tography and was found to be 80% pure by $^1$H NMR analysis. Two analytically pure samples of syn and anti ketols were obtained by preparative TLC using cyclohexane–ether (8:2): oil; IR 3400 (br), 2920, 1700, 1690, 1450, 1350, 1040, 1000, 920 cm$^{-1}$; $^1$H NMR 7.3 (m, 5 H, Ar), 4.89 (d, $J$ = 2.3 Hz, 1 H, C*H*OH), 2.90 (d, $J$ = 2.3 Hz, 1 H, OH), 2.07 (s, 3 H, H1), 1.98 (dq, $J$ = 7.5 and 15 Hz, 1 H, H4), 1.48 (dq, $J$ = 7.5 and 15 Hz, 1 H, H4), 1.06 (s, 3 H, C*H*$_3$CO), 0.88 (t, $J$ = 7.5 Hz, 3 H, H5); upon irradiation of the multiplet at 4.89 ppm a positive NOE effect is observed for signals at 2.07 (1.4%) and 1.06 (1.2%), and this is in agreement with a syn relative configuration if we assume that the title ketol adopts a H-bonded cyclic conformation; $^{13}$C NMR 9.0 (*C*H$_3$), 17.9 (*C*H$_3$), 27.0 (C4), 28.1 (*C*H$_3$), 56.0 (C3), 78.5 (*C*HOH), 127.8, 127.9, 128.0, 129.2, 130.0, 140.0, 215.9 (C2); MS $m/e$ (relative intensity) 100 (100), 85 (93), 43 (47), 51 (45), 77 (41), 107 (PhCHOH, 26), 79 (26), 105 (20), 106 (PhCHO, 17), 205 (M$^+$ - 1, 1). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.8. Found: C, 75.71; H, 8.84.

***anti*-3-(Phenylhydroxymethyl)-3-methyl-5-pentanone (Scheme V)**: oil; IR 3400 (br), 2920, 1700, 1690, 1450, 1350, 1040, 1000, 920 cm$^{-1}$; $^1$NMR 7.3 (m, 5 H, Ar), 4.97 (d, $J$ = 3.8 Hz, 1 H, C*H*OH), 2.85 (d, $J$ = 3.8 Hz, 1 H, OH), 2.10 (s, 3 H, H1), 1.75 (dq, $J$ = 7.5 and 15 Hz, 1 H, H4), 1.26 (dq, $J$ = 7.5 and 15 Hz, 1 H, H4), 1.05 (s, 3 H, C*H*$_3$CO), 0.80 (t, $J$ = 7.5 Hz, 3 H, H5); upon irradiation of the multiplet at 4.97 ppm a positive NOE effect is observed for signals at 2.10 (1.1%), 1.75 (2.5%), and 1.26 (0.8%), and this is in agreement with an anti relative configuration if we assume that the title ketol adopts a H-bonded cyclic conformation: $^{13}$C NMR 8.3 (*C*H$_3$), 15.0 (*C*H$_3$), 27.5 (*C*H$_3$), 29.4 (C4), 56.2 (C3), 78.2 (*C*HOH), 127.8, 127.9, 128.0, 129.2, 130.0, 140.0, 215.9 (C2); MS $m/e$ (relative intensity) 100 (100), 85 (93), 43 (47), 51 (45), 77 (41), 107 (PhCHOH, 26), 79 (26), 105 (20), 106 (PhCHO, 17), 205 (M$^+$ - 1, 1). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.8. Found: C, 75.63; H, 8.64.

***syn*-2-(Phenylmethyl)-3-hydroxy-3-phenylthiopropanoic acid, *S*-phenyl ester (Scheme VI)**: oil; 0.35 g; IR 3500 (br), 1690, 1600, 1450, 1320, 1050, 920, 740, 690 cm$^{-1}$; $^1$NMR 7.45–7.2 (m, 11 H, ArH), 7.13 (m, 2 H, ArH), 7.05 (m, 2 H, ArH), 5.12 (dd, $J$ = 2.4 and 5.2 Hz, 1 H, H3), 3.27 (m, 1 H, H2), 3.09 (q, $J$ = 13.5 Hz, 1 H, C*H*$_2$Ph) 3.06 (dd, $J$ = 13.5 and 20.3 Hz, 1 H, C*H*$_2$Ph), 2.79 (d, $J$ = 2.4 Hz, 1 H, OH); $^{13}$C NMR 33.5 (*C*H$_2$Ph), 63.1 (C2), 74.1 (C3), 126.5, 126.6, 128.1, 128.6, 128.7, 129.3, 129.4, 129.7, 134.5, 138.8, 202.2 (C1); MS $m/e$ (relative intensity) 110 (100), 91 (97), 77 (94), 105 (86), 133 (72), 107 (59), 51 (52), 161 (14), 221 (13), 242 (10), 348 (M$^+$, 6), 239 (M$^+$ - SPh, 3). Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.83; H, 5.79. Found: C, 75.67, H, 5.83.

***anti*-2-(Phenylmethyl)-3-hydroxy-3-phenylthiopropanoic Acid, *S*-Phenyl Ester (Scheme VI).** Flash chromatography afforded a fraction (1.08 g) containing the anti and the syn isomers in the 3:1 ratio. We could not isolate an analytically pure specimen of the anti product as it was always contaminated by the syn isomer; so we report here only its characteristic NMR signals, which clearly identify it: $^1$H NMR 4.88 (t, $J$ = 6.6 Hz, 1 H, H3), 3.30 (m, 1 H, H2), 3.00 (dd, $J$ = 9.5 and 13.1 Hz, 1 H, C*H*$_2$Ph), 2.99 (d, $J$ = 6.6 Hz, 1 H, OH), 2.80 (dd, $J$ = 5.8 and 13.1 Hz, 1 H, C*H*$_2$Ph); $^{13}$C NMR 36.3 (*C*H$_2$Ph), 62.3 (C2), 75.1 (C3), 126.4, 126.5, 126.9, 127.4, 128.3, 128.6, 128.7, 128.8, 129.2, 129.3, 129.4, 129.8, 134.6, 138.1, 142.0, 202.0 (C1).

**Acknowledgment.** We thank the Italian C.N.R. (Progetto Finalizzato Chimica Fine 2) for financial support.

# Synthetic Studies toward Rapamycin: A Solution to a Problem in Chirality Merger through Use of the Ireland Reaction

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*Received April 15, 1991*

A program directed toward a total synthesis of rapamycin is described. This paper reports the synthesis of enoate **36**, a fragment that would correspond to carbons 28–49 of rapamycin. The two building blocks required to reach **36** were allylic alcohol **5** and acid **6**. The former was obtained in a straightforward way from D-(+)-glucose. The route passed through a 5,6-methylene derivative (see structure **12**) that underwent Ferrier transformation to the hydroxycyclohexanone derivative **13**. The acid **6** was built from aldehyde **15**. An addition reaction of allyltrimethylsilane to **15** and a subsequent addition of crotylboronate **18** to aldehyde **17** were the key steps in the chain extension leading to the acid. The central issue of the synthesis was the merging of two chiral sectors (see A and B) to produce an ensemble in which the achiral spacer element consists of a single methylene carbon, $C_{39}$. This problem was solved by establishing an ester bond between **5** and **6**. The strategic $C_{40}$–$C_{39}$ carbon–carbon bond was generated by application of the Ireland ester enolate rearrangement. The extraneous carboxyl group (see structure **28**) was removed by photolysis of the *N*-hydroxyphthalimide ester (see transformation **30** → **31**).

## Background of the Problem and Synthetic Planning

Rapamycin (**1**), a metabolite of *Streptomyces hygroscopicus*, was first isolated from an Easter Island soil sample.[1,2] Though significant chemistry and extensive spectral measurements were carried out on rapamycin, elucidation of its structure relied on a crystallographic determination.[3,4] With the assignment of **1** secure, the structure of a related substance, 29-demethoxyrapamycin (**2**), could be established by spectroscopic means.[5] Early interest in these compounds arose from their antibiotic properties. During routine toxological studies, it was found that rapamycin alters the histology of lymphoid tissue.

Subsequent studies have centered around the immunosuppressive properties of **1**, with possible application to autoimmune diseases.[6] The scope of the inquiry broadened considerably following discovery of the extraordi-

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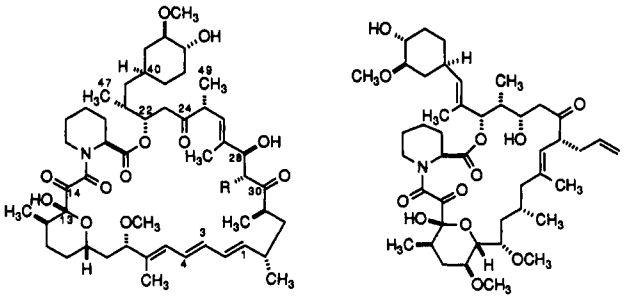

1 Rapamycin R = $OCH_3$
2 29-Demethoxyrapamycin R = H



3 FK-506

**Figure 1.**

narily potent immunosuppressive properties of FK-506 (**3**),[7] a compound bearing significant structural homology to **1** and **2** (Figure 1).

With the identification of a cytosolic protein (FKBP) possessing a high binding affinity for both KF-506 and rapamycin, there commenced an ongoing and detailed effort directed at elucidating the role of these compounds in T-cell deactivation.[8,9] Although both **1** and **3** bind FKBP with high affinity, the mechanisms for the undermining of T-cell function by the two drugs are strikingly different. For instance, FK-506 has a strong inhibitory effect on IL-2 production and expression, while rapamycin exerts little or no influence on these events. The immunosuppression of rapamycin seems to reside in its ability to impede cellular response to IL-2. Also, while **1** potentiates the effects of cyclosporin A on T-cell proliferation, it is a potent antagonist of FK-506. Likewise, FK-506 is an antagonist of the action of rapamycin.[10]

We have undertaken the goal of a total synthesis of rapamycin (**1**). The chemical challenges associated with such a venture are not to be taken lightly. The total synthesis of **3** was a major accomplishment in the field.[11-13] The presence of the triene array and the pattern of connectivity of stereogenic centers in rapamycin carry with them complexities beyond those found in FK-506 (**3**). A synthesis of rapamycin would therefore provide a setting for formulating and evaluating some new strategies.

Similarly daunting is the task of abstracting from the total molecular array of rapamycin a substructure that discharges both the binding and effector functions of the drug itself.[14] It is not improbable that analogue construction could be facilitated if comprehensive synthetic access to rapamycin could be assured. This capability, in concert with flexible degradative protocols,[15] could be very helpful in assembling substantial structural segments of **1** and **2**.

In this paper, we describe the synthesis of generalized system **4**, containing the region corresponding to $C_{28}$–$C_{49}$ of rapamycin.[16] The envisioned carbon 28 of **4** is so functionalized as to permit a range of possibilities for coupling to other subunits. It was noted from the outset that goal system **4** contains two loci of dissymmetry connected by the $C_{39}$ methylene group. In principle, one could consider a synthesis wherein stereochemical information would be communicated from one sector, thereby ordering the development of chirality in the other sector.[17] However, the likelihood for achieving the required induction in a straightforward way through a linear synthesis seemed none too promising.[18]

We also considered the possibility of a convergent approach in which two properly matched chiral building blocks would be coupled.[17] For instance, the merger of a unit comprising $C_{40}$–$C_{46}$[16] (see subunit A) and one embodying $C_{38}$–$C_{28}$[16] (see subunit B) would be a possibility. However, the prospects for intermolecular formation of a strategic carbon–carbon bond to join these domains are also not without complications. The difficulty arises from the fact that the achiral "spacer element" between the dissymmetric sectors in this region of the molecule consists of a single methylene carbon ($C_{39}$). A prospectus based on intermolecular attachment of either $C_{40}$–$C_{39}$ or $C_{39}$–$C_{38}$ would, in its simplest version, implicate a stereogenic carbon atom in the bond construction step. *As a general proposition, it is well to avoid strategies that call for exposure of prearranged stereogenic centers to carbon–carbon bond forming reactions if these centers are to be preserved in the product.*

In this paper, we describe an interesting approach to the problem of coupling the A and B subunits while exercising control over the final configurations at carbons 38 and 40. We envisioned that carbon–carbon bond formation between $C_{39}$ and $C_{40}$ could be accomplished intramolecularly through an Ireland ester enolate rearrangement (see intermediate **4b**, Figure 2).[19] This strategy allows the elements of chirality in fragments A and B to be joined initially through a simple esterification reaction (see intermediate **4a**). The critical $C_{39}$–$C_{40}$ bond in **4b** would be fashioned via chirality transfer from $C_{44}$ to $C_{40}$. Successful prosecution of this plan to reach **4** would require subsequent saturation of the $C_{44}$–$C_{45}$ olefin[16] and decarboxylation of the $C_{39a}$ carboxyl appendage.

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(17) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.

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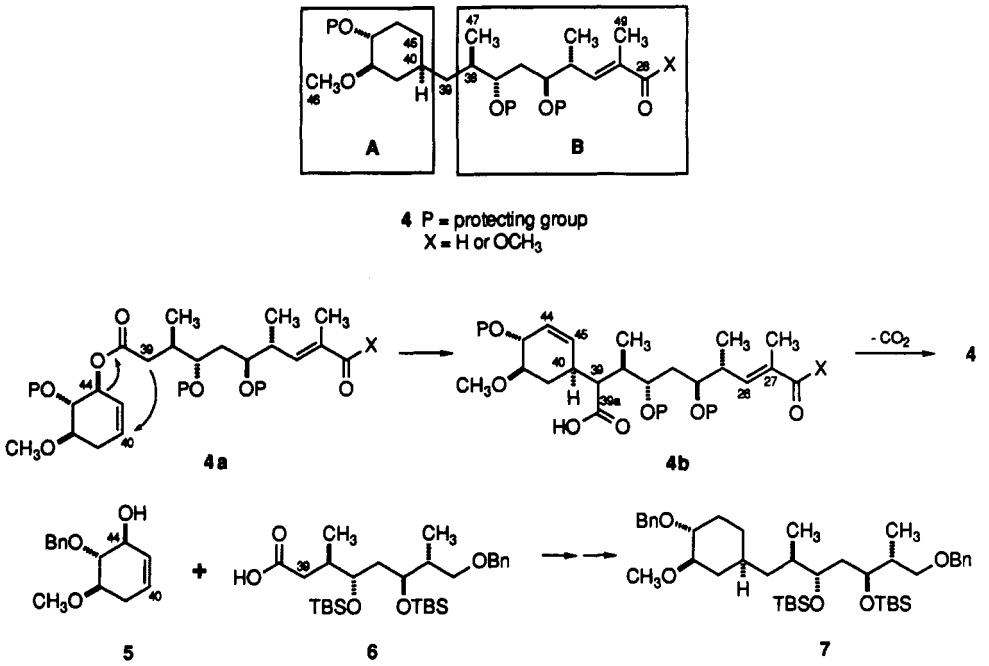


Figure 2.

These considerations led us, retrosynthetically, to a cyclohexenol (cf. **5**) and a carboxylic acid that we formulated as **6**. It should be noted that **6** represents a somewhat truncated version of the hypothetical B fragment discussed above (see structure **4**). However, we assumed that after the critical coupling and reduction phases, suitable chain extension would be possible. By shortening the B fragment in this way, a potential awkwardness in reduction of the $C_{44}$–$C_{45}$ double bond in the presence of a potentially reducible $C_{26}$–$C_{27}$ olefin is avoided. We first describe syntheses of **5** and **6**. We then describe their coupling and the functional group adjustments leading to **7**. Finally, we describe the conversion of **7** to a specific version of goal system **4**, i.e., compound **36**.

## Discussion of Results

The synthesis of **5** commenced with the 4,6-benzylideneacetal of 2-deoxy-D-glucose (**8**).[20] The free $C_3$ hydroxyl was methylated with NaH and MeI thereby providing **9** in 90% yield. Treatment of **9** with NBS in the presence of barium carbonate, following the Hanessian–Hullar protocol,[21] afforded the bromobenzoate **10** (93% yield). The $C_4$ benzoyl protecting group, which would not have been compatible with our contemplated reaction sequence, was cleaved with NaOMe. Alcohol **11** thus obtained reacted with 6 equiv of NaH and benzyl bromide giving compound **12** in 90% yield. Under these conditions, the base also deprotonated the $C_4$ hydroxyl group and effected elimination of the $C_6$ bromide. Treatment of **12** with aqueous $HgCl_2$ triggered a Ferrier transformation,[22] affording **13** as a 5:1 mixture of hydroxy epimers in 85% yield. This mixture suffered $\beta$-elimination under the influence of methanesulfonyl chloride in pyridine, providing a 91% yield of **14**. Finally, Luche reduction[23] of **14** gave the desired cyclohexenol **5** in 67% yield (Figure 3).

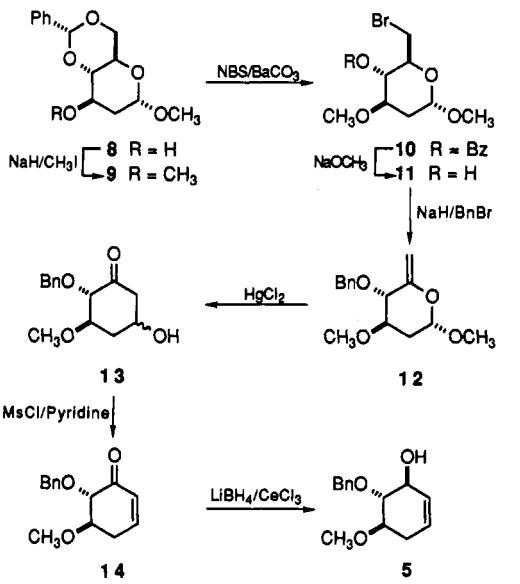


Figure 3.

The starting material selected for the synthesis of **6** was the well-known (*R*)-3-(benzyloxy)-2-methylpropanal (**15**),[24] which upon reaction with allyltrimethylsilane in the presence of titanium tetrachloride gave rise to an inseparable 7:1 mixture of **16a** and its hydroxy epimer (not shown here) in 75% combined yield (Figure 4).[25] Silylation of the hydroxyl group with *tert*-butyldimethylsilyl chloride (TBSCl) followed by ozonolytic cleavage of the terminal methylene group afforded **17**. This aldehyde reacted with the (*E*)-crotylboronate **18**[26] (derived from (*S,S*)-diisopropyl tartrate) affording a 3.5:1 ratio of **19**:**20**.[27] Separation was best achieved after desilylation of the

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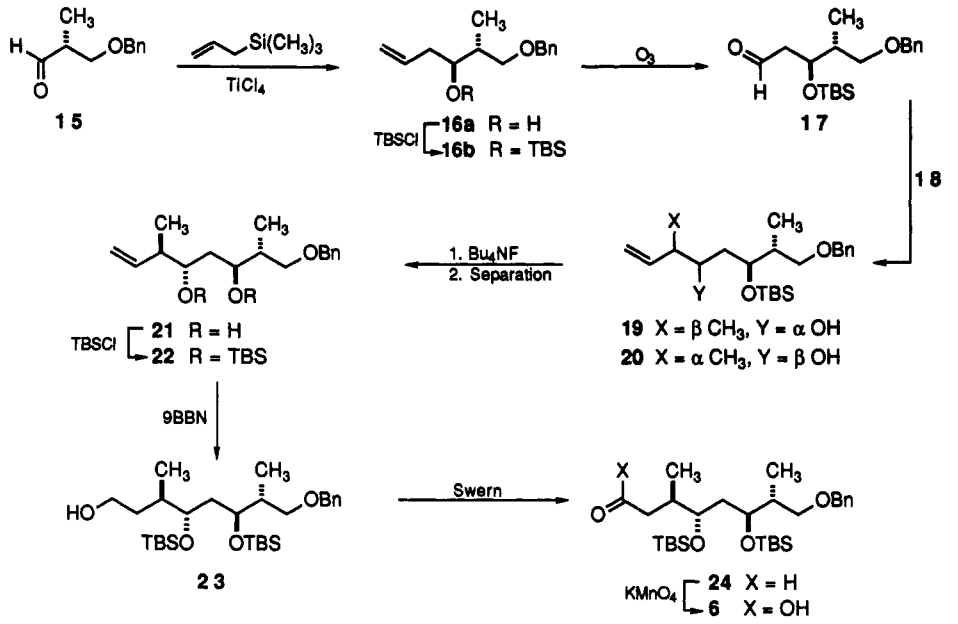


Figure 4.

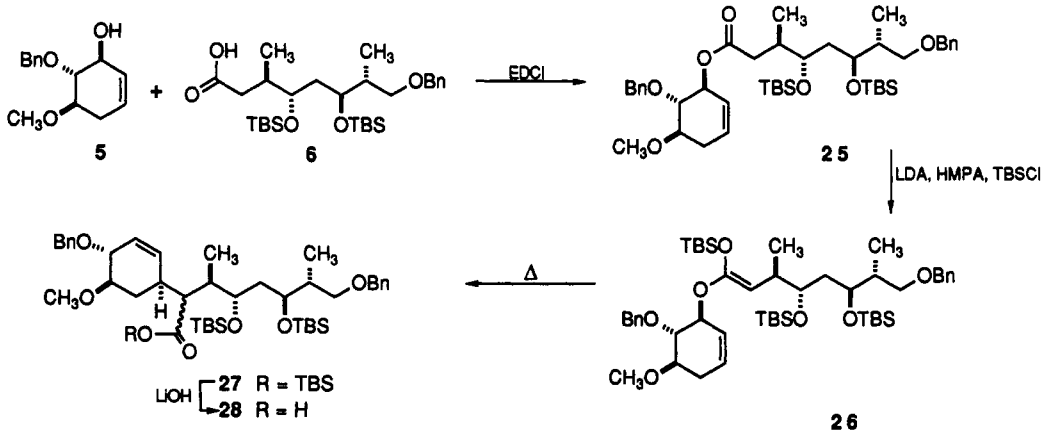


Figure 5.

product mixture. Careful chromatography allowed the isolation of **21** as an oily solid. Recrystallization of this material from hexanes yielded homogeneous diol.[28] Silylation of **21** with TBSCl afforded the bissilyl derivative **22** in 93% yield. Hydroboration (9-BBN)[29] followed by oxidation with basic hydrogen peroxide gave **23** in 98% yield. This alcohol was subjected to Swern oxidation,[30] and the resulting aldehyde **24** was transformed into acid **6** with buffered $KMnO_4$.[31]

With compounds **5** and **6** available, the stage was set for their coupling. Esterification was accomplished with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI)[32] in the presence of 4-(dimethylamino)pyridine (DMAP) providing a 75% yield of **25** (Figure 5). Generation of ketene acetal **26** was accomplished by treatment of **25** with lithium diisopropylamide (LDA) in a THF/HMPA mixture at −78 °C and quenching of the resultant lithium enolate with freshly sublimed TBSCl. Thermolysis of compound **26** in vigorously refluxing toluene produced **27**.[33,34] Hydrolysis (lithium hydroxide) of the silyl ester afforded the somewhat labile acid **28**.

At this juncture, removal of the $C_{39a}$ carboxyl group became our next goal. Initial efforts explored the feasibility of using a Barton-like free-radical decarboxylation to achieve this transformation.[35] Unfortunately, all attempts to form the required thiohydroxamic ester met with failure. Several of the conditions screened to activate acid **28** induced lactonization with the siloxy group (see compound **29**). It seemed that decarboxylation of **28** would require a procedure in which the activated precursor could be produced under extremely mild conditions.

Careful examination of the literature suggested such a method. Okada and Oda[36] have demonstrated that *N*-(acyloxy)phthalimides can be formed under very mild

(28) Recrystallization at this stage efficently removed the small amount of undesired isomer carried on from **16**.

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(33) Unusually harsh conditions were required for this rearrangement (see ref 19). A possible explanation for this result may lie in the fact that suprafacial rearrangement of **26** requires a cyclohexenol chair conformation in which all three ring substituents are axially disposed.

(34) Compound **27** was isolated as a ca. 3:1 mixture at $C_{39a}$. Since our synthesis strategy required removal of $C_{39a}$, this stereochemical issue was not examined in detail.

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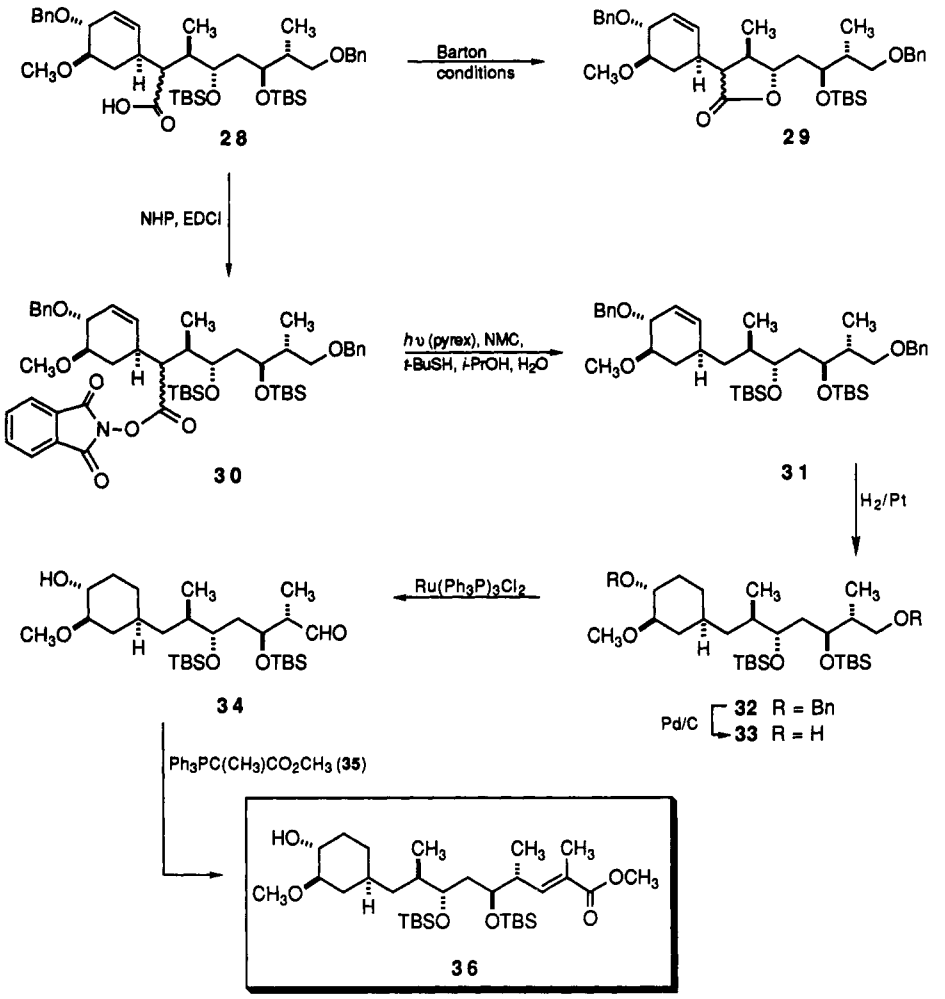


**Figure 6.**

conditions (EDCI) and that they readily decarboxylate when irradiated (Pyrex) in the presence of *N*-methylcarbazole (NMC) and *t*-BuSH. In the event, acid **28** was efficiently condensed with *N*-hydroxyphthalimide (NHP) in the presence of EDCI and DMAP providing the labile ester **30**. This material, when immediately subjected to photolysis (Pyrex) in the presence of *N*-methylcarbazole (NMC), *t*-BuSH, *i*-PrOH, and $H_2O$, afforded **31**. Purification and full characterization were best achieved at this stage, resulting in a ca. 45% yield of **31** from **25**.

Completion of the target molecule was accomplished in a straightforward manner. The $C_{44}$–$C_{45}$ double bond was reduced with hydrogen over platinum. Both *O*-benzyl groups of the resultant **32** were cleaved through the action of hydrogen over palladium on charcoal. Selective oxidation of the primary alcohol of **33** was accomplished with tris(triphenylphosphine)ruthenium(II) chloride in 73% yield.[37] Coupling of **34** with (carbomethoxyethylidene)-triphenylphosphorane (**35**) afforded enoate **36** as a 14:1 ratio of *E*/*Z* isomers in 64% yield (Figure 6).

It is appropriate to conclude this report with a description of an investigation directed toward providing rigorous support for the stereochemical assignment advanced for compound **21** (Figure 7). This compound becomes **6**, which is the coupling partner for **5**. The absolute and relative configurations of **5** follow rigorously from the method of synthesis and from unambiguous spectroscopic deductions.

(37) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

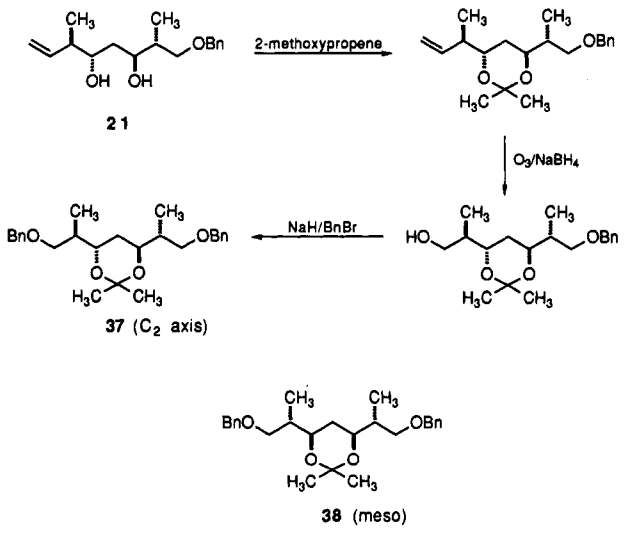


**Figure 7.**

In particular, we focus on the crotylation of compound **17**. The stereochemistry of **17** itself follows from that of **16**, which in turn arose from the allylation of **15**.[24] The stereochemistry of **16** has been well-established by earlier workers.[25] In proposing the structures of **19** and **20**, we were influenced by the strong trends in crotylation reactions via auxillary-mediated stereoselection as worked out by Roush.[26,27] However, there still remained to be demonstrated that these guidelines were in fact operative to the case at hand.

To confirm the assigned stereochemistry, we operated on diol **21**. The two hydroxyl groups were engaged as an acetonide through the action of 2-methoxypropene. The resultant product was subjected to ozonolysis, followed by reduction with sodium borohydride to produce the monoalcohol. The hydroxyl group was benzylated (sodium hydride/benzyl bromide) to render the termini of the system identical. Clearly, if the assignments to this point were correct, this diether is properly formulated as **37**. The alternative threo crotyl product (see structure **20**) would have been converted to **38**. The dibenzyl ether we obtained does not correspond to the meso compound **38**, as revealed by its optical activity, $[\alpha]^{23}_D$ −13.6°. Moreover, the $^{13}C$ spectrum of the dibenzyl ether **37** exhibits resonances for 12 unique carbons. This data is consistent with the $C_2$ symmetry of **37** but inconsistent with the dibenzyl ethers that would have arisen from either of the two potential erythro crotylation products of **17**. Therefore, the assignment of structure **21** is validated. All other stereochemical assignments follow rigorously from the synthetic methods that were used and from spectral measurements.

## Conclusions

The use of the Ireland allylic ester enolate rearrangement decarboxylation sequence as a device to merge otherwise awkwardly amalgamated chiral sectors has thus been demonstrated. The highly versatile intermediate **36** has been produced. A variety of ways exist to further develop functionality in **36**. Possibilities for differentiating the oxygens at carbons 22 and 24 have been identified at various stages of the synthesis. The optimal version of the $C_{28}$–$C_{49}$ fragment requiring installation of a pipecolinyl residue at the $C_{22}$ oxygen for coupling with a $C_1$–$C_{28}$ equivalent[38] en route to rapamycin is presently being determined.

## Experimental Section

**Methylation of 8. Preparation of 9.** A solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside[20] (**8**; 13.4 g of a 7:1 mixture of α and β anomers, 50.5 mmol) and DMF (50 mL) was added to a suspension of NaH (97%, 1.5 g, 60.5 mmol) and DMF (150 mL) at 0 °C, and the mixture was then allowed to warm to room temperature. After 20 min, the reaction mixture was treated with MeI (9.7 mL, 151.4 mmol) and the resulting solution was maintained at room temperature for 16 h. At this time, the reaction mixture was concentrated and the resulting residue was dissolved in $Et_2O$/EtOAc (1:1, 500 mL). This solution was washed with $H_2O$ (5 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 6:4 hexanes/EtOAc) giving 12.8 g (90%) of **9** as a 7:1 mixture of α and β anomers. Characteristic data for the α (major) anomer: $^1H$ NMR (250 MHz, $CDCl_3$) δ 7.50–7.32 (m, 5 H), 5.57 (s, 1 H), 4.79 (d, $J$ = 3.1 Hz, 1 H), 4.24 (d, $J$ = 5.5 Hz, 1 H), 3.85–3.70 (m, 3 H), 3.60–3.53 (m, 1 H), 3.48 (s, 3 H), 3.33 (s, 3 H), 2.30 (ddd, $J$ = 1.1, 5.1, 13.3 Hz, 1 H), 1.69 (ddd, $J$ = 3.8, 11.1, 13.4 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 137.5, 128.7, 128.0, 126.0, 101.4, 98.9, 83.5, 74.3, 69.0, 62.7, 58.2, 54.4, 35.7; IR ($CDCl_3$) 3080–2800, 1450, 1375, 1260, 1210, 1135, 1090, 1060, 1020, 985, 850, 810 $cm^{-1}$; MS (CI) $m/e$ 281.1384 (281.1389 calcd for $C_{15}H_{20}O_5$ + H). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.28; H, 7.30.

**Hanessian–Hullar[21] Cleavage of Benzylidene Acetal 9. Preparation of Bromo Benzoate 10.** A solution of **9** (4.99 g of a 7:1 mixture of α and β anomers, 17.8 mmol) and $CCl_4$ (180 mL) was treated with $BaCO_3$ (7.0 g) and NBS (3.80 g, 21.4 mmol) at room temperature. The resulting mixture was then heated at reflux for 7 h. The resulting mixture was filtered through Celite, and the filtrate was concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 1:1 hexanes/EtOAc) giving 6.4 g (93%) of **10** as a 7:1 mixture of α and β anomers. Characteristic data for the α (major) anomer: $^1H$ NMR (490 MHz, $CDCl_3$) δ 8.09–8.06 (m, 2 H), 7.61–7.57 (m, 1 H), 7.49–7.45 (m, 2 H), 5.06 (t, $J$ = 9.6 Hz, 1 H), 4.92 (d, $J$ = 2.6 Hz, 1 H), 4.05–4.01 (m, 1 H), 3.84 (ddd, $J$ = 5.1, 9.0, 11.4 Hz, 1 H), 3.51 (dd, $J$ = 2.4, 11.1 Hz, 1 H), 3.44 (s, 3 H), 3.43 (dd, $J$ = 8.0, 11.1 Hz, 1 H), 3.32 (s, 3 H), 2.33 (ddd, $J$ = 1.3, 5.1, 13.2 Hz, 1 H), 1.75 (ddd, $J$ = 3.7, 11.5, 13.2 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 165.5, 133.3, 129.8, 129.5, 128.4, 98.3, 75.8, 74.1, 69.9, 57.4, 55.0, 34.7, 32.2; IR ($CDCl_3$) 3100–2800, 1730, 1600, 1580, 1450, 1350, 1320, 1270, 1180, 1130, 1075, 1050, 1040, 1000, 970, 960, 800 $cm^{-1}$; MS (CI) $m/e$ 361.0487 (361.0474 calcd for $C_{15}H_{19}O_5Br$ + H). Anal. Calcd for $C_{15}H_{19}O_5Br$: C, 50.16; H, 5.33. Found: C, 50.10; H, 5.39.

**Cleavage of Benzoate 10. Preparation of Bromo Alcohol 11.** A solution of **10** (13.5 g of a 7:1 mixture of α and β anomers, 37.6 mmol) in methanol (400 mL) was allowed to react with sodium methoxide (1.01 g, 18.8 mmol) at room temperature for 12 h. The solution was concentrated, and the resulting viscous oil was redissolved in EtOAc (1 L), washed with water (4 × 75 mL) and brine (1 × 75 mL), dried ($MgSO_4$), and concentrated. The crude oil was chromatographed (silica gel, 240–400 mesh, 1:1 hexanes/EtOAc) to afford 7.82 g (81%) of **11** as a 7:1 mixture of α and β anomers. Characteristic data for the α (major) anomer: $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.88 (d, $J$ = 3.5 Hz, 1 H), 3.79–3.74 (m, 2 H), 3.62–3.41 (m, 2 H), 3.44–3.37 (m, 1 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 2.64 (br s, 1 H), 2.29 (ddd, $J$ = 1.3, 4.8, 12.9 Hz, 1 H), 1.59 (ddd, $J$ = 3.7, 11.9, 15.6 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 98.5, 78.2, 72.5, 70.5, 56.4, 54.8, 33.7, 33.6; IR ($CDCl_3$) 3580, 2940, 2910, 2840, 1130, 1110, 1085, 1050, 965 $cm^{-1}$; MS (EI) $m/e$ 256; MS (CI) $m/e$ 257.0214 (257.0212 calcd for $C_8H_{15}O_4Br$ + H); $[\alpha]^{23}_D$ 85.1° ($c$ 0.96, $CHCl_3$). Anal. Calcd for $C_8H_{15}O_4Br$: C, 37.79; H, 5.95; Br, 31.07. Found: C, 37.54; H, 5.79; Br, 31.25.

**Benzylation of 11. Preparation of 12.** To a suspension of NaH (95%, 2.4 g, 94.1 mmol) in anhydrous DMF (100 mL) was added a solution of **11** (4.0 g of a 7:1 mixture of α and β anomers, 15.7 mmol) and anhydrous DMF (60 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min, and then benzyl bromide (7.6 mL, 62.7 mmol) and $Bu_4NI$ (0.6 g, 1.57 mmol) was added. The mixture was then allowed to warm to room temperature where it was maintained for 21 h. The reaction mixture was then cooled to 0 °C and quenched with anhydrous MeOH (5.0 mL, 122.5 mmol). The reaction mixture was then concentrated. The residue was taken up in EtOAc (750 mL), washed with $H_2O$ (3 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$) and concentrated. The crude material was purified by chromatography (silica gel, 240–400 mesh, 7:3 hexanes/EtOAc) giving 3.76 g (90%) of **12** as a 7:1 mixture of α and β anomers. Characteristic data for the α (major) anomer: $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5 H), 4.85 (t, $J$ = 3.3 Hz, 1 H), 4.80–4.69 (m, 4 H), 3.83 (d, $J$ = 7.6 Hz, 1 H), 3.72–3.63 (m, 1 H), 3.47 (s, 3 H), 3.43 (s, 3 H), 2.26 (dt, $J$ = 3.9, 13.3 Hz, 1 H), 1.80 (ddd, $J$ = 3.4, 9.6, 13.2 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 154.5, 138.1, 128.1, 127.4, 127.3, 99.5, 96.6, 78.7, 77.3, 72.6, 57.5, 55.0, 34.1; IR ($CDCl_3$) 2925, 1655, 1450, 1360, 1215, 1115, 1045, 870 $cm^{-1}$; MS (EI) $m/e$ 264; MS (CI) $m/e$ 265.1455 (265.1440 calcd for $C_{15}H_{20}O_4$ + H); $[\alpha]^{23}_D$ 51.9° ($c$ 1.11, $CHCl_3$).

**Ferrier Rearrangement[22] of 12. Preparation of β-Hydroxycyclohexanone 13.** A solution of **12** (2.40 g of a 7:1 mixture of α and β anomers, 9.08 mmol) and acetone/$H_2O$ (2:1, 90 mL) was allowed to react with $HgCl_2$ (2.71 g, 9.98 mmol) at reflux. After 2 h, the reaction was allowed to cool and was diluted with EtOAc (750 mL). This mixture was washed with brine (3 × 25 mL), dried ($MgSO_4$), and concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 1:1 hexanes/EtOAc) giving 1.92 g (85%) of **13** as a 5:1 mixture of hydroxy epimers. Characteristic data for the major isomer: $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 4.66 (AB quartet, $J$ = 11.7 Hz, $\Delta\nu$ = 113 Hz, 2 H), 4.32–4.28 (m, 1 H), 3.90 (d, $J$ = 7.4 Hz, 1 H), 3.83–3.79 (m, 1 H), 3.46 (s, 3 H), 2.67–2.57 (m, 2 H), 2.34–2.29 (m, 1 H), 2.15–2.05 (br s, 1 H), 1.95 (ddd, $J$ = 3.1, 8.7, 13.7 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 196.6, 137.4, 128.1, 127.6, 127.1, 85.6, 79.1, 72.5, 65.0, 58.0, 47.4, 35.5; IR ($CDCl_3$) 3580, 2920, 1725, 1250, 1105, 1055 $cm^{-1}$; MS (EI) $m/e$ 250; MS (CI) $m/e$ 251.1279 (251.1283 calcd for $C_{14}H_{18}O_4$ + H). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.25. Found: C, 66.89; H, 7.25.

**Preparation of Cyclohexenone 14.** A solution of **13** (1.90 g of a 5:1 mixture of hydroxy epimers, 7.60 mmol) in pyridine (75

(38) Next paper in this issue.

mL) was allowed to react with methanesulfonyl chloride (1.8 mL, 22.8 mmol) at room temperature for 12 h. The solution was then concentrated and the residue diluted with EtOAc (750 mL) and washed with water (3 × 25 mL) and brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude isolate was chromatographed (silica gel, 240–400 mesh, 1:1 hexanes/EtOAc) giving 1.61 g (91%) of **14** as a pale yellow oil: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.45–7.28 (m, 5 H), 6.86–6.82 (m, 1 H), 6.05 (ddd, $J$ = 1.1, 2.5, 10.2 Hz, 1 H), 4.84 (AB quartet, $J$ = 11.6 Hz, $\Delta\nu$ = 119.5 Hz, 2 H), 3.98 (d, $J$ = 9.1 Hz, 1 H), 3.77–3.73 (m, 1 H), 3.50 (s, 3 H), 2.84 (ddt, $J$ = 0.9, 5.1, 18.7 Hz, 1 H), 2.44 (ddt, $J$ = 2.9, 8.0, 18.6 Hz, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 197.2, 145.9, 137.8, 128.4, 128.0, 127.8, 127.6, 127.4, 83.3, 79.3, 73.2, 58.0, 31.0; IR ($CDCl_3$) 3010, 2920, 1680, 1445, 1210, 1115, 1000 $cm^{-1}$; MS (EI) $m/e$ 233; MS (CI) $m/e$ 233.1188 (233.1178 calcd for $C_{14}H_{16}O_3$ + H); $[\alpha]^{23}_D$ 89.9° ($c$ 1.13, $CHCl_3$). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.38; H, 6.95. Found: C, 72.09; H, 7.11.

**Luche[23] Reduction of Enone 14. Preparation of 5.** To a solution of **14** (5.1 g, 21.9 mmol) in THF/MeOH (1:1, 220 mL) was added cerium(III) chloride heptahydrate (12.3 g, 33.0 mmol). The mixture was stirred until all of the cerium salt was dissolved. Then the resulting solution was cooled to −78 °C, and lithium borohydride (1.9 g, 89.0 mmol) was added in small portions. The reaction mixture was stirred for 0.5 h at −78 °C and then diluted with ether (400 mL). This mixture was quenched with the addition of 0.1 N HCl (50 mL) in a dropwise fashion. The resulting mixture was stirred for 0.5 h before brine (50 mL) was added. The organic layer was decanted, and the aqueous layer was extracted with ether (4 × 75 mL). The combined organic layers were washed with water (2 × 75 mL) and brine (1 × 75 mL), dried ($MgSO_4$), and concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 7:3 hexanes/EtOAc) giving 3.44 g (67%) of pure **5**: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 7.45–7.25 (m, 5 H), 5.68 (m, 2 H), 4.80 (AB quartet, $J$ = 11.7 Hz, $\Delta\nu$ = 62 Hz, 2 H), 4.15 (m, 1 H), 3.60 (m, 2 H), 3.44 (s, 3 H), 2.63–2.45 (m, 1 H), 2.39 (d, $J$ = 5.5 Hz, 1 H), 2.28–2.10 (m, 1 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 138.9, 128.4, 128.2, 127.5, 127.4, 124.6, 82.6, 78.6, 73.8, 70.4, 57.3, 29.6; IR (film) 3400, 2900, 1450, 1100 $cm^{-1}$; MS (CI) $m/e$ 235.1330 (235.1335 calcd for $C_{14}H_{18}O_3$ + H); $[\alpha]^{23}_D$ 40.30 ($c$ 0.75, $CHCl_3$).

**Silylation of Alcohol 16a. Preparation of 16b.** A solution of alcohol **16a**[25] (15.12 g of a 7:1 mixtue of anti and syn isomers, 68.63 mmol) and DMF (110 mL) was allowed to react with TBSCl (10.4 g, 69.0 mmol) and imidazole (5.62 g, 83.0 mmol) at room temperature. After 48 h, the mixture was poured into EtOAc (1L) and washed with $H_2O$ (2 × 500 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude material was chromatographed (silica gel, 240–400 mesh, 30:1 hexanes/EtOAc) yielding 22.4 g (98%) of **16b** as a colorless oil. Characteristic data for the product mixture: $^1H$ NMR (490 MHz, $CDCl_3$) $\delta$ 7.4–7.2 (m, 5 H), 5.85 (m, 1 H), 5.05 (m, 2 H), 4.50 (AB quartet, $J$ = 12.1 Hz, $\Delta\nu$ = 25 Hz, 2 H), 3.73 (app q, $J$ = 5.5 Hz, 1 H), 3.51 (dd, $J$ = 5.5, 9.1 Hz, 1 H), 3.33 (dd, $J$ = 6.9, 9.2 Hz, 1 H), 2.23 (m, 2 H), 1.98 (m, 1 H), 0.94 (d, $J$ = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); IR (film) 2990, 2970, 2880, 1260, 1100 $cm^{-1}$; MS (FAB) $m/e$ 335.2429 (335.2408 calcd for $C_{20}H_{34}O_2Si$ + H).

**Preparation of Siloxy Aldehyde 17.** A stream of $O_3$ was bubbled through a solution of **16b** (9.94 g, 29.7 mmol) in MeOH (6 mL), $CH_2Cl_2$ (54 mL), and pyridine (1 mL) at −78 °C until blue. The excess $O_3$ was then removed with a stream of $N_2$, and DMS (50 mL) was added. The resulting solution was allowed to warm to room temperature. After 15 h, the solution was concentrated. The crude material was chromatographed (silica gel, 240–400 mesh, 20:1 hexanes/EtOAc) giving 7.49 g (75%) of **17** as a colorless oil. Characteristic data for the major isomer: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 9.78 (t, $J$ = 2.4 Hz, 1 H), 7.4–7.2 (m, 5 H), 4.48 (AB quartet, $J$ = 12.1 Hz, $\Delta\nu$ = 16.5 Hz, 2 H), 4.36 (dd, $J$ = 5.0, 11.5 Hz, 1 H), 3.35 (m, 2 H), 2.50 (m, 2 H), 2.10 (m, 2 H), 0.92 (d, $J$ = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); IR (film) 2980, 2880, 1728, 1100 $cm^{-1}$.

**Crotylation of 17. Preparation of Diol 21.** Following the general procedure of Roush,[26] aldehyde **17** (6.59 g, 19.6 mmol) was allowed to react with (*S,S*)-diisopropyl tartrate–(*E*)-crotyl boronate in toluene (20 mL) at −78 °C. After 2 h at −78 °C, the reaction mixture was filtered through Celite and the Celite was washed with $Et_2O$ (700 mL). The combined filtrate was then treated with 15% aqueous NaOH (100 mL), and the resulting mixture was stirred vigorously for 16 h at room temperature. The aqueous layer was then separated and extracted with $Et_2O$ (4 × 30 mL). The organic material was combined, dried ($MgSO_4$), and concentrated. The crude residue was quickly passed through a plug of silica gel (9:1 hexanes/EtOAc), and the collected mixture of isomers was concentrated. The crude isolate was taken up in THF (10 mL) and treated with $Bu_4NF$ (22 mL of a 1.0 M solution in THF, 21.6 mmol). After 2 h at room temperature, the solution was diluted with $Et_2O$ (150 mL) and washed with water and brine. The organic material was dried ($MgSO_4$) and concentrated. The isolate was purified by chromatography (MPLC, silica gel, 3:1 hexanes/EtOAc) giving 3.1 g of **21** as an oily solid. This material was recrystallized from hexanes giving 2.54 g (47%) of analytically pure material: mp 49–51 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 7.40–7.25 (m, 5 H), 5.80 (m, 1 H), 5.20–5.00 (m, 2 H), 4.53 (s, 2 H), 4.03 (d, $J$ = 2.6 Hz, 1 H), 3.8 (m, 2 H), 3.61 (dd, $J$ = 4.4, 9.2 Hz, 1 H), 3.50 (app t, $J$ = 9.0 Hz, 1 H), 2.93 (d, $J$ = 3.1 Hz, 1 H), 2.25 (br q, $J$ = 6.9 Hz, 1 H), 2.0 (m, 1 H), 1.65 (m, 2 H), 1.03 (d, $J$ = 6.9 Hz, 3 H), 0.85 (d, $J$ = 6.9 Hz, 3 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 140.87, 137.80, 128.51, 127.82, 127.68, 115.57, 75.46, 73.96, 73.55, 71.63, 44.20, 38.17, 37.21, 15.88, 13.70; IR (film) 3425, 1460, 1100, 920 $cm^{-1}$; MS (FAB) $m/e$ 279.1985 (279.1961 calcd for $C_{17}H_{26}O_3$ + H); $[\alpha]^{23}_D$ −21.5° ($c$ 0.86, $CHCl_3$).

**Silylation of Diol 21. Preparation of 22.** A solution of diol **21** (2.42 g, 8.72 mmol) and DMF (15 mL) was allowed to react with TBSCl (2.89 g, 19.18 mmol) and imidazole (1.48 g, 21.79 mmol) at room temperature. After 20 h, the reaction mixture was diluted with $Et_2O$ (200 mL) and washed with $H_2O$ (3 × 50 mL) and brine (1 × 50 mL). The organic material was dried ($MgSO_4$) and concentrated. The crude material was subjected to chromatography (silica gel, 240–400 mesh, 15:1 hexanes/EtOAc) to give 4.1 g (93%) of **22** as a colorless oil: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 7.4–7.2 (m, 5 H), 5.8 (m, 1 H), 5.1–4.9 (m, 2 H), 4.49 (AB quartet, $J$ = 12.3 Hz, $\Delta\nu$ = 12.7 Hz, 2 H), 4.85 (m, 1 H), 4.76 (m, 1 H), 3.46 (dd, $J$ = 6.1, 9.3 Hz, 1 H), 3.23 (dd, $J$ = 7.3, 9.2 Hz, 1 H), 2.35 (m, 1 H), 2.0 (m, 1 H), 1.45 (m, 2 H), 2.01 (d, $J$ = 6.67 Hz, 3 H), 1.98 (d, $J$ = 6.88 Hz, 3 H), 0.87 (s, 18 H), 0.05 (s, 12 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 140.6, 139.0, 128.3, 127.5, 127.4, 114.7, 73.8, 73.2, 72.8, 72.1, 43.9, 39.6, 37.5, 26.1, 18.2, 14.7, 12.9, −3.9, −4.0; IR (film) 2800, 1470, 1260, 1070, 840, 780 $cm^{-1}$; $[\alpha]^{23}_D$ −9.07° ($c$ 0.28, $CHCl_3$).

**Hydroboration of 22. Preparation of Alcohol 23.** A solution of **22** (4.0 g, 7.91 mmol) and THF (5 mL) was allowed to react with 9-BBN (39.5 mL of a 0.5 M solution in THF, 19.73 mmol) at room temperature for 4 h. At this time, the reaction mixture was cooled to 0 °C and quenched with 3 M NaOH (6.6 mL, 19.74 mmol) and 30% $H_2O_2$ (6.0 mL, 56.8 mmol). The resulting mixture was stirred at 0 °C for 1 h and then diluted with $Et_2O$ (200 mL). The resulting solution was washed with water and brine. The organic material was dried ($MgSO_4$) and concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 10:1 hexanes/EtOAc) yielding 4.05 g (98%) of **23** as a colorless oil: $^1H$ NMR (490 MHz, $CDCl_3$) $\delta$ 7.38 (m, 5 H), 4.48 (AB quartet, $J$ = 12.1 Hz, $\Delta\nu$ = 5 Hz, 2 H), 3.93 (m, 1 H), 3.75 (m, 2 H), 3.60 (m, 1 H), 3.41 (dd, $J$ = 6.6, 9.3 Hz, 1 H), 3.24 (dd, $J$ = 7.0, 9.2 Hz, 1 H), 2.05 (m, 1 H), 1.89 (m, 1 H), 1.80 (m, 1 H), 1.55 (m, 2 H), 1.45 (m, 1 H), 0.92 (d, $J$ = 6.9 Hz, 3 H), 0.91 (d, $J$ = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.09 (d, $J$ = 3.15 Hz, 6 H), 0.06 (d, $J$ = 3.16 Hz, 6 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 138.8, 128.3, 127.4, 127.3, 74.1, 73.1, 72.8, 71.8, 60.5, 39.8, 36.5, 35.8, 35.2, 25.9, 18.1, 14.8, 12.1, −4.0, −4.2; IR (film) 3320, 2950, 1470, 1460, 1250, 1060 $cm^{-1}$; MS (FAB) 525.3840 (525.3797 calcd for $C_{29}H_{56}O_4Si_2$ + H); $[\alpha]^{23}_D$ −14.7° ($c$ 0.98, $CHCl_3$).

**Oxidation of Alcohol 23. Preparation of Aldehyde 24.** Alcohol **23** (1.50 g, 2.86 mmol) was oxidized in $CH_2Cl_2$ (4 mL) at −78 °C with oxalyl chloride (0.35 mL, 4.0 mmol), DMSO (0.33 mL, 4.29 mmol), and TEA (1.20 mL, 8.58 mmol) following the procedure described by Swern.[30] The reaction mixture was allowed to warm to room temperature, diluted with hexanes (100 mL), and washed with water and brine. The organic material was dried ($MgSO_4$) and concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 20:1 hexanes/EtOAc) giving 1.35 g (90%) of **24** as a colorless oil: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 9.8 (dd, $J$ = 1.5, 2.2 Hz, 1 H), 7.35 (m, 5 H), 4.48 (AB quartet, $J$ = 12.2 Hz, $\Delta\nu$ = 6.4 Hz, 2 H), 3.93 (m, 1 H), 3.70 (m,

1 H), 3.40 (dd, $J$ = 6.7, 9.3 Hz, 1 H), 3.23 (dd, $J$ = 6.8, 9.3 Hz, 1 H), 2.50–2.23 (m, 3 H), 2.05 (m, 1 H), 1.45 (m, 2 H), 0.95 (d, $J$ = 6.5 Hz, 3 H), 0.90 (d, $J$ = 6.9 Hz, 3 H), 0.87 (s, 18 H), 0.07–0.03 (m, 12 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 201.7, 138.8, 128.3, 127.5, 127.4, 73.9, 73.2, 72.8, 71.8, 46.4, 39.8, 37.4, 34.1, 25.9, 18.1, 15.8, 12.1, -4.0, -4.1; IR (film) 2900, 2860, 1660, 1320, 1080, 850 cm$^{-1}$; MS (FAB) $m/e$ 523.3654 (523.3641 calcd for $C_{29}H_{54}O_4Si_2$ + H); $[\alpha]^{23}_D$ -16.40 ($c$ 1.87, $CHCl_3$).

**Oxidation of Aldehyde 24. Preparation of Acid 6.** Aldehyde **24** (1.34 g, 2.58 mmol) was oxidized in $t$-BuOH (20 mL) and 5% aqueous $NaH_2PO_4$ (11 mL) with $KMnO_4$ (20.4 mL of a 0.38 M solution in $H_2O$, 7.75 mmol) according to the procedure described by Masamune.[31] After quenching and careful acidification (pH 4) with 1 N HCl, the product was isolated by extraction (EtOAc). The organic extracts were dried ($MgSO_4$) and concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 7:1 hexanes/EtOAc) giving 1.36 g (99%) of **6** as a colorless oil: $^1$H NMR (490 MHz, $CDCl_3$) $\delta$ 7.4–7.2 (m, 5 H), 4.80 (AB quartet, $J$ = 12.4 Hz, $\Delta\nu$ = 5.8 Hz, 2 H), 4.93 (m, 1 H), 4.78 (m, 1 H), 3.41 (dd, $J$ = 6.6, 9.2 Hz, 1 H), 3.24 (dd, $J$ = 6.8, 9.2 Hz, 1 H), 2.5–2.0 (m, 4 H), 1.45 (m, 2 H), 0.97 (d, $J$ = 6.5 Hz, 3 H), 0.91 (d, $J$ = 6.81 Hz, 3 H), 0.87 (s, 18 H), 0.07 (m, 12 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 178.9, 138.9, 128.3, 127.5, 127.4, 73.8, 73.3, 72.9, 72.0, 39.9, 37.6, 36.7, 36.0, 26.0, 18.2, 15.5, 12.4, -3.9, -4.1; IR (film) 3020, 2960, 1715, 1260, 1080 cm$^{-1}$; MS (FAB) $m/e$ 539.3592 (539.3590 calcd for $C_{29}H_{54}O_5Si_2$ + H); $[\alpha]^{23}_D$ -11.3° ($c$ 1.01, $CHCl_3$).

**Preparation of Ester 25.** A solution of acid **6** (1.36 g, 2.54 mmol) in $CH_2Cl_2$ (2.5 mL) was allowed to react with alcohol **5** (0.594 g, 2.54 mmol), EDCI (0.97 g, 5.07 mmol), and a catalytic amount of DMAP at room temperature. After 16 h, the solution was diluted with EtOAc (100 mL) and washed with $H_2O$. The organic phase was dried ($MgSO_4$) and concentrated. The crude isolate was purified by chromatography (silica gel, 240–400 mesh, 7:1 hexanes/EtOAc) yielding 1.89 g (75%) of **25** as a colorless oil: $^1$H NMR (490 MHz, $CDCl_3$) $\delta$ 7.4–7.2 (m, 5 H), 5.75 (m, 1 H), 5.52 (m, 1 H), 5.48 (m, 1 H), 4.80 (AB quartet, $J$ = 11.6 Hz, $\Delta\nu$ = 75.2 Hz, 2 H), 4.48 (AB quartet, $J$ = 12.1 Hz, $\Delta\nu$ = 13.7 Hz, 2 H), 3.90 (m, 1 H), 3.72 (m, 1 H), 3.67 (dd, $J$ = 7.1, 9.3 Hz, 1 H), 3.53 (m, 1 H), 3.48 (s, 3 H), 3.47 (m, 1 H), 3.23 (dd, $J$ = 7.0, 9.3 Hz, 1 H), 2.57 (app dt, $J$ = 5.2, 17.3 Hz, 1 H), 2.33 (dd, $J$ = 3.8, 15.2 Hz, 1 H), 2.15 (m, 1 H), 2.05 (m, 1 H), 1.40 (m, 2 H), 0.91 (d, $J$ = 6.8 Hz, 6 H), 0.87 (m, 18 H), 0.06 (m, 12 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 172.9, 138.9, 138.8, 128.3, 127.7, 127.4, 127.3, 126.9, 125.4, 81.3, 79.1, 74.3, 73.9, 73.5, 73.1, 72.7, 71.6, 58.0, 39.7, 37.1, 36.9, 35.9, 30.7, 25.9, 18.1, 15.3, 12.3, -4.0; IR (film) 2980, 1730, 1260, 1100, 850 cm$^{-1}$; MS (FAB) $m/e$ 755.4753 (755.4740 calcd for $C_{43}H_{70}O_7Si_2$ + H); $[\alpha]^{23}_D$ 32.0° ($c$ 3.56, $CHCl_3$).

**Claisen Rearrangement and Subsequent Decarboxylation of 25. Preparation of 31.** A solution of ester **25** (0.103 g, 0.137 mmol) and THF (1 mL) was added to a solution of LDA (prepared from $i$-$Pr_2NH$ (38.0 mL, 0.274 mmol) and $n$-BuLi (0.18 mL of a 1.54 M solution in hexanes, 0.274 mmol)) and THF/HMPA (4:1, 1.25 mL) at -78 °C. After 15 min, a solution of freshly sublimed TBSCl (0.062 g, 0.411 mmol) and THF (0.23 mL) was added. The resulting solution was then allowed to warm to room temperature. After 0.5 h at room temperature, the reaction mixture was diluted with 3% TEA in pentane (50 mL). This solution was washed with $H_2O$, dried ($Na_2SO_4$), and concentrated. The crude isolate was taken up in toluene (5 mL) and maintained at vigorous reflux for 2 h. The solution was then cooled and concentrated. The crude material was taken up in THF (5 mL) and allowed to react with LiOH (1.4 mL of a 0.1 N aqueous solution, 0.14 mmol). After 2 h, the THF was removed in vacuo and the resulting aqueous material was acidified to pH 4 with 0.1 N HCl and extracted with EtOAc. The organic extracts were dried ($MgSO_4$) and concentrated. The crude material was taken up in $CH_2Cl_2$ (2 mL) and allowed to react with $N$-hydroxyphthalimide (0.022 g, 0.137 mmol), EDCI (0.052 g, 0.274 mmol), and a catalytic amount of DMAP. After 8 h, the reaction mixture was diluted with EtOAc (50 mL) and washed with $H_2O$ (5 × 10 mL). The organic material was dried ($Na_2SO_4$) and concentrated. This material was taken up in $i$-PrOH/$H_2O$/$t$-BuSH (93:5:2, 5 mL) and treated with $N$-methylcarbazole (0.012 g, 0.069 mmol). The resulting solution was subjected to photolysis (Pyrex) for 2 h and then concentrated. The residue thus obtained was subjected to chromatography (silica gel, 240–400 mesh, 30:1 hexanes/EtOAc) giving 0.050 g (54%) of **31** as a colorless oil: $^1$H NMR (490 MHz, $CDCl_3$) $\delta$ 7.5–7.2 (m, 10 H), 5.61 (br s, 1 H), 4.75 (AB quartet, $J$ = 11.8 Hz, $\Delta\nu$ = 28 Hz, 2 H), 4.49 (AB quartet, $J$ = 12.1 Hz, $\Delta\nu$ = 14.9 Hz, 2 H), 4.04 (m, 1 H), 3.92 (m, 1 H), 3.72 (m, 1 H), 3.48 (s, 3 H), 3.47 (m, 1 H), 3.41 (m, 1 H), 3.23 (dd, $J$ = 7.0, 9.3 Hz, 1 H), 2.30 (m, 1 H), 2.08 (m, 2 H), 1.75 (m, 1 H), 1.50–1.25 (m, 3 H), 1.18 (m, 2 H), 1.08 (m, 1 H), 0.95–0.83 (m, 24 H), 0.08 (d, $J$ = 3.4 Hz, 6 H), 0.05 (d, $J$ = 3.8 Hz, 6 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 139.5, 139.1, 134.2, 128.3, 127.8, 127.6, 127.5, 127.4, 126.7, 81.8, 80.0, 74.0, 73.3, 73.1, 72.1, 72.0, 57.2, 40.3, 39.5, 36.2, 33.8, 33.6, 26.1, 18.2, 14.4, 12.1, -3.7, -3.8, -3.9, -4.0; IR (film) 2940, 1500, 1250, 1060, 830 cm$^{-1}$; MS (FAB) $m/e$ 733.4699 (733.4662 calcd for $C_{42}H_{70}O_5Si_2Na$); $[\alpha]^{23}_D$ -62.40 ($c$ 3.11, $CHCl_3$).

**Hydrogenation and Debenzylation of 31. Preparation of Diol 33.** A solution of **31** (0.045 g, 0.066 mmol) and EtOH (5 mL) was treated with Raney nickel (ca. 30 mg), and the resulting mixture was stirred for 30 min. The reaction mixture was then filtered and the filtrate concentrated. The residue was taken up in EtOAc (5 mL) and subjected to hydrogenation (balloon) over Pt (from $PtO_2$, ca. 10 mg) for 45 min. The reaction mixture was then filtered and the filtrate concentrated. The crude isolate was taken up in EtOAc (5 mL) and subjected to hydrogenation (balloon) over Pd/C (10% Pd on carbon, ca. 25 mg) for 6 h. At this time, the reaction mixture was filtered and the filtrate concentrated. The crude material was purified by chromatography (silica gel, 240–400 mesh, 3:1 hexanes/EtOAc) providing 0.023 g (66%) of **33** as a colorless oil: $^1$H NMR (490 MHz, $CDCl_3$) $\delta$ 3.85 (m, 1 H), 3.78 (dt, $J$ = 4.0, 11.0 Hz, 1 H), 3.68 (dt, $J$ = 3.2, 8.5 Hz, 1 H), 3.53 (m, 1 H), 3.45–3.35 (m, 1 H), 3.40 (s, 3 H), 2.95 (ddd, $J$ = 4.3, 8.8, 11.2 Hz, 1 H), 2.65 (br s, 1 H), 2.27 (dd, $J$ = 4.0, 6.9 Hz, 1 H), 2.10 (dq, $J$ = 4.6, 12.4 Hz, 1 H), 2.01 (dq, $J$ = 4.5, 12.9 Hz, 1 H), 2.82 (m, 1 H), 2.75–2.65 (m, 2 H), 1.63–1.55 (m, 1 H), 1.46 (ddd, $J$ = 3.3, 6.3, 14.3 Hz, 1 H), 2.42–2.25 (m, 2 H), 2.13 (m, 2 H), 1.00 (d, $J$ = 7.0 Hz, 3 H), 0.98–0.80 (m, 18 H), 0.86 (d, $J$ = 6.8 Hz, 3 H), 0.72 (app q, $J$ = 11.8 Hz, 1 H), 0.10 (d, $J$ = 2.9 Hz, 6 H), 0.07 (d, $J$ = 3.9 Hz, 6 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 84.6, 74.3, 74.0, 73.9, 65.0, 56.4, 40.0, 39.7, 36.5, 35.8, 34.7, 33.4, 31.5, 31.3, 25.9, 18.1, 14.1, 13.2, -4.0, -4.2, -4.3; IR ($CDCl_3$) 2910, 2900, 1440, 1240, 1080, 1100 cm$^{-1}$; MS (FAB) $m/e$ 533.4071 (533.4059 calcd for $C_{28}H_{60}O_5Si_2$ + H); $[\alpha]^{23}_D$ -25.20 ($c$ 1.4, $CHCl_3$).

**Selective Oxidation of Diol 33. Preparation of Aldehyde 34.** A solution of diol **33** (0.029 g, 0.055 mmol) and benzene (0.5 mL) was allowed to react with $Ru(Ph_3P)_3Cl_2$ (0.052 g, 0.55 mmol) at room temperature. After 12 h, an additional charge of $Ru(Ph_3P)_3Cl_2$ was added. After 6 h, the reaction mixture was passed through a plug of silica gel (2:1 hexanes/EtOAc). The fractions that contained the desired aldehyde were pooled and concentrated. The crude residue was purified by chromatography (silica gel, 240–400 mesh, 4:1 hexanes/EtOAc) giving 0.021 g (73%) of **34** as a yellow oil: $^1$H NMR (490 MHz $CDCl_3$) $\delta$ 9.73 (d, $J$ = 1.5 Hz, 1 H), 4.17 (app quintet, $J$ = 3.5 Hz, 1 H), 3.74 (dt, $J$ = 2.8, 8.6 Hz, 1 H), 3.45–3.35 (m, 1 H), 3.41 (s, 3 H), 2.95 (ddd, $J$ = 4.3, 8.8, 11.2 Hz, 1 H), 2.64 (br s, 1 H), 2.58 (m, 1 H), 2.23 (m, 1 H), 2.05 (m, 1 H), 1.73 (m, 2 H), 1.53 (m, 1 H), 1.45–1.25 (m, 5 H), 1.10 (d, $J$ = 6.9 Hz, 3 H), 1.0 (m, 1 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.83 (d, $J$ = 6.8 Hz, 3 H), 0.75 (m, 1 H), 0.10 (d, $J$ = 8.1 Hz, 6 H), 0.07 (d, $J$ = 4.3 Hz, 6 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 203.9, 84.6, 74.0, 73.3, 70.9, 56.4, 52.9, 39.9, 37.4, 36.0, 34.7, 33.3, 31.3, 25.9, 25.8, 18.0, 14.1, 9.2, -3.9, -4.0, -4.3; IR ($CDCl_3$) 2970, 1720, 1260, 1060, 850 cm$^{-1}$; $[\alpha]^{23}_D$ -23.3° ($c$ 0.73, $CHCl_3$).

**Preparation of Enoate 36.** A solution of **34** (0.019 g, 0.037 mmol) and toluene (0.5 mL) was allowed to react with (carbomethoxyethylidene)triphenylphosphorane (**35**; 0.089 g, 0.256 mmol) at 80 °C for 36 h. The solution was then cooled and concentrated. The crude residue was purified by chromatography (silica gel, 240–400 mesh, 4:1 hexanes/EtOAc) giving 0.014 g (64%) of **36** as a colorless oil: $^1$H NMR (490 MHz, $CDCl_3$) $\delta$ 6.67 (dd, $J$ = 1.4, 9.9 Hz, 1 H), 3.72 (s, 3 H), 3.68 (dd, $J$ = 5.3, 8.5 Hz, 1 H), 3.64 (m, 1 H), 3.42–3.37 (m, 1 H), 3.40 (m, 3 H), 2.96 (ddd, $J$ = 4.3, 8.8, 11.2 Hz, 1 H), 2.66 (m, 1 H), 2.10 (m, 1 H), 2.04 (m, 1 H), 1.86 (d, $J$ = 1.4 Hz, 3 H), 1.73–1.70 (m, 2 H), 1.41–1.24 (m, 3 H), 1.11 (m, 2 H), 1.00 (d, $J$ = 6.9 Hz, 3 H), 0.95–0.8 (m, 2 H), 0.91 (s, 9 H), 0.85 (s, 9 H), 0.83 (d, $J$ = 6.8 Hz, 3 H), 0.72 (m, 1 H), 0.10 (d, $J$ = 8.2 Hz, 6 H), 0.03 (d, $J$ = 9.2 Hz, 6 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 168.7, 144.2, 127.6, 84.7, 74.1, 73.7, 73.1, 56.5,

51.7, 39.7, 36.9, 36.0, 34.8, 33.4, 31.4, 25.9, 25.8, 18.2, 18.1, 14.7, 14.6, 12.8, -3.9, -4.1, -4.3; IR ($CHCl_3$) 2920, 2860, 1705, 1460, 1260, 1090 $cm^{-1}$; MS (FAB) *m/e* 601.4328 (601.4321 calcd for $C_{32}H_{64}O_6Si_2$ + H); $[\alpha]^{23}_D$ -21.1° (*c* 1.4, $CHCl_3$).

**Structure Proof for Diol 21. Preparation of Dibenzyl Ether 37.** Diol **21** (0.080 g, 0.288 mmol) was dissolved in 2-methoxypropene (5 mL). The resulting solution was treated with Amberlyst -15 (ca. 100 mg) and then stirred at room temperature for 2.5 h. At this time, the mixture was filtered and concentrated. The crude isolate was then taken up in a 1:1 mixture of methanol and $CH_2Cl_2$ (5 mL) and treated at -78 °C with ozone until the solution remained blue. At this point, the reaction was degassed with argon and treated with $NaBH_4$ (ca. 100 mg). After being stirred at room temperature for 2 h, the reaction mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$. The organic material was dried ($K_2CO_3$) and concentrated. The crude material was taken up in DMF (0.5 mL) and treated with benzyl bromide (46 mL, 0.39 mmol), $Bu_4NI$ (cat.), and NaH (ca. 50 mg of a 60% dispersion in oil). This mixture was maintained at room temperature for 16 h. The reaction was quenched with $H_2O$ (10 mL), and the resulting mixture was extracted with hexanes. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (silica gel, 240-400 mesh, 10:1 hexanes/EtOAc) to provide 0.050 g of **37** (47%) as a pure colorless oil: $^1H$ NMR (250 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5 H), 4.50 (s, 4 H), 3.72 (app q, *J* = 8.0 Hz, 2 H), 3.53 (dd, *J* = 4.5, 9.0 Hz, 2 H), 3.38 (dd, *J* = 6.3, 9.0 Hz, 2 H), 1.85 (m, 2 H), 1.62 (app t, *J* = 8.0 Hz, 2 H), 1.30 (s, 6 H), 0.96 (d, *J* = 6.7 Hz, 6 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) δ 138.9, 128.3, 127.5, 127.4, 100.3, 73.1, 72.2, 67.9, 38.7, 34.0, 24.4, 12.8; IR (film) 2900, 1450, 1380, 1230, 1100 $cm^{-1}$; MS (EI) *m/e* 397 ($M^+ - CH_3$); $[\alpha]^{23}_D$ -13.7° (*c* 0.35, $CHCl_3$).

**Acknowledgment.** This research was supported by PHS Grant AI 16943. An NSF Postdoctoral Fellowship (CHE-8907478) to M.J.F. and an MEC/Fulbright Fellowship (FU89 10568484) to J.J. are gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

**Registry No.** **1**, 53123-88-9; **5**, 135708-74-6; **6**, 135708-83-7; α-**8**, 67968-51-8; β-**8**, 131615-73-1; α-**9**, 126373-46-4; β-**9**, 135818-56-3; α-**10**, 18933-65-8; β-**10**, 135708-66-6; α-**11**, 135708-67-7; β-**11**, 135708-68-8; α-**12**, 135708-69-9; β-**12**, 135708-70-2; α-**13**, 135708-71-3; β-**13**, 135708-72-4; **14**, 135708-73-5; *anti*-**16a**, 94233-74-6; *syn*-**16a**, 94233-73-5; *anti*-**16b**, 135708-75-7; *syn*-**16b**, 135708-76-8; α-**17**, 135708-77-9; β-**17**, 135708-78-0; **18**, 99687-40-8; **21**, 135708-79-1; **22**, 135708-80-4; **23**, 135708-81-5; **24**, 135708-82-6; **25**, 135708-84-8; **26**, 135708-85-9; **27** (isomer 1), 135708-86-0; **27** (isomer 2), 135818-57-4; **28** (isomer 1), 135708-87-1; **28** (isomer 2), 135818-58-5; **29** (isomer 1), 135708-88-2; **29** (isomer 2), 135818-59-6; **30** (isomer 1), 135708-89-3; **30** (isomer 2), 135818-60-9; **31**, 135708-90-6; **33**, 135708-91-7; **34**, 135708-92-8; **35**, 2605-68-7; **36**, 135708-93-9; **37**, 135734-22-4.

**Supplementary Material Available:** NMR spectra for compounds **5**, **6**, **21-25**, **31**, **33**, **34**, **36**, and **37** (12 pages). Ordering information is given on any current masthead page.

# Application of the Ibuka-Yamamoto Reaction to a Problem in Stereochemical Communication: A Strategy for the Stereospecific Synthesis and Stabilization of the Triene Substructure of Rapamycin through Sulfone Substitution

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*Received April 15, 1991*

The aldehydes **49** and **55** corresponding to carbons 13-30 in a projected total synthesis of rapamycin have been synthesized. The LACDAC technology was used to elaborate dithiane enal **5**. The aldehyde **4** was synthesized from D-(+)-glucose. A critical element of that construction involved cuprate-induced displacement reactions on enoates **7** and **8** (see formation of esters **9a** and **9b**) to correlate the stereochemistry of carbons 8 and 12. The feasibility of conducting a Nozaki-Kishi reaction between iodosulfone **6** and aldehyde **4** was a major simplification. Julia coupling between sulfone **5** and aldehyde **43** was followed by acetylation and elimination of acetic acid. The triene sulfone **54** was obtained stereospecifically. The $C_4$ sulfone linkage is a considerable stabilizing element on the $C_1$-$C_6$ triene. Its presence allows for removal of the dithiane linkage (see formation of aldehyde **55**). Cleavage of the sulfone is accomplished with sodium analgam without reduction of an aldehyde function at $C_{30}$ (see formation of **49**).

## Background of the Problem and Synthetic Planning

In the preceding paper,[1] we reviewed background issues concerning the immunosuppressant rapamycin (**1**)[2] and reported the synthesis of a major segment of the molecule containing $C_{47}$-$C_{28}$ (see compound **2**).[3] Below, we describe the outcome of a program that focused on generalized system **3**, encompassing $C_{30}$-$C_{13}$. In the preliminary stages, the oxygen protecting groups could not be specified and the nature of the acyl carbon at $C_{30}$ was not formulated in detail. To converge on rapamycin, it would be necessary to interpolate the $C_{29}$ methine center (bearing a methoxy group) between $C_{30}$ of **3** and $C_{28}$ of **2**. It would also be necessary to introduce $C_{14}$ and $C_{15}$ as a "$C_2$ fragment" (presumably via an aldehyde ultimately derived from $C_{13}$)[3,4]

(1) Preceding paper in this issue.
(2) (a) Sehgal, S. N.; Baker, H.; Vézina, C. *J. Antibiot.* **1975**, *28*, 727. (b) Vézina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721. (c) Findlay, J. A.; Radics, L. *Can. J. Chem.* **1980**, *58*, 579. (d) Swindells, D. C. N.; White, P. S.; Findlay, J. A. *Can. J. Chem.* **1978**, *56*, 2491.

(3) The numbering system for rapamycin has been previously defined. See ref 2c.

0022-3263/91/1956-5834$02.50/0 