbon. Unfortunately, the reaction under the same inversion conditions caused extensive E2 elimination, owing to the occurrence of conformational change, furnishing the olefin **29** in 71% yield.

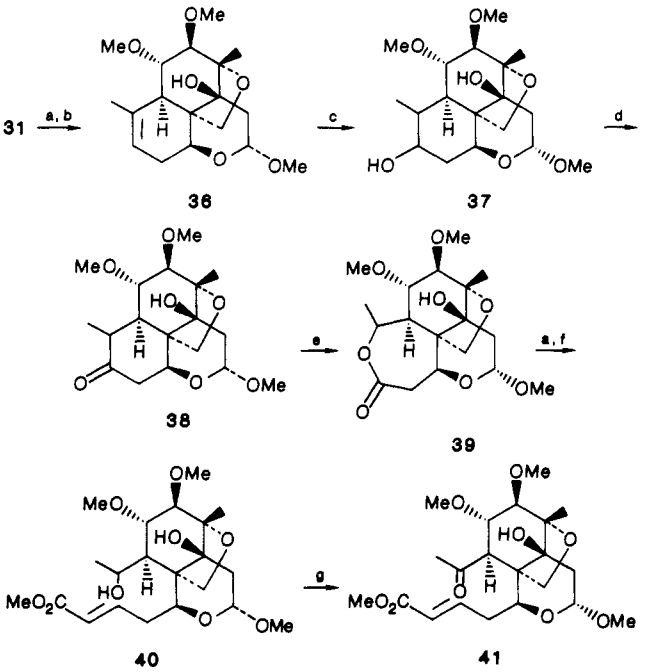
However, the problem was nicely solved by using a simple oxidation–reduction sequence. Initially, oxidation of the alcohol **22** to the diketone **30** was examined. Although the use of variety of oxidizing reagents proved unsatisfactory, greatly improved yield was realized by the oxidation with trifluoroacetic anhydride, dimethyl sulfoxide, and triethylamine in dichloromethane at −78 °C[18] (100%) (Table II). Conversion of the diketone **30**, which is somewhat unstable, to the desired acetate **25** was cleanly accomplished by chemo- and stereoselective reduction with lithium triethylborohydride[19] in tetrahydrofuran at −78 °C followed by acylation to furnish **25**, quantitatively (eq 2).



(2)

reagents: (a) $(CF_3CO)_2O$, DMSO, NEt_3, CH_2Cl_2; (b) $LiBH(Et)_3$, THF; (c) Ac_2O, pyridine, 4-DMAP

Scheme VII[a]



[a] Reagents: (a) DIBAL-H, THF; (b) $(MeO)_3CH$, *p*-TsOH, MeOH; (c) $BH_3{\cdot}SMe_2$, THF and then H_2O_2, NaOH; (d) PDC, CH_2Cl_2; (e) MCPBA, CH_2Cl_2; (f) $(MeO)_2POCH_2CO_2Me$, NaH, DME; (g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2.

Subjecting the acetate **25** to an intramolecular Claisen condensation with lithium diisopropylamide in tetrahydrofuran at −78 °C, we were able to obtain the lactone **31** in 92% yield as a sole product (Scheme VI). In the intramolecular cyclization of the enolate anion derived from **25**, the nucleophilic attack is expected to occur preferentially on the less hindered *re* face of the carbonyl; thus the configuration at C-12 would be assigned as shown. Next, we attempted to complete the construction of the tetracyclic lactone **33** by a dehydration–conjugate reduction sequence through the unsaturated lactone **32**, easily prepared from **31** by treating with thionyl chloride in pyridine. However, all attempts to reduce selectively the conjugated olefin function via 1,4-reduction ($NaHTe$,[6a,21] Et_3SiH-$(Ph_3P)_3RhCl$,[22] DIBAL-H–MeCu,[23] or L-Selectride[24]) or dissolving metal reduction were unsuccessful or met with only 1,2-reduction.[25] Although treatment of **32** with calcium[26] in liquid ammonia–*tert*-butyl alcohol afforded a detectable reduction product that was not the desired lactone **33** but lactonic alcohol, which was characterized as its acetate **34**. Furthermore, attempted catalytic reduction of the acetonide **35**, prepared from **32** with the same conditions as for **26**, using a variety of conditions proved to be unsuccessful.

Disappointed by the failure to reduce the conjugate olefin, we returned to the Claisen product **31** in hopes of being able to reduce its functionality at later stage of the synthesis. Protection of the lactone carbonyl was per-

(17) The structure of **28** was deduced from the assumption that osmylation would occur from a less hindered side of mesylate **26**.
(18) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
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(22) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, 5085.
(23) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537.
(24) Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1975**, *40*, 2846.
(25) The reduction with DIBAL-H–MeCu or L-Selectride resulted in only 1,2-reduction.
(26) Barton, D. H. R.; Lier, E. F.; MaGhie, J. F. *J. Chem. Soc. C* **1968**, 1031.
(27) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5085.

formed by sequential reduction of **31** with diisobutylaluminum hydride and acetalization to provide **36**, as a single product, quantitatively (Scheme VII). In the ^1H NMR spectrum of **36**, the methine attached to acetal carbon appears at δ 5.03 as a triplet with J = 8 Hz, indicating the configuration at the acetal carbon should be *R*. For the epimerization at C-4 and the subsequent A ring construction, **36** was submitted to the conditions of hydroboration-oxidation, yielding the alcohol **37**, which was then oxidized with pyridinium dichromate in dichloromethane to provide the ketone **38** as a sole product in 69% yield from **36**. Treatment of **38** with *m*-chloroperbenzoic acid in dichloromethane yielded the lactone **39**, which was sequentially treated with diisobutylaluminum hydride and methyl (dimethylphosphinyl)acetate–sodium hydride in dimethoxyethane to provide the conjugated ester **40** in 84% yield from **38**. The alcohol moiety in **40** was then oxidized with the conditions of Swern to furnish the methyl ketone **41** in 87% yield. Epimerization of the axially oriented acetyl group at C-4 in **41** to the equatorial position, removal of the hydroxyl group at C-12, and further transformations directed toward (-)-quassimarin are currently being investigated.

In summary, we have explored the intramolecular Diels–Alder reaction as a method for constructing the BCE ring system of (-)-quassimarin and found it to proceed in a highly endo-selective mode furnishing the tricyclic adduct epimeric with the natural series at C-4 and C-8. Then, the cycloadduct has simply been transformed to tetracyclic lactone, a promising precursor for the target. In addition, during the course of this study, we have developed a highly diastereoselective construction of dihydrofuranone with chiral quaternary carbon via magnesium ion controlled addition of allenyl anion to α-alkoxy ketone.

Experimental Section

Melting points were determined on a Yanako micromelting point apparatus and are uncorrected. ^1H NMR spectra were recorded on JEOL PMX-60 (60 MHz), JEOL FX-90 (90 MHz), JEOL PS-100 (100 MHz), JEOL GX-400 (400 MHz), and JEOL GX-500 (500 MHz) spectrometers in deuteriochloroform solution with tetramethylsilane as the internal standard. Chemical shifts are reported in δ units. When peak multiplicities are reported the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broadened. ^{13}C NMR spectra were obtained on a JEOL FX-90 (22.5 MHz) or a JEOL PS-100 (25 MHz) spectrometer. Infrared spectra were obtained on a Hitachi 125 grating spectrophotometer using chloroform solutions. Ordinary mass spectra were measured with a Hitachi M-52G instrument, while high-resolution mass spectroscopy was performed on a JEOL TMS-01SG-2 spectrometer. All optical rotations were measured in chloroform solution on a JASCO DIP-340 polarimeter, unless otherwise noted. All reactions were run under an atmosphere of dry nitrogen. Solvents were freshly distilled prior to use: tetrahydrofuran (THF) was distilled from sodium and kept over sodium wire; dichloromethane (CH_2Cl_2) was distilled from phosphorus pentoxide and kept over 4-Å molecular sieves. Unless otherwise noted, all reaction mixtures were dried, after workup, over anhydrous magnesium sulfate. Column chromatography was carried out with silica gel (Wako gel C-200). All chromatography solvents were distilled prior to use.

(+)-(2*R*,3*R*)-Diethyl Di-*O*-methyltartrate (8). A solution of L-(+)diethyl tartrate (60.4 g, 0.293 mol) in dry ether (200 mL) was added dropwise to a suspension of sodium hydride (60% in oil: 21.1 g, 0.528 mol) in dry ether (700 mL) at room temperature, and the mixture was refluxed for 1 h. After decantation of the resulting mixture, to the precipitation was added dropwise methyl iodide (166.1 g, 1.17 mol) at room temperature, and stirring was continued for 12 h. The mixture was filtered through Celite, and the filtrate was concentrated to give a residue, which was submitted to vacuum distillation, bp 86–91 °C at 0.4 mmHg, to give 48.6 g (71%) of **8** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1760; ^1H NMR (60 MHz) δ 1.33 (6 H, t, J = 7.0 Hz), 3.52 (6 H, s), 4.28 (2 H, s), 4.34 (4 H, q, J = 7.0 Hz); $[\alpha]^{20}_D$ +77° (ethanol, *c* 1.30) (lit.[8] $[\alpha]^{20}_D$ +80°).

(+)-(2*S*,3*S*)-4-(Benzyloxy)-2,3-dimethoxy-1-butanol (10). A solution of the ester **8** (87.5 g, 0.347 mol) in dry THF (200 mL) was added dropwise to a suspension of $LiAlH_4$ (26.0 g, 0.673 mol) in dry THF (600 mL) at 0 °C. After being stirred for 1 h, the mixture was quenched by the slow addition of ether containing water. After filtration through Celite, the filtrate was concentrated in vacuo to yield 52.4 g of the crude diol **9**, which was carried on to the next step without further purification: IR ($CHCl_3$) [cm^{-1}] 3400; ^1H NMR (60 MHz) δ 3.40 (6 H, s); mass spectrum, *m/z* 150 (M^+).

A solution of the crude **9** (52.4 g, 0.350 mol) in dry dimethylformamide (DMF) (150 mL) added dropwise to a suspension of sodium hydride (60% in oil; 14.7 g, 0.367 mol) in dry DMF (600 mL) at -30 °C, and stirring was continued for 1 h. A solution of benzyl bromide (40.7 mL, 0.343 mol) in dry DMF (100 mL) was added to the reaction mixture at the same temperature. After being stirred for 1 h, the mixture was treated with ethanol (50 mL) and evaporated in vacuo to give a residue, which was extracted with chloroform. The organic phase was washed with brine and dried, and the solvent was evaporated in vacuo to give a residue, which was submitted to vacuum distillation, bp 130–151 °C at 0.2 mmHg, to yield 65.0 g (73%) of **10** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3450; ^1H NMR (90 MHz) δ 3.47 (6 H, s), 4.56 (2 H, s), 7.33 (5 H, s); mass spectrum, *m/z* 240 (M^+); $[\alpha]^{28}_D$ +14.2° (*c* 0.72). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C 64.69; H, 8.51.

(+)-(2*S*,3*S*)-1-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethoxybutane (11). *tert*-Butyldimethylsilyl chloride (0.755 g, 5.00 mmol) was added to a solution of the alcohol **10** (1.00 g, 4.17 mmol), imidazole (0.567 g, 8.33 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in dry CH_2Cl_2 (20 mL). After the mixture was stirred for 3 h, water was added to the mixture, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried. Evaporation of the solvent in vacuo followed by column chromatography (eluting with 1:4 AcOEt/*n*-hexane) yielded 1.48 g (100%) of the silyl ether **11** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1100; ^1H NMR (90 MHz) δ 0.05 (6 H, s), 0.89 (9 H, s), 3.43 (3 H, s), 3.46 (3 H, s), 3.50–3.65 (6 H, m), 4.55 (2 H, s), 7.33 (5 H, s); mass spectrum, *m/z* 354 (M^+); $[\alpha]^{28}_D$ +18.6° (*c* 0.86). Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.37; H, 9.67. Found: C, 64.00; H, 10.16.

(+)-(2*S*,3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dimethoxy-1-butanol (12). A solution of **11** (31.9 g, 0.0901 mol) in dry THF (100 mL) was added dropwise to liquid NH_3 (500 mL) at -78 °C. After the mixture was stirred for 10 min, lithium (3.15 g, 0.450 mmol) was added to the mixture, and stirring was continued for 25 min. The mixture was treated with ethanol (200 mL), and the solvent was evaporated off. The residue was diluted with water and extracted with ether. The organic phase was washed with brine and dried, and then the solvent was evaporated in vacuo to give a residue, which was submitted to vacuum distillation, bp 70 °C at 0.4 mmHg, to yield 21.7 g (91%) of the alcohol **12** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3420; ^1H NMR (90 MHz) δ 0.08 (6 H, s), 0.90 (9 H, s), 3.47 (3 H, s), 3.48 (3 H, s), 3.30–3.50 (2 H, m), 3.65–3.80 (4 H, m); $[\alpha]^{26}_D$ +16.7° (*c* 0.96); mass spectrum, *m/z* 264 (M^+). Anal. Calcd for $C_{12}H_{28}O_4Si$: C, 54.51; H, 10.67. Found: C, 54.46; H, 10.97.

(+)-(4*S*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-4,5-dimethoxy-2(*E*)-hexen-1-ol (14) and (+)-(4*S*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-4,5-dimethoxy-2-(*Z*)-hexen-1-ol (15). Dimethyl sulfoxide (DMSO) (0.697 mL, 9.83 mmol) was added to a solution of oxalyl chloride (0.428 mL, 4.92 mmol) in dry CH_2Cl_2 (20 mL) at -78 °C, and then a solution of the alcohol **12** (1.15 g, 4.47 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to the mixture. After the mixture was stirred for 15 min, triethylamine (NEt_3) (3.09 mL, 22.3 mmol) was added to the reaction mixture. Stirring was continued for 30 min at room temperature, and water (20 mL) wad added to the mixture. The aqueous phase was extracted with CH_2Cl_2, and then the organic phase was washed with brine and dried. Evaporation of the solvent yielded 1.20 g of the crude aldehyde as a colorless oil, which was carried on to the next step without further purification: IR ($CHCl_3$) [cm^{-1}] 1735; ^1H NMR (60 MHz) δ 0.00 (6 H, s), 0.83 (9

H, s), 3.30 (3 H, s), 3.41 (3 H, s), 9.63 (1 H, s).

A mixture of the aldehyde (1.20 g, 4.58 mmol) and (α-carbethoxyethylidene)triphenylphosphorane (1.78 g, 4.92 mmol) in dry benzene(40 mL) was stirred for 4.5 h at 70 °C. The solvent was evaporated off in vacuo, and then *n*-hexane (150 mL) was added to the residue. After filtration through Celite, and the filtrate was concentrated in vacuo to give 1.30 g of the crude ester **13**, a mixture of two isomers, which was carried on to the next step without further purifications.

A solution of the crude ester **13** (1.30 g) in dry THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.255 g, 6.70 mmol) in dry THF (20 mL) at 0 °C, stirring was continued for 1 h, and then the reaction mixture was quenched with ether containing water. After filtration through Celite, the filtrate was concentrated in vacuo, followed by column chromatography (eluting with 2:3 AcOEt/*n*-hexane) to yield 0.05 g (4%) of **15** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3400; ^1H NMR (100 MHz) δ 0.08 (6 H, s), 0.88 (9 H, s), 1.86 (3 H, d, J = 2.0 Hz), 3.24 (3 H, s), 3.46 (3 H, s), 5.12 (1 H, d, J = 10.0 Hz); mass specturm, m/z 189 [M^+ – $Si(CH_3)_2C(CH_3)_3$]; $[\alpha]^{23}_D$ +20.0° (*c* 1.70). Anal. Calcd for $C_{15}H_{32}O_4Si$: C, 59.17; H, 10.59. Found: C, 59.12; H, 11.06.

From the later fractions, 1.05 g (79%) of **14** was obtained as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3400; ^1H NMR (100 MHz) δ 0.07 (6 H, s), 0.88 (9 H, s), 1.74 (3 H, d, J = 2.0 Hz), 3.24 (3 H, s), 3.44 (3 H, s), 3.68 (2 H, t, J = 6.0 Hz), 5.44 (1 H, dd, J = 10.0 and 2.0 Hz); mass spectrum, m/z 189 [M^+ – $Si(CH_3)_2C(CH_3)_3$]: $[\alpha]^{23}_D$ +20.6° (*c* 0.72). Anal. Calcd for $C_{15}H_{32}O_4Si$; C, 59.17; H, 10.59. Found: C, 59.15; H, 10.87.

(+)-(2*S*,3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-methyl-2,3-dimethoxy-4(*E*),6-heptadiene (16). A mixture of the alcohol **14** (13.33 g, 0.436 mol) and manganese oxide (65.0 g, 0.747 mol) in dry CH_2Cl_2 (400 mL) was stirred for 4 h at room temperature. After filtration through Celite, the filtrate was concentrated in vacuo to give 12.50 g of the aldehyde as a colorless oil, which was used in the next reaction without further purification: IR ($CHCl_3$) [cm^{-1}] 1690; ^1H NMR (60 MHz) δ 0.00 (6 H, s), 0.83 (9 H, s), 1.76 (3 H, br s), 3.23 (3 H, s), 3.33 (3 H, s), 4.30 (1 H, dd, J = 9.0 and 4.0 Hz), 6.43 (1 H, dd, J = 9 and 1 Hz).

n-Butyllithium (68.1 mL, 1.52 M in *n*-hexane, 0.104 mol) was added to a suspension of methyltriphenylphosphonium bromide (36.0 g, 0.104 mol) in dry THF (300 mL) at 0 °C, and stirring was continued for 1 h. A solution of the aldehyde (12.50 g) in dry THF (50 mL) was added to the mixture at the same temperature. After being stirred for 1.5 h at room temperature, the mixture was diluted with saturated aqueous ammonium chloride, and the solvent was evaporated in vacuo. The residue was extracted with ether, and the organic phase was washed with brine and dried. Evaporation of the solvent in vacuo followed by column chromatography (eluting with 1:9 ether/*n*-hexane) yielded 10.96 g (83%) of the diene **16** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1100; ^1H NMR (90 MHz) δ 0.06 (6 H, s), 0.90 (9 H, s), 1.83 (3 H, d, J = 1.0 Hz), 3.20 (2 H, d, J = 6.0 Hz), 3.26 (3 H, s), 3.46 (3 H, s), 3.69 (1 H, t, J = 6.0 Hz), 4.19 (1 H, dd, J = 10.0 and 4.0 Hz), 5.07 (1 H, d, J = 10.0 Hz), 5.21 (1 H, d, J = 16.0 Hz), 5.50 (1 H, d, J = 10.0 Hz), 6.34 (1 H, dd, J = 16.0 and 10.0 Hz); mass spectrum, m/z 268 (M^+ – CH_3OH); $[\alpha]^{26}_D$ +29.0° (*c* 1.26); exact mass calcd for $C_{15}H_{28}O_2Si$ 268.1865, found 268.1844.

(+)-(2*S*,3*S*)-5-Methyl-2,3-dimethoxy-4(*E*),6-heptadien-1-ol (17). A mixture of silyl ether **16** (10.96 g, 0.0365 mol) and tetra-*n*-butylammonium fluoride (36.5 mL, 1 M in THF, 0.0365 mol) in dry THF (200 mL) was stirred for 2 h at room temperature. After removal of the solvent, water (50 mL) was added to the residue, and the aqueous phase was extracted with chloroform. The organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 2:3 AcOEt/*n*-hexane) yielded 6.80 g (100%) of the alcohol **17** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3400; ^1H NMR (60 MHz) δ 1.88 (3 H, br s), 2.65 (1 H, m, D_2O exchangeable), 3.25 (3 H, s), 3.50 (3 H, s), 3.58 (2 H, m), 4.15 (1 H, dd, J = 9.0 and 6.0 Hz), 5.07 (1 H, d, J = 8.0 Hz), 5.17 (1 H, d, J = 17.0 Hz), 5.32 (1 H, d, J = 9.0 Hz), 6.36 (1 H, dd, J = 8.0 and 17.0 Hz); mass spectrum, m/z 186 (M^+); $[\alpha]^{27}_D$ +12.6° (*c* 2.50); exact mass calcd for $C_{10}H_{18}O_3$ 186.1255, found 186.1265.

(+)-(2*S*)-2-[(1*S*,2*S*)-4-Methyl-1,2-dimethoxy-3(*E*),5-hexadienyl]-2-methyl-2,3,4,5-tetrahydrofuran-3-one (20). DMSO (6.37 mL, 0.0899 mol) was added to a solution of oxalyl chloride (3.91 mL, 0.0449 mol) in dry CH_2Cl_2 (120 mL), and a solution of the alcohol **17** (7.60 g, 0.0409 mol) in dry CH_2Cl_2 (30 mL) was added dropwise to the mixture at –78 °C. After the mixture was stirred for 15 min, NEt_3 (28.3 mL, 0.264 mol) was added to the reaction mixture, and stirring was continued for 1 h at room temperature. Water (50 mL) was added to the resulting mixture, the aqueous phase was extracted with CH_2Cl_2, and then the organic phase was washed with brine and dried. Evaporation of the solvent yielded 8.40 g of the crude aldehyde as a pale yellow oil, which was carried on to the next step without further purification.

A solution of the crude aldehyde (8.30 g) in dry ether (40 mL) was added dropwise to a solution of methylmagnesium bromide (29.1 mL, 3 M in ether, 0.0882 mol) in dry ether (170 mL) at –78 °C. After being stirred for 1 h, the mixture was quenched with saturated aqueous ammonium chloride, and the aqueous phase was extracted with ether. The organic phase was washed with brine and dried. Evaporation of the solvent yielded 5.62 g of the crude alcohol **18**, a mixture of two diastereomers, which was used in the next reaction without further purification: IR ($CHCl_3$) [cm^{-1}] 3400.

DMSO (4.38 mL, 0.0618 mol) was added to a solution of oxalyl chloride (2.70 mL, 0.0309 mol) in dry CH_2Cl_2 (120 mL), and a solution of the crude alcohol **18** (5.62 g) in dry CH_2Cl_2 (30 mL) was added to the resulting solution at –78 °C. Stirring was continued for 15 min, and then NEt_3 (19.4 mL, 0.141 mol) was added to the mixture. After the mixture was stirred for 1 h at room temperature, water (50 mL) was added to the resulting mixture, the aqueous phase was extracted with CH_2Cl_2, and the organic phase was washed with brine and dried. Evaporation of the solvent yielded to 5.74 g of the crude ketone **7** as a pale yellow oil: IR ($CHCl_3$) [cm^{-1}] 1715; ^1H NMR (60 MHz) δ 1.80 (3 H, br s), 2.17 (3 H, s), 3.15 (3 H, s), 3.36 (3 H, s), 3.43 (1 H, d, J = 3.0 Hz), 4.25 (1 H, dd, J = 9.0 and 3.0 Hz), 5.02 (1 H, d, J = 10.0 Hz), 5.15 (1 H, d, J = 17.0 Hz), 5.42 (1 H, d, J = 9.0 Hz), 6.35 (1 H, dd, J = 17.0 and 10.0 Hz). This crude **7** was used for the next reaction without further purification.

α-Methoxyallene (7.90 g, 0.112 mol) was added to a solution of *n*-butyllithium (72.0 mL, 1.56 M in *n*-hexane, 0.112 mol) in dry THF (150 mL) at –78 °C, and stirring was continued for 1 h. The mixture was added to anhydrous magnesium bromide (25.9 g, 0.141 mol), generated in situ from 1,2-dibromoethane (12.1 mL, 0.141 mol) and magnesium (3.41 g, 0.141 mol), by cannulation. After the mixture was stirred for 10 min at room temperature and then cooled to –78 °C, stirring was continued for 20 min. A solution of the crude ketone **7** (5.75 g) in dry THF (50 mL) was added dropwise to the reaction mixture at –78 °C. After being stirred for 1 h, the resulting mixture was treated with saturated aqueous ammonium chloride, and then the solvent was evaporated off under reduced pressure. The aqueous phase was extracted with AcOEt, and the organic phase was washed with brine and dried. Evaporation of the solvent yielded 8.47 g of the crude alcohol **19** as an unstable oil, which was immediately carried on the the next step without further purification.

A mixture of the alcohol **19** (8.47 g), potassium *tert*-butoxide (9.40 g, 0.0843 mol), and a catalytic amount of 18-crown-6 in dry *tert*-butyl alcohol (150 mL) was refluxed for 20 min and then cooled to 0 °C. Aqueous hydrochloric acid (3 N, 50 mL) was added to the reaction mixture and stirred for 1 h at room temperature. The mixture was neutralized with sodium hydrogen carbonate, and then most of *tert*-butyl alcohol was removed under reduced pressure. The residue was diluted with ether, and the aqueous phase was extracted with ether. The organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:9 AcOEt/*n*-hexane) yielded 4.75 g (46%) of the dihydrofuranone **20** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1750; ^1H NMR (100 MHz) δ 1.16 (3 H, s), 1.86 (3 H, d, J = 1.0 Hz), 2.48 (2 H, dt, J = 3.0 and 8.0 Hz), 3.22 (3 H, s), 3.24 (1 H, d, J = 5.0 Hz), 3.40 (3 H, s), 4.18 (2 H, q, J = 8.0 Hz), 4.31 (1 H, dd, J = 5.0 and 7.0 Hz), 5.06 (1 H, d, J = 11.0 Hz), 5.22 (1 H, d, J = 18.0 Hz), 5.43 (1 H, d, J = 7.0 Hz), 6.38 (1 H, dd, J = 11.0 and 18.0 Hz); ^{13}C NMR (25 MHz) δ 12.39 (q), 20.08 (q), 36.28 (t), 56.01 (q) 61.76 (q), 63.29 (t), 77.38 (d), 82.25 (s), 88.00 (d), 113.43 (t), 129.57 (d), 138.03 (d), 140.67 (s), 215.52 (s); mass spectrum, m/z 254(M^+); $[\alpha]^{28}_D$ +114.4° (*c* 0.82). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.88; H, 8.94.

(2*S*)-4(*E*)-(Acetoxymethylene)-2-[(1*S*,2*S*)-4-methyl-1,2-dimethoxy-3(*E*),5-hexadienyl]-2-methyl-2,3,4,5-tetrahydrofuran-3-one (6). A solution of **20** (3.25 g, 0.0128 mol) in dry dimethoxyethane (DME) (20 mL) was added dropwise to a suspension of sodium hydride (60% in oil; 1.80 g, 0.0448 mol) in dry DME (100 mL) at room temperature, the mixture was stirred for 1 h, and then ethyl formate (3.60 mL, 0.0448 mol) was added dropwise to the mixture. After being stirred for 5 h at room temperature, the mixture was diluted with water (20 mL), and the solvent was removed under reduced pressure. The residue was diluted with ether and water, and the aqueous phase was acidified with 10% aqueous sulfuric acid at 0 °C and was then extracted with CH_2Cl_2. The CH_2Cl_2 phase was washed with brine and dried. Evaporation of the solvent yielded 3.60 g of the crude vinylogous carboxylic acid **21** as a pale yellow oil, which was used for the next step without further purification: mass spectrum, m/z 282 (M^+); exact mass calcd for $C_{15}H_{22}O_5$ 282.1468, found 282.1475.

Acetic anhydride (1.69 mL, 0.179 mol), pyridine (1.45 mL, 0.179 mol), and a catalytic amount of DMAP was added to a solution of **21** (3.60 g) at room temperature, and stirring was continued for 30 min. Evaporation of the solvent in vacuo followed by column chromatography (eluting with 3:7 AcOEt/*n*-hexane) yielded 3.87 g (93%) of the acetate **6** as an unstable colorless oil: IR ($CHCl_3$) [cm^{-1}] 1775, 1735, 1660; ^1H NMR (60 MHz) δ 1.20 (3 H, s), 1.85 (3 H, br s), 2.23 (3 H, s), 3.23 (3 H, s), 3.38 (1 H, d, J = 5.0 Hz), 3.40 (3 H, s), 4.28 (1 H, dd, J = 10.0 and 5.0 Hz), 4.75 (2 H, d, J = 3.0 Hz), 5.05 (1 H, d, J = 11.0 Hz), 5.20 (1 H, d, J = 17.0 Hz), 5.46 (1 H, d, J = 10.0 Hz), 6.43 (1 H, dd, J = 17.0 and 11.0 Hz), 8.07 (1 H, t, J = 3.0 Hz); mass spectrum, m/z 324 (M^+); exact mass calcd for $C_{17}H_{24}O_6$ 324.1571, found 324.1563.

(−)-(4α)-1β,5-Dimethyl-2α,3β-dimethoxy-11-oxa-2-oxotricyclo[7.2.1.0^{4,9}]dodec-5-en-8α-ol (22) and (−)-(4β)-1β,5-Dimethyl-2α,3β-dimethoxy-11-oxa-12-oxotricyclo[7.2.1.0^{4,9}]dodec-5-en-8α-ol (23). A solution of the acetate **6** (3.87 g, 0.0119 mol) in dry toluene (200 mL) was refluxed for 3 h. Evaporation of the solvent in vacuo yielded the adduct (3.87 g), which was used for the next step without further purification.

A solution of the crude adduct (3.87 g) and lithium hydroxide monohydrate (1.00 g, 0.0237 mol) in a mixture of methanol (80 mL)–CH_2Cl_2 (20 mL)–water (40 mL) was stirred for 4 h at room temperature. After removal of the solvents, the residue was diluted with water and extracted with AcOEt. The extract was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/*n*-hexane) yielded 0.09 g (2.6%) of the alcohol **23** as colorless needles, mp 153–155 °C, after recrystallization from benzene and *n*-hexane: IR ($CHCl_3$) [cm^{-1}] 3550, 1760, 1100; ^1H NMR (90 MHz) δ 1.34 (3 H, s), 1.73 (3 H, br s), 2.30 (1 H, m, D_2O exchangeable), 2.72 (1 H, m), 3.43 (3 H, s), 3.45 (3 H, s), 4.14 (1 H, dd, J = 8.0 and 1.0 Hz), 4.50 (1 H, d, J = 8.0 Hz), 5.48 (1 H, m); mass spectrum, m/z 282 (M^+); $[\alpha]^{27}_D$ −178.4° (c 1.14). Anal. Calcd for $C_{15}H_{22}O_5$; C, 63.81; H, 7.86. Found: C, 63.55; H, 8.12.

From the later fractions, 2.69 g (80%) of the alcohol **22** was obtained as colorless needles, mp 147–148 °C, after recrystallization from ether and *n*-hexane: IR ($CHCl_3$) [cm^{-1}] 3400, 1760, 1100; ^1H NMR (100 MHz) δ 1.25 (3 H, s), 1.48 (1 H, m, D_2O exchangeable), 1.76 (3 H, br s), 2.08 (1 H, m), 3.08 (1 H, m), 3.34 (1 H, m), 3.38 (3 H, s), 3.48 (3 H, s), 3.54 (1 H, t, J = 2.0 Hz), 3.81 (1 H, br s), 3.94 (1 H, d, J = 8.0 Hz), 3.96 (1 H, m), 4.52 (1 H, d, J = 8.0 Hz), 5.34 (1 H, m); ^{13}C NMR (25 MHz) δ 15.79 (q), 22.37 (q), 32.41 (t), 48.26 (d), 51.72 (s), 57.65 (q), 59.12 (q), 66.81 (d), 72.51 (t), 76.73 (d), 78.85 (s), 91.64 (d), 121.00 (d), 129.99 (s), 209.59 (s); mass spectrum, m/z 282 (M^+); $[\alpha]^{26}_D$ −116.7° (c 1.02). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.54; H, 8.08. Crystal data: tetragonal, space group $P4_1$; Z = 4, a = 13.502 (2) Å, b = 13.502 (3) Å, c = 8.357 (2) Å, α = 90°, β = 90°, γ = 90°; crystal dimensions, 0.6 × 0.2 × mm; scan speed, 5°/min; D_c = 1.23 g cm^{-1}; R_w = 0.106.

(−)-(4α)-8α-Acetoxy-1β,5-dimethyl-2β,3α-dimethoxy-11-oxa-12-oxotricyclo[7.2.1.0^{4,9}]dodec-5-ene (24). Acetic anhydride (0.006 mL, 0.060 mmol), pyridine (0.005 mL, 0.060 mmol) and a catalytic amount of DMAP were added to a solution of the alcohol **22** (8.5 mg, 0.030 mmol) in dry CH_2Cl_2 (1 mL) at room temperature, and the mixture was stirred for 2 h. Evaporation of the solvent followed by column chromatography (eluting with 1:4 AcOEt/*n*-hexane) yielded 9.8 mg (100%) of the acetate **24** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1760, 1735; ^1H NMR (400 MHz) δ 1.27 (3 H, s), 1.78 (3 H, br s), 2.04 (3 H, s), 2.09 (1 H, d, J = 19.0 Hz), 3.13 (1 H, dd, J = 19.0 and 5.1 Hz), 3.35 (1 H, br s), 3.41 (3 H, s), 3.51 (3 H, s), 3.56 (1 H, br s), 3.85 (1 H, s), 3.89 (1 H, d, J = 8.1 Hz), 4.39 (1 H, d, J = 8.1 Hz), 5.13 (1 H, d, J = 5.1 Hz), 5.40 (1 H, m); mass spectrum, m/z 324 (M^+); $[\alpha]^{26}_D$ −192.5° (c 0.98). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.46; H, 7.18.

(−)-(4β)-8α-Acetoxy-1β,5-dimethyl-2β,3α-dimethoxy-11-oxa-12-oxotricyclo[7.2.1.0^{4,9}]dodec-5-ene (5). The alcohol **23** (5.0 mg, 0.0177 mmol) was acetylated with acetic anhydride (0.005 mL, 0.0532 mmol), pyridine (0.005 mL, 0.0532 mmol), and a catalytic amount of DMAP as described for **24** to affored 6.0 mg (100%) of the acetate **5** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1770, 1735; ^1H NMR (400 MHz) δ 1.34 (3 H, s), 1.72 (3 H, br s), 1.81 (1 H, dd, J = 14.0 and 11.0 Hz), 2.00 (3 H, s), 2.47 (1 H, dt, J = 14.0 and 5.9 Hz), 2.79 (1 H, d, J = 1.0 Hz), 3.43 (3 H, s), 3.45 (3 H, s), 3.51 (1 H, d, J = 5.1 Hz), 3.56 (1 H, s), 4.12 (1 H, dd, J = 8.1 and 1.0 Hz), 4.59 (1 H, d, J = 8.1 Hz), 5.21 (1 H, dd, J = 11.0 and 5.9 Hz), 5.46 (1 H, m); mass spectrum, m/z 324 (M^+); $[\alpha]^{28}_D$ −140.1° (c 0.70). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.80; H, 7.76.

Inversion at C-8 in 22. Methanesulfonyl chloride (0.51 mL, 1.93 mmol), NEt_3(0.36 mL, 2.57 mmol), and a catalytic amount of DMAP were added to a solution of the alcohol **22** (181 mg, 0.642 mmol) in dry CH_2Cl_2 (4 mL), and stirring was continued for 4 h at room temperature. Water (2 mL) was added to the mixture, and the aqueous phase was extracted with chloroform. The organic phase was washed with brine and dried. Evaporation of the solvent yielded 231 mg of the mesylate **26** as a colorless oil, which was used for the next step without further purification. An analytical sample of **26** could be obtained by column chromatography (eluting with 1:4 AcOEt/*n*-hexane) as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1765, 1330, 1170; ^1H NMR (60 MHz) δ 1.25 (3 H, s), 1.77 (3 H, br s), 2.98 (3 H, s), 3.38 (3 H, s), 3.48 (3 H, s), 4.00 (1 H, d, J = 8.0 Hz), 4.47 (1 H, d, J = 8.0 Hz), 4.95 (1 H, m), 5.33 (1 H, m); mass spectrum, m/z 360 (M^+); $[\alpha]^{28}_D$ −112.4° (c 1.25); exact mass calcd for $C_{16}H_{24}O_7S$ 360.1243, found 360.1253.

Cesium acetate (1.85 g, 9.63 mmol) and 18-crown-6 (0.961 g, 4.49 mmol) was added to a solution of the mesylate **26** (231 mg) in dry toluene (10 mL), and the mixture was refluxed for 4 h. Water (4 mL) was added to the reaction mixture, and the aqueous phase was extracted with ether. The organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:4 AcOEt/*n*-hexane) yielded 89 mg (52%) of the diene **27** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1760, 1450; ^1H NMR (100 MHz) δ 1.24 (3 H, s), 1.78 (3 H, s), 3.40 (3 H, s), 3.44 (3 H, s), 3.96 (1 H, d, J = 8.0 Hz), 4.52 (1 H, d, J = 8.0 Hz), 5.26 (1 H, d, J = 10.0 Hz), 5.76 (1 H, m), 6.20 (1 H, dd, J = 10.0 and 5.0 Hz); mass spectrum, m/z 264 (M^+); $[\alpha]^{28}_D$ +115.0° (c 1.00); exact mass calcd for $C_{15}H_{20}O_4$ 264.1360, found 264.1329.

From the later fractions, 99 mg (48%) of the acetate **25** was obtained. This compound was identified by comparison with the authentic sample.

Acetonide 28. A solution of the mesylate **27** (15 mg, 0.0417 mmol) in acetone (0.5 mL) was added to a mixture of *N*-methylmorpholine *N*-oxide (11 mg, 0.0833 mmol), osmium tetraoxide (0.5 mg, 0.002 mmol), *tert*-butyl alcohol (0.01 mL), and water (0.7 mL). After being stirred for 7 h at room temperature, sodium hydrosulfite and talc were added to the mixture. After filtration through Celite, the filtrate was extracted with AcOEt. The organic phase was washed with brine and dried. Evaporation of the solvent yielded 19 mg of the crude diol, which was used for the next step without further purification.

A catalytic amount of *p*-toluenesulfonic acid and 2,2-dimethoxypropane (0.015 mL, 0.125 mmol) were added to a solution of the diol (19 mg) in dry DMF (1 mL). Stirring was continued for 12 h at room temperature and further for 1 h at 70 °C. The solvent was removed in vacuo, and the resiude was extracted with chloroform. The extract was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) yielded 18 mg (100%) of the acetonide **28** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1760, 1355, 1100; ^1H NMR (60 MHz) δ 1.06 (3 H, s), 1.23 (3 H, s), 1.36 (3 H, s), 1.53 (3 H,

s), 2.53 (2 H, m), 3.03 (3 H, s), 3.38 (3 H, s), 3.47 (3 H, s), 4.03 (1 H, d, J = 8.0 Hz) 4.42 (1 H, d, J = 8.0 Hz), 4.90 (1 H, m); mass spectrum, m/z 434 (M^+); $[\alpha]^{27}_D$ −47.7° (c 0.53); exact mass calcd for $C_{19}H_{30}O_9S$ 436.1611, found 436.1612.

Attempted Inversion at C-8 in 28. Cesium acetate (40 mg, 0.207 mmol) and 18-crown-6 (44 mg, 0.207 mmol) were added to a solution of the mesylate **28** (18 mg, 0.0415 mmol) in dry toluene (1 mL), and then the mixture was refluxed for 18 h. Water (5 mL) was added to the reaction mixture, and the aqueous phase was extracted with AcOEt. The organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:4 AcOEt/n-hexane) yielded 10 mg (71%) of the olefin **29** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1760, 1100; ^1H NMR (60 MHz) δ 1.10 (3 H, s), 1.28 (3 H, s), 1.41 (3 H, s), 1.51 (3 H, s), 2.85 (1 H, m), 3.40 (3 H, s), 3.45 (3 H, s), 3.58 (2 H, br s), 3.93 (1 H, d, J = 8.0 Hz), 4.13 (1 H, d, J = 4.0 Hz), 4.23 (1 H, d, J = 8.0 Hz), 5.57 (1 H, d, J = 10.0 Hz), 6.13 (1 H, dd, J = 10.0 and 4.0 Hz); mass spectrum, m/z 338 (M^+); $[\alpha]^{27}_D$ +102.7° (c 0.83); exact mass calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1737.

(−)-(4α)-1β,5-Dimethyl-2β,3α-dimethoxy-11-oxa-8,12-dioxotricyclo[7.2.1.0^{4,9}]dodec-5-ene (30). (a) Oxidation with $(CF_3CO)_2O$–DMSO–NEt_3. DMSO (0.018 mL, 0.247 mmol) was added to a solution of oxalyl chloride (0.017 mL, 0.123 mmol) in dry CH_2Cl_2 (1 mL), and a solution of the alcohol **22** (29 mg, 0.0103 mmol) in dry CH_2Cl_2 (1 mL), and a solution of the alcohol **22** (29 mg, 0.0103 mmol) in dry CH_2Cl_2 (1 mL) was added to the resulting solution at −78 °C. After the mixture was stirred for 30 min, NEt_3 (0.071 mL, 0.514 mmol) was added to the mixture, and stirring was continued for 30 min at the same temperature. Water (1 mL) was added to the mixture, and the aqueous phase was extracted with CH_2Cl_2. The extract was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/n-hexane) yielded 27 mg (100%, based on consumed **22**) of the diketone **30** as colorless needles, mp 137–139 °C, after recrystallization from ether and n-hexane: IR ($CHCl_3$) [cm^{-1}] 1770, 1715, 1090; ^1H NMR (90 MHz) δ 1.29 (3 H, s), 1.80 (3 H, br s), 2.97 (1 H, m), 3.44 (3 H, s), 3.47 (3 H, s), 3.60 (1 H, t, J = 1.0 Hz), 3.79 (1 H, br s), 4.41 (1 H, d, J = 9.0 Hz), 4.58 (1 H, d, J = 9.0 Hz), 5.67 (1 H, m); mass spectrum, m/z 280 (M^+); $[\alpha]^{27}_D$ −116.0° (c 1.30); exact mass calcd for $C_{15}H_{20}O_5$ 280.1310, found 280.1319. From the later fractions, 2 mg of **22** was recovered.

(b) Oxidation with PCC. A solution of the alcohol **22** (26 mg, 0.0922 mmol) was added one portion to the suspension of PCC (34 mg, 0.184 mmol) in dry CH_2Cl_2 (1 mL), and stirring was continued for 7 h at room temperature. After addition of Florisil, the mixture was diluted with ether and filtered through Celite. Concentration of the filtrate followed by column chromatography (eluting with 1:4 AcOEt/n-hexane) yielded 4 mg (15%) of the diketone **30**.

(c) Oxidation with PDC. A solution of the alcohol **22** (29 mg, 0.103 mmol) was added to the suspension of PDC (116 mg, 0.309 mmol) in dry CH_2Cl_2 (1 mL), and stirring was continued for 7 h at room temperature. The reaction mixture was treated with the same as above to give 4 mg (27%, based on consumed **22**) of the diketone **30** and 14 mg of **22**.

(d) Swern Oxidation. DMSO (0.029 mL, 0.414 mmol) was added to a solution of oxalyl chloride (0.018 mg, 0.207 mmol) in dry CH_2Cl_2 (1 mL), and then a solution of the alcohol **22** (53 mg, 0.188 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at −78 °C. After the mixture was stirred for 15 min, NEt_3 (0.13 mL, 0.940 mmol) was added, and the mixture was stirred for 1 h. Water (1 mL) was added to the mixture, and the aqueous phase was extracted with CH_2Cl_2, the extract was washed with brine and dried. Treatment as above yielded 15 mg (19%) of the diketone **30**.

(e) Jones Oxidation. The alcohol **22** (35 mg, 0.124 mmol) in acetone (2 mL) was treated with Jones reagent (0.085 mL) at 0 °C. After the mixture was stirred for 2 h at 0 °C, an excess of isopropyl alcohol and saturated aqueous sodium hydrogen carbonate were added. The aqueous phase was extracted with ether, and the extract was washed and dried. Treatment as above yielded 8.0 mg (23%) of the diketone **30**.

(f) Corey–Kim Oxidation. Dimethyl sulfide (0.025 mL, 0.346 mmol) was added to a solution of N-chlorosuccinimide (33 mg, 0.249 mmol) in dry toluene (1 mL) at −25 °C. After the mixture was stirred for 10 min, a solution of the alcohol **22** (39 mg, 0.138 mmol) in dry toluene (1 mL) was added to the mixture. Stirring was continued for 1.5 h, and then NEt_3 (0.034 mL, 0.249 mmol) was added to the mixture. after the mixture was stirred for 10 min, water (1 mL) was added, and the aqueous phase was extracted with ether. The extract was washed with brine and dried. Treatment as above yielded 24 mg (62%) of the diketone **30**.

Preparation of 25 from 30. Lithium triethylborohydride (0.0629 mL, 1 M in THF, 0.0629 mmol) was added dropwise to a solution of the diketone **30** (16 mg, 0.0571 mmol) at −78 °C. After being stirred for 30 min, the mixture was treated with water, and the solvent was removed in vacuo. The residue was extracted with AcOEt. The extract was washed with brine and dried. Evaporation of the solvent yielded 18 mg of the crude alcohol as a colorless oil, which was used in the next step without further purification: mass spectrum, m/z 282 (M^+).

Acetic anhydride (0.012 mL, 0.128 mmol), pyridine (0.010 mL, 0.128 mmol), and a catalytic amount of DMAP were added to a solution of the alcohol (18 mg) in dry CH_2Cl_2 (1 mL). After the mixture was stirred for 1 h at room temperature, evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/n-hexane) yielded 18 mg (98%) of the acetate **25**. This compound was identified with the authentic sample.

The Intramolecular Diels–Alder Reaction of Vinylogous Carboxylic Acid 21. Method A. A solution of **21** (15 mg, 0.0591 mmol) and a catalytic amount of methylene blue in dry xylene (1 mL) was heated in a sealed tube at 150 °C for 9 h. After removal of the solvent in vacuo, dry CH_2Cl_2 (1 mL), acetic anhydride (0.01 mL), pyridine (0.01 mL), and a catalytic amount of DMAP were added to the residue, and the mixture was stirred for 1 h at room temperature. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/n-hexane) yielded 2.0 mg (12%) of the acetate **25** as colorless needles, mp 86–87 °C, after recrystallization from ether and n-hexane: IR ($CHCl_3$) [cm^{-1}] 1770, 1740, 1100; ^1H NMR (500 MHz) δ 1.29 (3 H, s), 1.72 (3 H, br s), 2.05 (3 H, s), 2.47 (1 H, m), 3.09 (1 H, m), 3.17 (1 H, br s), 3.40 (3 H, s), 3.48 (3 H, s), 3.53 (1 H, s), 3.75 (1 H, s), 4.02 (1 H, d, J = 8.0 Hz), 4.33 (1 H, d, J = 8.0 Hz), 4.97 (1 H, dd, J = 9.0 and 7.0 Hz), 5.44 (1 H, m); mass spectrum, m/z 324 (M^+); $[\alpha]^{29}_D$ −83.0° (c 1.54). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.97; H, 7.59.

Method B. The compound **21** (10.0 mg, 0.035 mmol) was stirred with water (1 mL) at 80 °C for 8 h. The same treatment as above gave 2.0 mg (17%) of **24**. This compound was identified with the authentic sample.

Method C. The compound **21** (31 mg, 0.110 mmol) was stirred with a catalytic amount of tetrabutylammonium hydrogen sulfate, water (1 mL), and *tert*-butyl alcohol (0.6 mL) at 80 °C for 14 h, 11 mg (31%) of the mixture of **24** and **25** was obtained.

The Intramolecular Claisen Condensation of 25. n-Butyllithium (0.89 mL, 1.21M in n-hexane, 1.08 mmol) was added to a solution of diisopropylamine (0.16 mL, 1.44 mmol) in dry THF (7 mL) at −78 °C. After the mixture was stirred for 20 min, a solution of **25** in dry THF (3 mL) was added dropwise, and the mixture was stirred for 1 h at −78 °C. After quenching with saturated aqueous ammonium chloride, removal of the solvent gave a residue, which was extracted with AcOEt, and the organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/n-hexane) yielded 24 mg of recovered **25** and 174 mg (92%, based on consumed **25**) of **31** as colorless needles, mp 127–128 °C, after recrystallization from ether and n-hexane: IR ($CHCl_3$) [cm^{-1}] 3450, 1730; ^1H NMR (90 MHz) δ 1.30 (3 H, s), 1.83 (3 H, br s), 3.38 (1 H, br s), 3.47 (3 H, s), 3.49 (3 H, s), 3.86 (3 H, br s), 3.90 (1 H, d, J = 9.0 Hz), 4.01 (1 H, d, J = 9.0 Hz), 4.59 (1 H, t, J = 8.0 Hz), 5.42 (1 H, m); mass spectrum, m/z 324 (M^+); $[\alpha]^{25}_D$ +32.5° (c 0.75). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.69; H, 7.55.

Dehydration of 31. Thionyl chloride (0.080 mL, 1.05 mmol) was added to a solution of the lactone **31** (170 mg, 0.525 mmol) in pyridine (5 mL) at 0 °C. After the mixture was stirred for 1 h, removal of the solvent gave a residue, which was extracted with chloroform. The organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:4 AcOEt/n-hexane) yielded 166 mg (100%) of the

unsaturated lactone **32** as colorless needles, mp 140–141 °C, after recrystallization from ether and *n*-hexane: IR ($CHCl_3$) [cm^{-1}] 1720, 1100; ^1H NMR (100 MHz) δ 1.46 (3 H, s), 1.80 (3 H, br s), 2.04 (1 H, dq, J = 16.0 and 3.0 Hz), 2.54 (1 H, m), 2.60 (1 H, dq, J = 16.0, and 3.0 Hz), 3.24 (1 H, d, J = 3.0 Hz), 3.36 (1 H, d, J = 3.0 Hz), 3.42 (3 H, s), 3.48 (3 H, s), 3.68 (1 H, d, J = 8.0 Hz), 4.08 (1 H, d, J = 8.0 Hz), 4.78 (1 H, t, J = 3.0 Hz), 5.64 (1 H, m); mass spectrum, m/z 306 (M^+); $[\alpha]^{24}_D$ -10.3° (c 1.05). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 60.68; H, 7.36.

Dissolving Metal Reduction of 32. Calcium (55 mg, 1.37 mol, was added to liquid NH_3 (10 mL) at -78 °C, and a solution of **32** (42 mg, 0.137 mmol) in dry THF (2 mL) was added to the mixture. After the mixture was stirred for 10 min at -78 °C, *tert*-butyl alcohol (0.5 mL) was added to the mixture. Stirring was continued for 1.5 h, and then ammonium chloride (100 mg) was added to the mixture. After removal of the solvent, the residue was extracted with AcOEt, and the organic phase was washed with brine and dried. Evaporation of the solvent yielded 19 mg of the crude alcohol, which was used for the next step without further purification: IR ($CHCl_3$) [cm^{-1}] 3400, 1730, 1080; ^1H NMR (90 MHz) δ 1.73 (6 H, br s), 3.33 (3 H, s), 3.40 (3 H, s), 5.20 (1 H, m); mass spectrum, m/z 308 (M^+).

Acetic anhydride (0.013 mL, 0.137 mmol), pyridine (0.011 mL, 0.137 mmol), and a catalytic amount of DMAP were added to a solution of the crude alcohol (19 mg) in dry CH_2Cl_2 (1 mL). After the mixture was stirred for 1 h at room temperature, evaporation of the solvent followed by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) yielded 17 mg (36%) of the acetate **34** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1735, 1080; ^1H NMR (500 MHz) δ 1.75 (6 H, br s), 2.01 (1 H, m), 2.09 (3 H, s), 2.42 (1 H, dt, J = 13.0 and 5.0 Hz), 2.91 (1 H, br s), 3.29 (1 H, d, J = 18.0 Hz), 3.39 (3 H, s), 3.43 (1 H, d, J = 18.0 Hz), 3.49 (3 H, s), 3.86 (1 H, br s), 4.13 (1 H, d, J = 12.0 Hz), 4.52 (1 H, d, J = 12.0 Hz), 4.62 (1 H, dd, J = 11.0 and 5.0 Hz), 5.35 (1 H, br d, J = 6.0 Hz); mass spectrum, m/z 350; $[\alpha]^{26}_D$ +238.8° (c 0.45); exact mass calcd for $C_{18}H_{22}O_5$ (M^+ - $HOCH_3$) 318.1467, found 318.1488.

Acetonide 35. A solution of **32** (10.0 mg, 0.0327 mmol) in acetone (0.5 mL) was added to a mixture of *N*-methylmorpholine *N*-oxide (10.0 mg, 0.0719 mmol), osmium tetraoxide (0.5 mg, 0.002 mmol), *tert*-butyl alcohol (0.01 mL), and water (0.5 mL) at room temperature. After the mixture was stirred for 1 h, sodium hydrosulfite and talc were added to the mixture. After filtration through Celite, evaporation of the solvent gave a residue, which was extracted with AcOEt, and the organic phase was washed with brine and dried. Evaporation of the solvent yielded 10.0 mg of the crude oil, which was carried on the next step without further purification: IR ($CHCl_3$) [cm^{-1}] 3450, 1720; ^1H NMR (60 MHz) δ 1.26 (3 H s), 1.48 (3 H, s), 3.57 (6 H, s), 4.57 (1 H, t, J = 5.0 Hz), 5.77 (1 H, s); mass spectrum, m/z 340 (M^+).

2,2-Dimethoxypropane (0.016 mL, 0.131 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate were added to a solution of the crude diol (10.0 mg) in DMF (1 mL), and the mixture was stirred for 8 h at 70 °C. Evaporation of the solvent followed by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) yielded 10.0 mg (81%) of the acetonide **35** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 1720, 1100; ^1H NMR (100 MHz) δ 1.18 (3 H, s), 1.26 (3 H, s), 1.40 (3 H, s), 1.46 (3 H, s), 2.34 (1 H, br s), 2.80 (2 H, m), 3.34 (1 H, br s), 3.40 (3 H, s), 3.43 (3 H, s), 3.52 (1 H, br s), 3.68 (1 H, d, J = 8.0 Hz), 4.10 (1 H, d, J = 8.0 Hz), 4.32 (1 H, t, J = 7.0 Hz), 4.70 (1 H, m), 5.80 (1 H, s); mass spectrum, m/z 380 (M^+); exact mass calcd for $C_{20}H_{28}O_7$ 380.1833, found 380.1831.

Methyl Acetal 36. Diisobutylaluminum hydride (0.28 mL, 1 M in *n*-hexane, 0.278 mmol) was added dropwise to a solution of the lactone **31** (41 mg, 0.127 mmol) in dry toluene (2 mL) at -78 °C. After being stirred for 1 h, the mixture was quenched with water and filtered through Celite. The filtrate was concentrated, and evaporation of the solvent yielded 50 mg of the crude lactol as a colorless oil, which was used for the next reaction without further purification: mass spectrum, m/z 308 (M^+ - H_2O).

Trimethyl orthoformate (0.021 mL, 0.190 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added to a solution of the crude lactol (50 mg) in dry methanol (2 mL), and the mixture was refluxed for 30 min. After removal of the solvent, the residue was extracted with chloroform. The organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) yielded 43 mg (100%) of the acetal **36** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3450, 1080; ^1H NMR (90 MHz) δ 1.27 (3 H, s) 1.79 (3 H, br s), 3.31 (1 H, br s), 3.44 (3 H, s), 3.48 (6 H, s), 3.78 (2 H, br s), 3.78 (1 H, d, J = 8.0 Hz), 4.13 (1 H, dd, J = 10.0 and 8.0 Hz), 4.14 (1 H, d, J = 8.0 Hz), 5.03 (1 H, t, J = 8.0 Hz); ^{13}C NMR (22.5 MHz) δ 16.97 (q), 21.68 (q), 27.04 (t), 36.63 (t), 45.19 (s), 49.25 (d), 55.97 (q), 56.62 (q), 59.22 (q), 70.27 (d), 74.50 (t), 77.70 (d), 78.83 (s), 79.86 (s), 88.96 (d), 95.36 (d), 121.85 (d), 133.01 (s); mass spectrum, m/z 322 (M^+ - H_2O); $[\alpha]^{23}_D$ -35.2° (c 0.95); exact mass calcd for $C_{18}H_{26}O_5$ (M^+ - H_2O) 322.1779, found 322.1773.

Hydroboration–Oxidation of 36. Borane methyl sulfide complex (0.015 mL, 10 M solution, 0.152 mmol) was added to a solution of the acetal **36** (43 mg, 0.127 mmol) in dry THF (2 mL) at 0 °C. After the mixture was stirred for 5 h, 10% aqueous sodium hydroxide (0.13 mL) and 30% aqueous hydrogen peroxide (0.02 mL) were added, and the mixture was stirred for 1.5 h at 50 °C. After removal of the solvent, the residue was extracted with AcOEt, and the organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/*n*-hexane) yielded 36 mg (80%) of the alcohol **37**, a mixture of diastereomers, as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3450, 1080; ^1H NMR (90 MHz) δ 1.00 (3 H d, J = 7.0 Hz), 1.25 (3 H s), 3.40 (3 H s), 3.49 (3 H, s), 3.51 (3 H, s), 4.85 (1 H, m); mass spectrum, m/z 326 (M^+ - H_2O); exact mass calcd for $C_{17}H_{26}O_6$ (M^+ - H_2O) 326.1730, found 326.1741.

PDC Oxidation of 37. A solution of the alcohol **37** (36 mg, 0.101 mmol) in dry CH_2Cl_2 (1 mL) was added one portion to a suspension of PDC (113 mg, 0.312 mmol) in dry CH_2Cl_2 (2 mL) at room temperature, and the mixture was stirred for 10 h. After addition of Florisil, the mixture was diluted with ether and filtered through Celite. Concentration of the filtrate in vacuo followed by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) yielded 31 mg (86%) of the ketone **38** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3450, 1710, 1080; ^1H NMR (90 MHz) δ 1.22 (3 H, d, J = 7.0 Hz), 1.30 (3 H, s), 3.35 (1 H, br s), 3.40 (3 H, s), 3.48 (3 H, s), 3.52 (3 H, s), 3.74 (1 H, d, J = 9.0 Hz), 3.95 (1 H, dd, J = 13.0 and 8.0 Hz), 4.17 (1 H, d, J = 9.0 Hz), 4.93 (1 H, dd, J = 9.0 and 5.0 Hz); ^{13}C NMR (22.5 MHz) δ 15.62 (q), 16.86 (q), 36.74 (t), 40.32 (t), 46.00 (s), 47.47 (d), 48.39 (d), 56.14 (q), 57.27 (q), 59.22 (q), 71.79 (d), 75.63 (t), 76.00 (s), 88.58 (d), 95.57 (d), 210.30 (s); mass spectrum, m/z 324 (M^+ - $HOCH_3$); $[\alpha]^{26}_D$ -38.7° (c 1.20); exact mass calcd for $C_{18}H_{28}O_7$ 356.1835, found 356.1863.

Baeyer–Villiger Oxidation of 38. *m*-Chloroperbenzoic acid (15 mg, 0.0843 mmol) and a catalytic amount of lithium carbonate were added to a solution of the ketone **38** (20 mg, 0.0562 mmol) in dry CH_2Cl_2 (1 mL), and the mixture was stirred for 15 h at room temperature. After addition of 10% aqueous sodium thiosulfate (0.5 mL), the aqueous phase was extracted with chloroform. The organic phase was washed with 10% aqueous potassium carbonate followed by brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/*n*-hexane) yielded 20 mg (96%) of the lactone **39** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3450, 1725, 1080; ^1H NMR (90 MHz) δ 1.29 (3 H, s), 1.50 (3 H, d, J = 7.0 Hz), 1.82 (2 H, d, J = 6.0 Hz), 2.38 (1 H, t, J = 4.0 Hz), 3.29 (3 H, m), 3.42 (3 H, s), 3.49 (3 H, s), 3.52 (3 H, s), 3.64 (1 H, d, J = 8.0 Hz), 3.99 (1 H, br s), 4.19 (1 H, q, J = 7.0 Hz), 4.23 (1 H, d, J = 8.0 Hz), 4.55 (1 H, dd, J = 7.0 and 4.0 Hz), 4.85 (1 H, t, J = 6.0 Hz); mass spectrum, m/z 372 (M^+); $[\alpha]^{25}_D$ -39.2° (c 1.40); exact mass calcd for $C_{18}H_{28}O_8$ 372.1783, found 372.1765.

Unsaturated Ester 40. Diisobutylaluminum hydride (0.053 mL, 1 M in *n*-hexane, 0.053 mmol) was added to a solution of the lactone **39** (9.0 mg, 0.0242 mmol) in dry toluene (1 mL) at -78 °C. After being stirred for 40 min, the mixture was quenched with water and filtered through Celite. Concentration of the filtrate followed by column chromatography (eluting with 9:1 AcOEt–*n*-hexane) yielded 10.0 mg (100%) of the acetal, a mixture of diastereomers, as a colorless oil; mass spectrum, m/z 356 (M^+ - H_2O).

To a suspension of sodium hydride (60% in oil; 6.3 mg, 0.160 mmol) in dry DME (1.5 mL) was added methyl (dimethylphosphinyl)acetate (0.017 mL, 0.107 mmol) at room temperature. After the mixture was stirred for 30 min, a solution of the lactol (10.0 mg) in dry DME (1.5 mL) was added, and the resulting mixture was stirred for 40 min. After addition of water, the solvent was evaporated in vacuo to give the residue, which was extracted

with ether, and the organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 3:7 AcOEt/*n*-hexane) yielded 9.0 mg (87%) of the unsaturated ester **40** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3400, 1720, 1100; ^1H NMR (90 MHz) δ 1.28 (3 H, s), 1.32 (3 H, d, J = 8.0 Hz), 1.68 (3 H, m), 3.26 (1 H, br s), 3.37 (3 H, s), 3.42 (3 H, s), 3.45 (3 H, s), 3.62 (1 H, d, J = 8.0 Hz), 3.74 (3 H, s), 3.94 (1 H, br s), 4.14 (1 H, d, J = 8.0 Hz), 4.38 (1 H, dd, J = 14.0 and 7.0 Hz), 4.98 (1 H, t, J = 8.0 Hz), 5.94 (1 H, d, J = 16.0 Hz), 6.94 (1 H, dd, J = 16.0 and 7.0 Hz); mass spectrum, m/z 381 ($M^+ - H_2O - OCH_3$); $[\alpha]^{26}_D$ -47.6° (c 1.57); exact mass calcd for $C_{20}H_{29}O_7$ 381.1912, found 381.1906.

Methyl Ketone 41. DMSO (0.027 mL, 0.379 mmol) was added to a solution of oxalyl chloride (0.016 mL, 0.189 mmol) in dry CH_2Cl_2 (1 mL), and a solution of the alcohol **40** (37 mg, 0.0861 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at -78 °C. After the mixture was stirred for 15 min, NEt_3 (0.120 mL, 0.861 mmol) was added, and stirring was continued for 30 min at room temperature. Water (1 mL) was added, the aqueous phase was extracted wtih CH_2Cl_2, and the organic phase was washed with brine and dried. Evaporation of the solvent followed by column chromatography (eluting with 1:1 AcOEt/*n*-hexane) yielded 32 mg (87%) of the ketone **41** as a colorless oil: IR ($CHCl_3$) [cm^{-1}] 3350, 1720, 1100; ^1H NMR (500 MHz) δ 1.22 (3 H, s), 1.57 (3 H, s), 1.65 (1 H, dd, J = 14.0 and 6.0 Hz), 2.40 (1 H, br s), 2.76 (1 H, m), 3.14 (1 H, br s), 3.39 (6 H, s), 3.41 (3 H, s), 3.49 (1 H, d, J = 9.0 Hz), 3.73 (3 H, s), 3.79 (1 H, br s), 4.08 (1 H, dd, J = 10.0 and 5.0 Hz), 4.89 (1 H, d, J = 9.0 Hz), 5.01 (1 H, t, J = 7.0 Hz), 5.96 (1 H, d, J = 16.0 Hz), 6.65 (1 H, br s, D_2O exchangeable), 6.88 (1 H, dt, J = 16.0 and 7.0 Hz); mass spectrum, m/z 397 ($M^+ - OCH_3$); $[\alpha]^{27}_D$ -108.9 (c 0.30); exact mass calcd for $C_{21}H_{29}O_8$ 397.1862, found 397.1867.

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2′-Nitrobenzhydryl Polystyrene Resin: A New Photosensitive Polymeric Support for Peptide Synthesis

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2′-Nitrobenzhydryl polystyrene resin (NBH-resin) was prepared from the commercially available styrene–divinylbenzene cross-linked polymer by a two-step polymer analogous reaction. This resin was employed as a photolytically cleavable polymeric protective support for carboxyl function in amino acids under neutral conditions. The 2′-nitrobenzhydryl resin possesses good stability in 4 N HCl–dioxane required for the deprotection of the temporary N^{α}-*tert*-butyloxycarbonyl protecting group. The advantage of the new resin over the already reported benzhydryl resin is its increased acid stability during the N^{α} deblocking, which permits the peptide synthesis with the commonly available Boc-amino acids. The applicability of this resin is illustrated with the solid-phase synthesis of some model peptides.

Benzhydryl resins have been widely used for the polymer-supported solid-phase synthesis of peptides.[1-4] The cleavage of the finished peptides and peptide amides from these resins after synthesis is usually achieved by treatment with trifluoroacetic acid, trifluoromethanesulfonic acid, or anhydrous HF. The benzhydryl ester linkages are reported to be less stable in acidolytic conditions of N^{α}-*tert*-butyloxycarbonyl (Boc) group removal. In order to overcome this difficulty Southard et al. have employed an enamine-type amino protecting group, cleavable under very mild acid conditions.[2,5] But the use of ordinary benzhydryl resin in solid-phase peptide synthesis is limited because it cannot be used with the commonly available Boc-amino acids. This prompted us to investigate on the use of photoremovable 2′-nitrobenzhydryl polystyrene resin for the solid-phase peptide synthesis. In this paper we report the preparation and use of a new polymeric support, 2′-nitrobenzhydryl polystyrene resin (NBH-resin) which permits peptide synthesis with Boc-amino acids and the final cleavage of the attached peptide under neutral conditions on irradiation at 350 nm in alcoholic solutions. The principle of the photolytic deprotection of the carboxyl group by making use of the internal photoredox reaction of *o*-nitro aromatic compounds is exploited here.[6-8]

Results and Discussion

Preparation of NBH-resin from Cross-Linked Polystyrene. The NBH-resin (**4**) was prepared from the

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