JOC Article

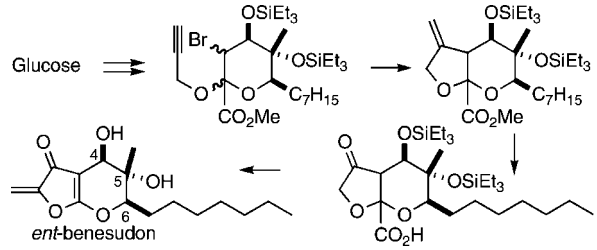
The Naturally Occurring Ketene Acetal Benesudon: Total Synthesis and Assignment of Relative and Absolute Stereochemistry

Derrick L. J. Clive,* Minaruzzaman, and Haikang Yang

Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

derrick.clive@ualberta.ca

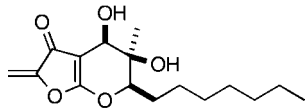
Received May 15, 2008



The densely functionalized ketene acetal benesudon, which is a bioactive fungal metabolite, was synthesized from D-glucose by a route involving radical cyclization to form the five-membered ring, and oxidative decarboxylation to generate the key central double bond. The originally suggested stereochemistry for the quaternary center C(5) must be revised, as both C(5) epimers were prepared and a comparison with an authentic sample was made. The absolute configuration of benesudon is 4*S*,5*R*,6*S*.

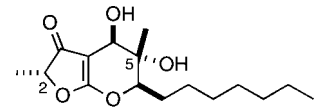
Introduction

Benesudon, originally assigned the structure and relative stereochemistry shown in **1**, is a metabolite isolated from an uncommon terrestrial fungus.[1] The substance shows antibacterial and antifungal activity and has a cytotoxic effect with IC_{90} values of 1−2 μg/mL.[1] Although structure **1** is compact, it still incorporates several features within its small framework: ketene acetal, α-methylene ketone, enol ether, and vinylogous ester subunits are readily discernible and are also interrelated.



1

Assignment of the gross structure was made by application of appropriate spectroscopic techniques, especially ^{1}H and ^{13}C NMR measurements, and the relative stereochemistry shown was supported by the observed nuclear Overhauser effects. However, during our synthetic work, the isolation and structure determination of a related compound—aigialone **2**—was reported.[2] This substance, which is a metabolite of a marine fungus, is crystalline and its relative stereochemistry was established by X-ray analysis. Apart from the presence of a methyl group at C(2) instead of the methylene of benesudon, the noteworthy feature of aigialone is the relative stereochemistry, which differs at C(5) from that suggested for benesudon. The X-ray data also showed that in the solid state the new metabolite has the two hydroxyl groups and the heptyl chain pseudoaxial, and nuclear Overhauser data for deuteriochloroform solutions could be rationalized on the basis of this unusual conformation. The two compounds **1** and **2** were obtained from different organisms and, while the X-ray data for **2** suggested the need for stereochemical revision of structure **1**, we did not regard the evidence as compelling and so we continued with our route to **1**; however, our work showed that revision is indeed required.[3]



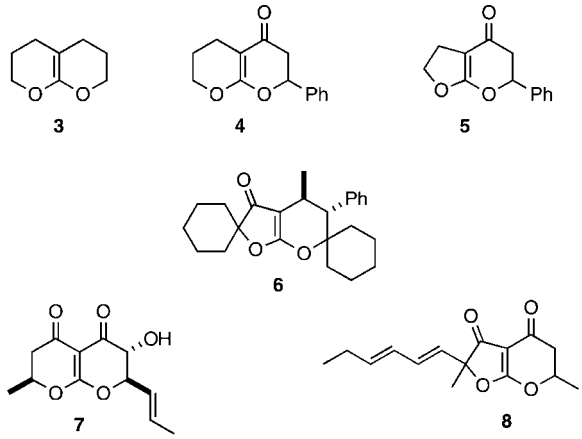
2

The structure type represented by benesudon is rare, not only among natural products but also in its own right, and an examination of both the Beilstein and SciFinder Scholar databases for ketene acetals embedded within bicyclic systems retrieves very few examples besides benzo-fused compounds (i.e., chromones) and γ-pyranones. The only relevant substances we have been able to locate, apart from model compounds made

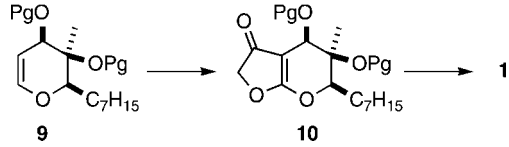
(1) Thines, E.; Arendholz, W.-R.; Anke, H.; Sterner, O. *J. Antibiot.* **1997**, *50*, 13–17.

10.1021/jo801028y CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/02/2008

SCHEME 1. Bicyclic Ketene Acetals



SCHEME 2. Initial Plan

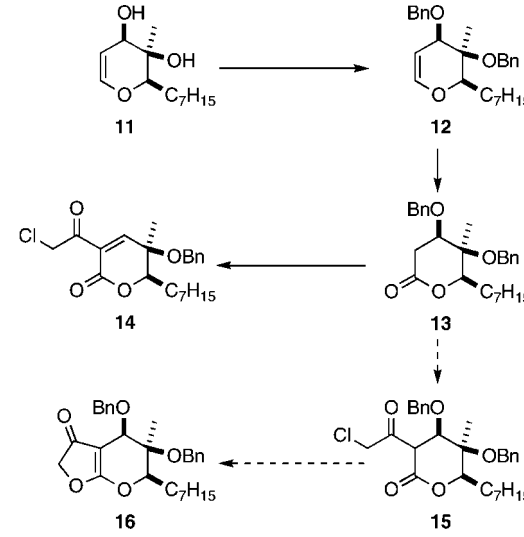


during our own studies, are those shown in Scheme 1. The ketene acetals **3**,[4] **4**,[5] **5**,[5] and **6**[6] are totally synthetic products, while **7**[7] (trichodion) and **8**[8] (cyclogregatin) were isolated from fungi. The former natural product is an inhibitor of inflammatory signal transduction pathways,[7a] and the latter has weak antimicrobial, antifungal, and cytotoxic activity. Compounds **3**−**5**, **7**, and **8** were known before we started our synthetic work, while **6**, which is formed by a complicated rearrangement, was reported after[9] we had begun. Where the carbonyl group resides within a six-membered ring, as in the relatively simple structures **4** and **5**, synthetic access by Diels−Alder cycloaddition is straightforward,[5] but the presence of a carbonyl group in the five-membered ring makes the identification of potential synthetic routes more complicated; no general approaches were available when we started and, as far as we are aware, the only such method is that developed in the present investigation.

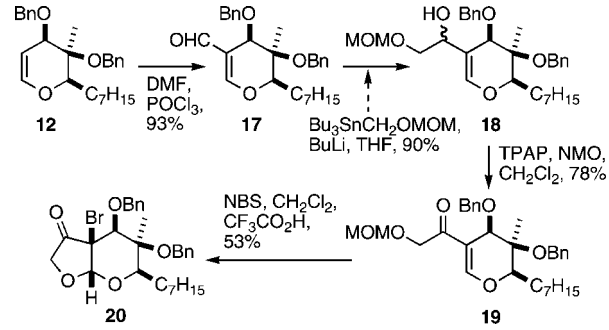
Results and Discussion

Initial Approaches. In our initial studies we underestimated the difficulties we would encounter in trying to introduce the central double bond that is characteristic of benesudon. Our first approach was based on a compound of type **9** onto which we hoped to build a five-membered ring (**9** → **10**, Scheme 2). From that point, methylenation and deprotection would generate the target. To simplify our work we decided to use methyl α-D-glucopyranoside as the source of the six-membered ring **9**. This decision implies an arbitrary assumption that benesudon has the same absolute configuration as D-glucose at the corresponding asymmetric centers.

SCHEME 3. Attempted Acylation of a δ-Lactone



SCHEME 4. Formation of the Five-Membered Ring without the Central Double Bond

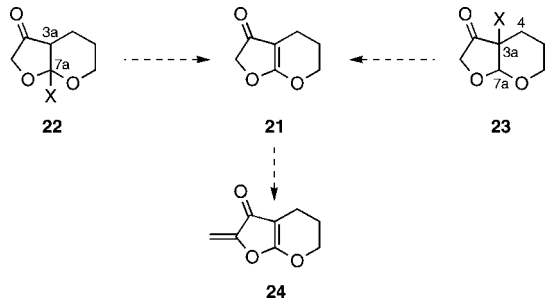


With this plan in mind, the diol **11**, whose synthesis from D-glucose is described later, was protected by benzylation and then oxidized to the lactone **13**. Deprotonation with LDA at −78 °C[10] and treatment with $ClCH_2COCl$ did effect acylation, but we were unable to prevent loss of the secondary benzyloxy group so that the product we isolated was the enone **14**. Our intention had been to explore the pathway **13** → **15** → **16**, but this route was blocked by the ready expulsion of the benzyloxy group (Scheme 3).

Our next approach was again based on **12**, but this time the compound was subjected to Vilsmeier−Haack formylation (Scheme 4, **12** → **17**), and the product was exposed to the action of $MeOCH_2OCH_2Li$, generated in situ from $MeOCH_2OCH_2SnBu_3$[11] and BuLi. Oxidation of the resulting alcohols with TPAP/NMO produced ketone **19**, and treatment with NBS and CF_3CO_2H generated the cyclized product **20** in 53% yield. While the gross structure of **20** is clear from its NMR spectra, the ring fusion stereochemistry is a tentative assignment; cis ring fusion would be expected but whether the bromine is cis or trans to the adjacent benzyloxy group was not estab-

(2) Vongvilai, P.; Isaka, M.; Kittakoop, P.; Srikitikulchai, P.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2004**, *67*, 457–460.
(3) Preliminary communication: Clive, D. L. J.; Minaruzzaman, *Org. Lett.* **2007**, *9*, 5315–5317.
(4) McElvain, S. M.; McKay, G. R., Jr *J. Am. Chem. Soc.* **1955**, *77*, 5601–5606.
(5) Sestelo, J. P.; Real, M. M.; Sarandeses, L. A. *J. Org. Chem.* **2001**, *66*, 1395–1402.
(6) Schobert, R.; Bieser, A.; Mullen, G.; Gordon, G. *Tetrahedron Lett.* **2005**, *46*, 5459–5462.
(7) (a) Erkel, G.; Retner, J.; Anke, T.; Sterner, O. *J. Antibiot.* **2000**, *53*, 1401–1404. (b) Erkel, G. *FEBS Lett.* **2000**, *477*, 219–223. (c) Bashyal, B. P.; Wijeratne, E. M. K.; Faeth, S. H.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2005**, *68*, 724–728.
(8) Anke, H.; Casser, I.; Schrage, M.; Steglich, W. *J. Antibiot.* **1988**, *41*, 1681–1684.
(9) Clive, D. L. J.; Minaruzzaman; Yang, H. *Org. Lett.* **2005**, *7*, 5581–5583.
(10) Cf.: Mckay, C.; Simpson, T. J.; Willis, C. L.; Forrest, A. K.; O'Hanlon, P. J. *Chem. Commun.* **2000**, 1109–1110.
(11) (a) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806–810. (b) Still, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.

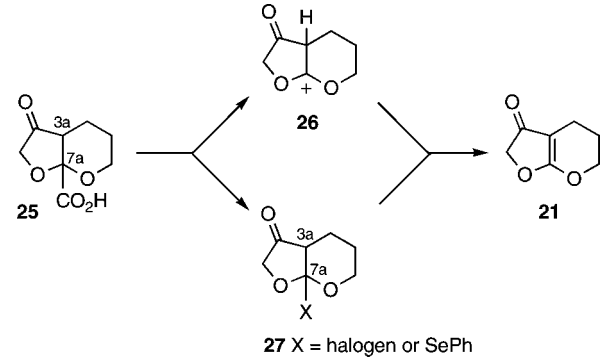
SCHEME 5. Potential Routes to the Core Structure 21



lished.[12] With the bicyclic skeleton in hand we then tried to introduce the central double bond, but all attempts to this end were unsuccessful,[13] and we were eventually forced to adopt the conservative approach of studying a simple model compound in the hope of being able to devise a robust route to the ketene acetal core structure characteristic of benesudon. Accordingly, our target became the model **21** (Scheme 5), which we expected would be easily convertible into the α-methylene ketene acetal **24**.

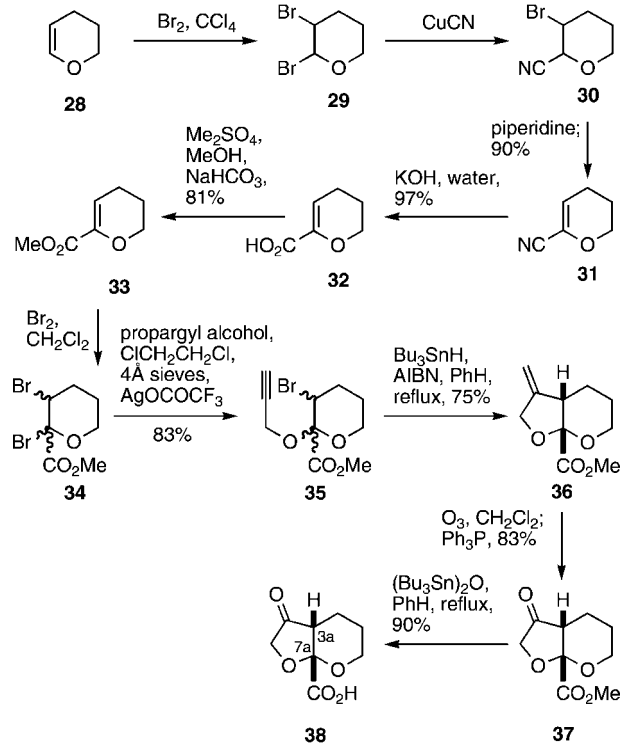
Synthesis of the Core Structure. In principle, **21** should be accessible from compounds of type **22** or **23** by a proper choice of the substituent X. The stereochemical requirements of the two routes depend on the nature of X. If this group is PhSe, then X and the adjacent ring fusion hydrogen must be cis, while if X is a halogen then the ring fusion stereochemistry should preferably be trans so as to allow for an anti elimination pathway. However, there is an additional factor in that for intermediates of type **23** the group X should also have a relative stereochemistry with respect to the substituent that will be at C(4) such that elimination toward C(4) is mechanistically blocked. If X is a heteroatom (e.g., as in SePh) then compounds of type **22** might be difficult to handle because of their inherent lability. This disadvantage for routes via **22** is offset, however, by the fact that **22** requires at most only one stereochemical restriction—the relationship of X to the adjacent ring fusion hydrogen, while for **23** the stereochemical relationship to two hydrogens—those at both C(4) and C(7a)—must be considered. In the event, our experimental work leading to the model compound **21** was based exclusively on an approach via **22**, and we decided to set X = CO_2H. This choice would offer the possibility of replacing the carboxyl group by a halogen or by PhSe (Scheme 6, **25** → **27**), using the derived Barton ester, and might also serve directly for introduction of the C(3a)−C(7a) double bond by oxidative decarboxylation (Scheme 6, **25** → **26** → **21**).

SCHEME 6. Potential Methods for Generating the Ketene Acetal System



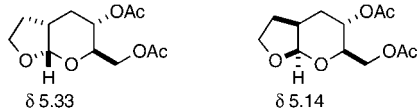
27 X = halogen or SePh

SCHEME 7. Preparation of Acid 38 for Oxidative Decarboxylation



Our route to **25** began with dihydropyran, which was converted, following a published method,[15] into the unsaturated acid **32** (Scheme 7). Base hydrolysis and esterification then gave ester **33**. Reaction with Br_2 formed the dibromides **34** and addition to a mixture of propargyl alcohol, 4Å molecular sieves, and $AgOCOCF_3$[16] provided the bromoethers **35**. These are correctly constituted for radical cyclization, and reaction with Bu_3SnH in the presence of AIBN brought about the desired 5-*exo digonal* closure (**35** → **36**). Ozonolysis then gave ketone **37**. At this point, we had to hydrolyze the ester group in **37**,

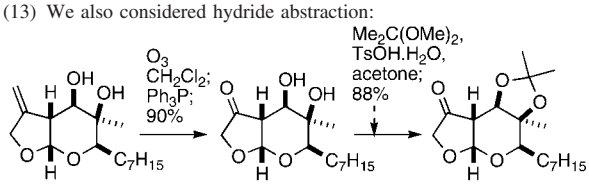
(12) The chemical shift of the acetal **H** in **20** is 5.45 ppm. The two reference compounds **i** and **ii** shown below have the indicated chemical shifts for the acetal **H**: De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1988**, *29*, 6585–6588.



δ 5.33 δ 5.14

i **ii**

(13) We also considered hydride abstraction:



iii **iv** **v**

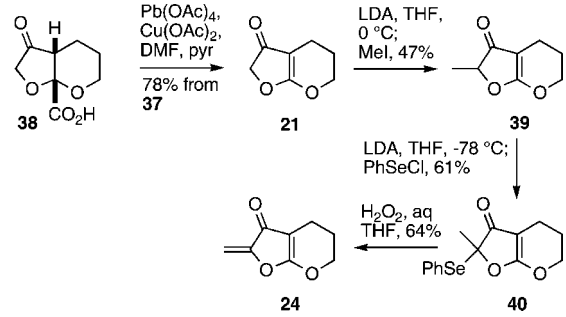
Treatment of **v** with Ph_3CBF_4 (see ref 14) produced a complex mixture. The structure of **iii** was confirmed by X-ray analysis. For preparation of **iii**, see the Supporting Information.

(14) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542–552.

(15) Hoffmann, H. M. R.; Giesel, K.; Lies, R.; Ismail, Z. M. *Synthesis* **1986**, 548–551.

(16) Paulsen, H.; Wulff, A.; Brenken, M. *Liebigs Ann. Chem.* **1991**, 1127–1145.

SCHEME 8. Formation of the Core Structure of Benesudon



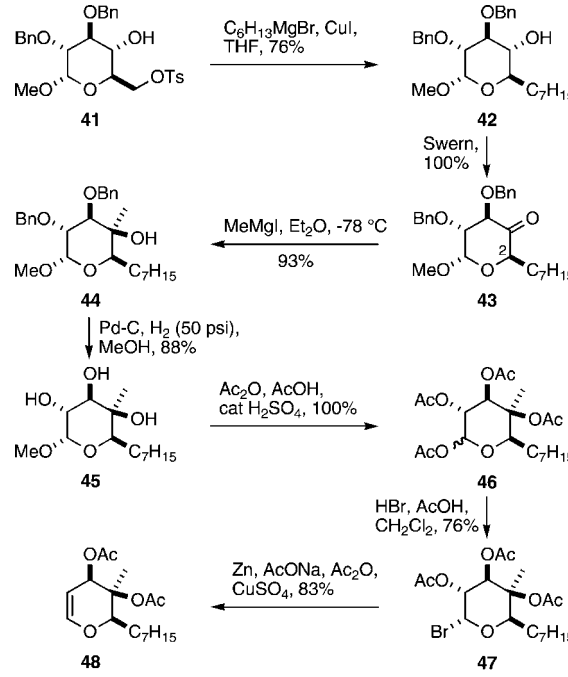
but this initially proved to be troublesome, and experiments with LiOH in aqueous MeOH were unsuccessful. However, when $(Bu_3Sn)_2O$[17] was eventually tried the reaction worked smoothly (ca. 90%), although the product **38** was not very stable and was best used within an hour of its isolation.

Having obtained the acid **38** we were now in a position to examine the replacement of the carboxyl by PhSe, PhS, or a 2-pyridylthio group,[18] so that oxidation via a selenoxide or sulfoxide would generate the crucial C(3a)−C(7a) double bond. Surprisingly, experiments directed to this end were unpromising and so we had to investigate the remaining pathway of oxidative decarboxylation, using $Pb(OAc)_4$ in the presence of a cupric salt.[19] Our first experiment involved treating the acid with $Pb(OAc)_4$ and $Cu(OAc)_2 \cdot H_2O$ in the presence of pyridine under conditions close to those reported in the literature for oxidative decarboxylation[19a] and, although the yield was very low, a small amount of **21** was indeed isolated (Scheme 8). We then repeated the experiment a number of times, varying the conditions slightly in each run, until we found a reliable procedure that gave the desired product in satisfactory yield (78% from ester **37**). In this optimized method, $Cu(OAc)_2 \cdot H_2O$ is added to a solution of freshly prepared carboxylic acid **38** in dry PhH, followed after a few minutes by addition at 30 min intervals, and in the dark, of several portions of $Pb(OAc)_4$; finally, the mixture is refluxed.

To construct the α-methylene unit, the ketene acetal **21** was first methylated in the standard way (Scheme 8, LDA, THF, MeI). The yield in this step was poor because of extensive bis-methylation, but little effort was made to optimize the conditions because this reaction was only part of a model study. Phenylselenation of **39** and selenoxide fragmentation then gave **24**, the core structure of benesudon, as a sharp-melting solid. Unlike its parent acid **38**, the complete core structure **24** was easily handled and did not seem to be noticeably sensitive.

Synthesis of Benesudon: Originally Proposed Stereochemistry. Once we had established a method for constructing the ketene acetal subunit we returned to the task of making the natural product and, as stated above, based our approach on the use of D-glucose. This was converted in four simple steps by known procedures into the tosylate **41**.[20] Homologation with the organocuprate made from *n*-$C_6H_{13}MgBr$ gave alcohol **42**,[20]

SCHEME 9. Preparation of the Key Glycal



which was then oxidized under Swern conditions (**42** → **43**). All the substituents of the ketone are equatorial and there was little danger of epimerization adjacent to the carbonyl group. Reaction with MeMgI in Et_2O afforded tertiary alcohol **44** with little of the epimeric alcohol, the ratio of the two being 24:1 in favor of **44**. Later in this work we would need the isomeric tertiary alcohol and it is fortunate that the stereochemical outcome of the reaction can be controlled by a proper choice of reagent (organolithium or Grignard reagent), solvent, and temperature.[21,22] In the present case, the choice of ethereal MeMgI was made by analogy with the stereochemistry reported[21] for reaction of a related ketone differing only in the nature of the C(2) substituent (CH_2OCPh_3 instead of C_7H_{15}). The correctness of our stereochemical assignment was established by X-ray analysis of a compound made from **44** during our initial studies.[23] Debenzylation by hydrogenolysis (**44** → **45**) and acetylation led to the tetraacetates **46**, and at this stage the anomeric acetoxy group was replaced by bromine in the standard way. Finally, Zn reduction produced glycal **48** (Scheme 9). This compound represents the portion of our target (**1**) onto which we planned to build the remainder of the ketene acetal, using methods developed in making the unsubstituted core structure.

In our model study, simple bromine addition and reaction with CuCN (Scheme 7, **28** → **32**) had served to introduce the nitrile group, but this method did not work when applied to **48** (or to the corresponding bis-*O*-benzyl analogue), and so a different approach was needed. Reaction of glycal **48** with NBS in MeOH gave the expected 2-bromoglucosides **49**, and the

(17) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *J. Org. Chem.* **1994**, *59*, 7259–7266.

(18) (a) Replacement of carboxyl by PhSe or PhS: Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Heterocycles* **1987**, *25*, 449–462. (b) Replacement of carboxyl by thiopyridyl unit: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.

(19) (a) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215–2226. (b) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279–421. (c) Kochi, A. J.; Bacha, J. D. *J. Org. Chem.* **1968**, *33*, 2746–2754. (d) Ogibin, Yu. N.; Katzin, M. I.; Nikishin, G. I. *Synthesis* **1974**, 889–890.

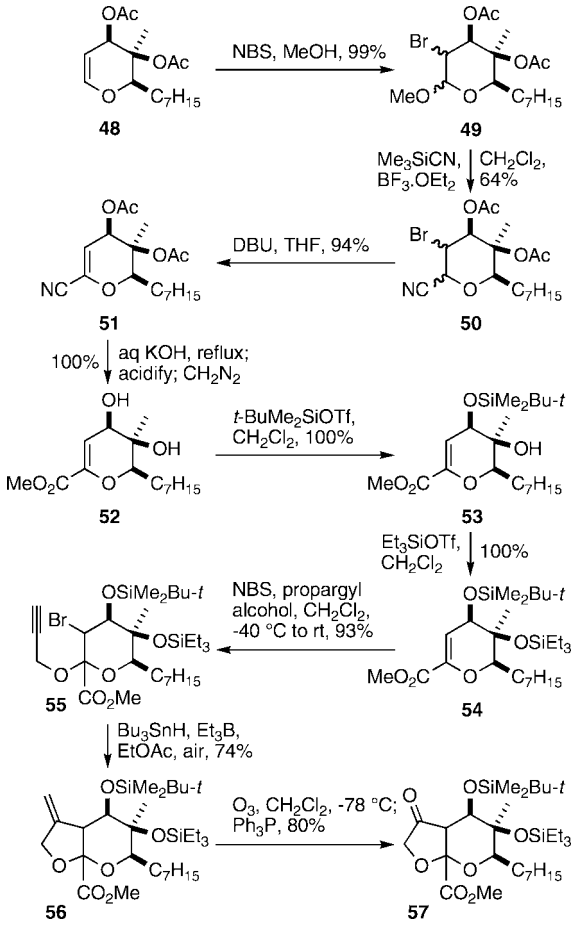
(20) (a) Toshima, H.; Sato, H.; Ichihara, A. *Tetrahedron* **1999**, *55*, 2581–2590. (b) Davis, N. J.; Flitsch, S. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 359–368.

(21) Cf.: Sato, K.; Kubo, K.; Hong, N.; Kodama, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 938–942.

(22) Cf.: Miljkovic, M.; Gligorijevic, M.; Satoh, T.; Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 1379–1384.

(23) See ref 13. Compound **iii**, whose structure was confirmed by X-ray analysis, was made from **44**. Hence the stereochemistry of **44** at the quaternary carbon is established.

SCHEME 10. Elaboration of Glycal 48

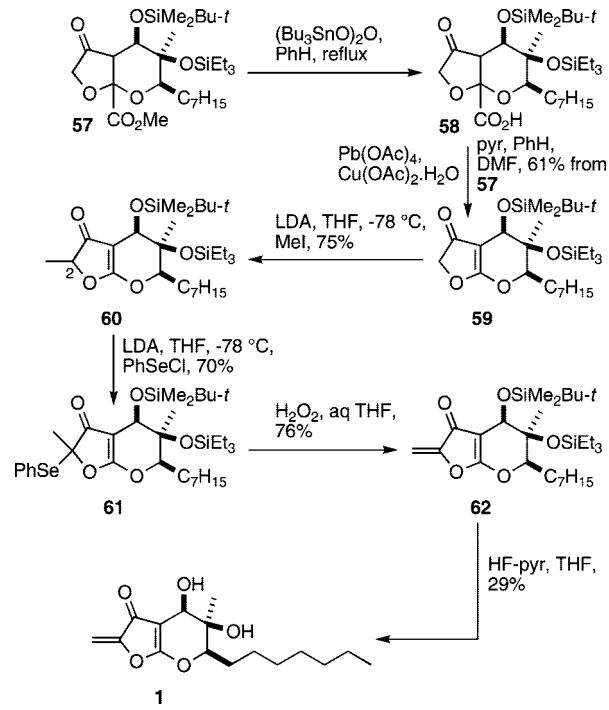


anomeric methoxy group was then replaced by reaction with Me_3SiCN in the presence of $BF_3 \cdot OEt_2$.[24] Base treatment now caused elimination to the unsaturated nitrile **51**. As in the model study, this was hydrolyzed with aqueous KOH and the resulting acid was methylated.

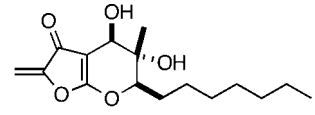
We initially intended to protect both hydroxyls of **52** as their *tert*-butyldimethylsilyl ethers, but only the secondary hydroxyl could be protected; the remaining tertiary hydroxyl was therefore masked as its triethylsilyl ether (**52** → **53** → **54**; Scheme 10). Next, to attach the acetylenic side chain we tried the method that had been successful in the preparation of the core structure, but this procedure did not work in the present case. However, after several trial experiments we were able to find conditions that did allow conversion of **54** into **55**; these involved use of propargyl alcohol and NBS in CH_2Cl_2. Likewise, the conditions previously used for the radical cyclization in making the core structure were also unsuccessful, but when we tried Bu_3SnH and Et_3B in the presence of air,[25] cyclization occurred satisfactorily (74%). Finally, ozonolysis took us to the point where the next critical step was introduction of the central double bond and, for this reaction (Scheme 11), both the tin oxide-mediated ester hydrolysis and the oxidative decarboxylation occurred satisfactorily under the conditions established in our route to the core structure. Methylation of ketone **59** under standard conditions then provided compound **60** as a single isomer whose stereochemistry at C(2) was not established. Phenylselenation

(24) (a) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528–529. (b) Sato, K.; Sasaki, M. *Org. Lett.* **2005**, *7*, 2441–2444.

SCHEME 11. Formation of the Originally Proposed Structure of Benesudon

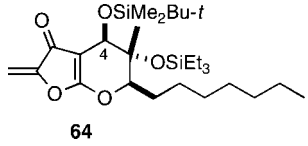


in the usual way proceeded without incident, as did the subsequent oxidation and fragmentation of the selenoxide, bringing the route to **62**, a protected version of the target. Removing the silicon protecting groups was troublesome and use of Bu_4NF in THF with or without AcOH was unsuccessful; it appears that the desired product **1** is sensitive to fluoride ion. Use of HF−pyridine was the most promising method and gave **1** in 29% yield. We did not optimize these conditions mainly because the NMR spectra, especially the ^{13}C NMR spectrum, of **1** differed significantly from those reported for natural benesudon. There was no doubt about the gross structure assigned to benesudon, and so only a stereochemical alteration was necessary, and the most likely candidate was **63** with a relative stereochemistry analogous to that of aigialone (**2**).



63

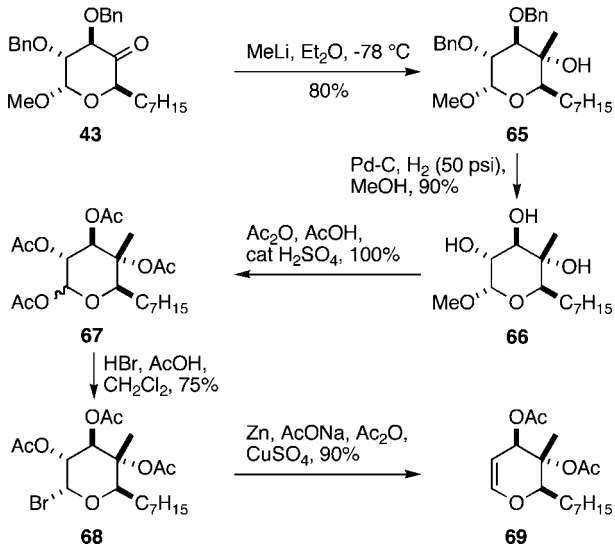
Synthesis of Benesudon. In principle, the route we had used to make **1** should be applicable to **63** because, as mentioned earlier, the stereochemical outcome of the addition of organometallic reagents to ketone **43** can be controlled, and this should be the only step that requires alteration. In the event, matters were not nearly so simple; conversion of ketone **43** to the tertiary alcohol with stereochemistry corresponding to **63** was readily achieved, but this stereochemical alteration exerted a profound influence on other reactions so that appreciable modification of the subsequent route was necessary. Moreover, the structure **63** appeared to be even more sensitive to fluoride ion than **1** and, although we were able to reach **64**,[26] it was impossible to remove the *t*-$BuMe_2Si$ group without destroying the material. Consequently, we had to repeat the whole sequence with a more labile protecting group for the C(4) hydroxyl and we selected



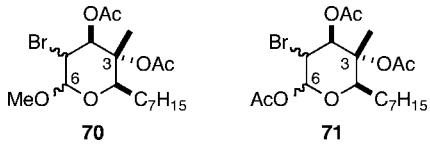
64

Et_3Si—a choice that proved just satisfactory. For this route (Scheme 12) we treated ketone **43** with MeLi in Et_2O and obtained **65** with opposite stereochemistry[21,22] to that produced by the action of MeMgI in the same solvent (cf. Scheme 9). As before, the benzyl groups were removed by hydrogenolysis, and then peracetylation, followed by treatment with HBr−AcOH gave the bromide **68**. This was converted into glycal **69** by reaction with Zn.

SCHEME 12. Preparation of the Key Glycal with Revised Stereochemistry



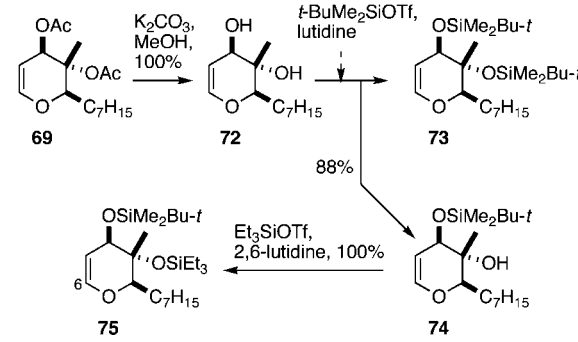
At this point our expectations that the route would follow closely what we had done before were quickly dispelled. Compound **69** was converted into methoxy bromides **70**[27] (as we had done in the series leading to **1**) but we were unable to replace the anomeric methoxy group by cyanide, using Me_3SiCN in the presence of Lewis acids. It could be replaced by an acetoxy group (to form **71**[28]), but even an acetoxy substituent at the anomeric position could not be replaced by cyanide in acceptable yield. We assume that there is a stereoelectronic effect exerted by the C(3) oxygen function that deactivates the anomeric position. Such effects have been observed before and studied extensively.[29] Their magnitude is strongest when the C(3) oxygen substituent is equatorial, which we assume to be the case with **70** and **71**.



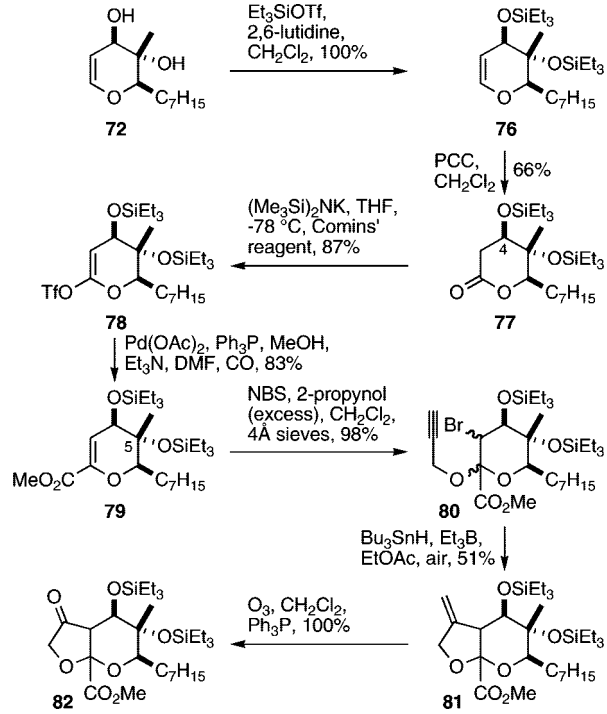
70 71

Our earlier system (**49**) presumably has this oxygen axial, and so is free from a large deactivating effect at C(6). In the present case the deactivation was sufficiently strong to thwart further progress in our intended route. We wondered if replacement of the acetyl group on the C(3) oxygen by a siloxy unit would result in a smaller degree of deactivation; accordingly, diacetate

SCHEME 13. Silylation of Diol 72



SCHEME 14. Elaboration of Glycal 72



69 was hydrolyzed and we tried to prepare **73** (Scheme 13), but obtained mainly **74**. The tertiary hydroxyl of **74** was therefore protected as its triethylsilyl ether (**75**), but with this compound also we could not introduce a nitrile group at C(6), using methods we had tried with the acetylated analogue **69**.

It was clear that a different procedure had to be developed to ultimately introduce an ester group at C(6). This was eventually achieved, starting from **75**, and we were then able to reach **64**, which, as mentioned earlier, could not be deprotected without destroying the compound. This experience caused us to select Et_3Si as the protecting group for *both* hydroxyls of **72**. The bis-silylation was easily achieved with $Et_3SiOSO_2CF_3$ (Scheme 14, **72** → **76**) and we then subjected **76** to the same procedures we had developed in making **64**.

Protection of both hydroxyl groups in **72** as triethylsilyl ethers has the added advantage that both hydroxyls are masked at the

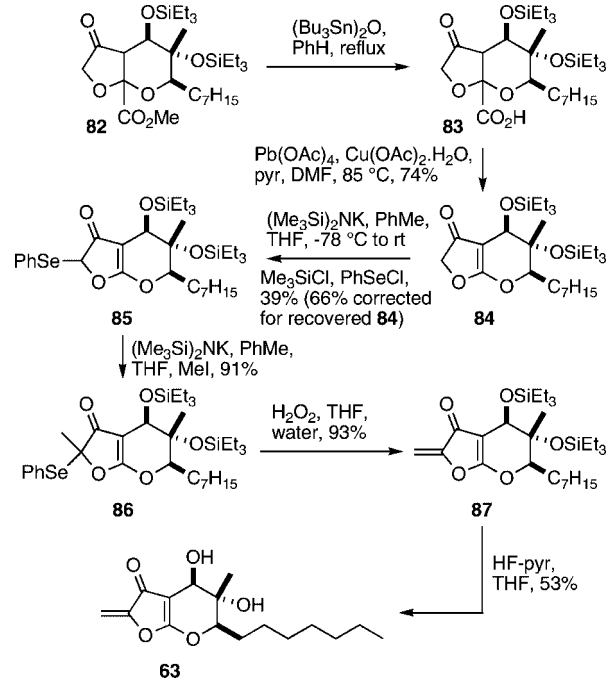
(25) Cf.: Yamazaki, O.; Yamaguchi, K.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 5440–5442.
(26) See the Supporting Information for a flow chart summarizing the route.
(27) Compound **70** was a mixture of isomers (two major isomers in a ratio of 3.5:1).
(28) Compound **71** was a mixture of two isomers (2:1).
(29) Cf.: (a) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259–265. (b) Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3419–3421.

same time. Oxidation with PCC then produced lactone **77**[30] in acceptable yield. We did not detect, but did not specifically look for, the product arising by elimination of the C(4) $OSiEt_3$ group and, in fact, lactone **77** was a stable and well-behaved compound. When the lactone was treated at a low temperature with $(Me_3Si)_2NK$ and then with the Comins' reagent 2-[*N*,*N*-bis(trifluoromethylsulfonylamino]pyridine[31] it was possible to isolate the desired enol triflate in good yield. Formation of an enolate from a β-oxygenated δ-lactone without loss of the oxygen substituent is unusual, and only a few cases appear to have been reported.[10,32,33] Palladium-mediated carbonylation[34] of **78** in the presence of MeOH then served to introduce the ester group, bringing the synthesis to **79**, which corresponds to **54** (Scheme 10) but has different forms of hydroxyl protection and the opposite stereochemistry at C(5). Introducing the propargyl unit at C(2) by bromoetherification, as had been done earlier in our route to **55** (Scheme 10), proved to be very troublesome until we recognized that a large excess of propargyl alcohol must be present and the best conditions involved the use of 1:1 propargyl alcohol−dichloromethane in the presence of NBS and powdered 4Å molecular sieves. Under these conditions the reaction worked well (**79** → **80**, 98%). Radical cyclization (**80** → **81**) under the same conditions used to make **56** (Bu_3SnH, Et_3B, air, EtOAc, room temperature), followed by ozonolysis, gave the keto ester **82**.

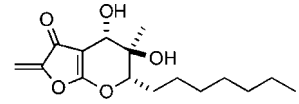
The ester group was hydrolyzed, using $(Bu_3Sn)_2O$, and the central double bond was formed by the oxidative decarboxylation that had been optimized for this task. In the present case, the yield from **82** was very satisfactory (74%). With ketene acetal **84** in hand, we had only to attach the exo methylene and remove the silyl groups. The first of these tasks proved more difficult than anticipated, because methylation of **84** led to extensive bis-methylation, and attempts to phenylselenate the monomethylated product that we were able to isolate gave very low yields (<20%). Therefore, we reversed the order of these two steps, but found initially that phenylselenation of **84** resulted in extensive bis-phenylselenation. This outcome is understandable by virtue of the fact that the first phenylseleno group facilitates proton exchange so as to generate a furanoid system. Fortunately, this difficulty could be largely suppressed by quenching the enolate derived from **84** with Me_3SiCl, followed by addition of PhSeCl. By this means it was possible to convert **84** into **85** in 39% yield together with what we assume to be the corresponding bis-phenylselenated product. The latter was converted back into **84** by treatment with Ph_3P in wet CH_2Cl_2, the overall yield of **85** then being 66% after correction for recovered **84**.

Once the phenylseleno group was in place, methylation worked well, as did the selenoxide elimination (**86** → **87**). Finally, application of the HF−pyridine method for desilylation gave the target structure **63** (Scheme 15).

SCHEME 15. Formation of *ent*-Benesudon



The ^1H and ^{13}C NMR spectra of **63** showed slight differences from the reported[1] data. Fortunately, the original sample of the natural product had been preserved at a low temperature and we were able to obtain this material. When we measured the spectra on our own instruments the results were identical with those obtained with synthetic **63**. However, the optical rotation of the two samples was different, the synthetic material being dextrorotatory with $[\alpha]_D$ +124.2 (*c* 0.11, $CHCl_3$) and the natural compound being levorotatory with $[\alpha]_D$ −120.5 (*c* 0.1, $CHCl_3$). Accordingly, natural benesudon has the 4*S*,5*R*,6*S* configuration shown in **88**, and the compound we had made is *ent*-benesudon.



88 (natural benesudon)

Conclusion

Our synthesis of *ent*-benesudon establishes the relative and absolute stereochemistry of the natural product. The method we have developed for constructing the unusual ketene acetal subunit is probably general.

Experimental Section

(3a*R*,7a*R*)-*rel*-Hexahydro-3-oxo-7a*H*-furo[2,3-*b*]pyran-7a-carboxylic Acid (38). $(Bu_3Sn)_2O$ (0.97 mL, 1.94 mmol) was added to a solution of **37** (96 mg, 0.48 mmol) in dry PhH (7.5 mL), and the solution was refluxed under N_2 for 5 h. The solvent was evaporated and EtOAc (10 mL) was added to the residue. The EtOAc solution was extracted with saturated aqueous $NaHCO_3$ (2 × 10 mL), and the aqueous extract was acidified to pH 1 (pH paper) with ice-cold 2 N hydrochloric acid and extracted with EtOAc (4 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated at room temperature. The crude acid **38** (80.4 mg, ca. 90%) was used immediately, without further purification: FTIR (CH_2Cl_2, cast) 3500−2500, 1766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43−1.54 (m, 2 H), 1.90−2.01 (m, 1 H), 2.16−2.26 (m, 1 H), 2.89 (dd, *J* =

(30) Rollin, P.; SinalAdy, P. *Carbohydr. Res.* **1981**, *98*, 139–142.
(31) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
(32) Cf.: (a) Mlynarski, J.; Banaszek, A. *Tetrahedron* **1999**, *55*, 2785–2794. (b) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467–5468.
(33) (a) For use of $Me_3SiOSO_2CF_3/Et_3N$ to prepare a ketene acetal from a δ-lactone with a β-siloxy group, see: Chao, Y.-s.; Hartman, G. D.; Halczenko, W.; Duggan, M. E.; Imagire, J. S.; Smith, R. L.; Pitzenberger, S. M.; Fitzpatrick, S. L.; Alberts, A. W.; Bostedor, R.; Germershausen, J. I.; Gilfillan, J. L.; Hunt, V. *J. Med. Chem.* **1992**, *35*, 3813–3821. (b) For use of an unprotected hydroxyl β to the carbonyl, see: Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Heterocycles* **2003**, *59*, 347–358. (c) Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2004**, *69*, 6294–6304.
(34) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109–1112.

6.3, 3.4 Hz, 1 H), 2.6−3.4 (br, 1 H), 3.70−3.77 (m, 1 H), 3.94−4.02 (m, 1 H), 4.27 (AB q, $\Delta\nu_{AB}$ = 25.2 Hz, J = 16.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.9 (t), 21.0 (t), 47.0 (d), 65.0 (t), 70.5 (t), 101.8 (s), 169.5 (s), 210.5 (s); exact mass (electrospray) m/z calcd for $C_8H_{11}O_5$ (M + H) 187.0601, found 187.0603.

5,6-Dihydro-4*H*-furo[2,3-*b*]pyran-3(2*H*)-one (21). $Cu(OAc)_2\cdot H_2O$ (56 mg, 0.28 mmol) was added to a stirred solution of the above crude acid **38** in dry PhH (2.5 mL) (N_2 atmosphere), and stirring was continued for 5 min. The flask was then wrapped in aluminum foil and $Pb(OAc)_4$ (118 mg, 0.27 mmol) was tipped in. Stirring was continued for 30 min, and another portion of $Pb(OAc)_4$ (55 mg, 0.13 mmol) was added, followed by PhH (1.5 mL). Stirring was again continued for 30 min and a further portion of $Pb(OAc)_4$ (88 mg, 0.20 mmol) was then added, followed by PhH (1 mL) and dry DMF (0.4 mL). The flask was fitted with a reflux condenser and flushed well with N_2 for 30 min (in some experiments, the apparatus was evacuated with the house vacuum and then filled with N_2, and the process was repeated twice more). The mixture was refluxed for 11 h (oil bath at 84 °C). The aluminum foil was removed, and refluxing was continued for 1 h. The resulting green solution was cooled to room temperature and evaporated to a thick oil, which was applied directly to a flash chromatography column made up with silica gel (1.5 × 26 cm). Flash chromatography, using 1:1 EtOAc−hexane and then pure EtOAc, gave **21** (52 mg, 78% over two steps) as a white solid: mp 60−62 °C; FTIR (CH_2Cl_2, cast) 1705, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91−1.99 (m, 2 H), 2.33 (t, J = 6.2 Hz, 2 H), 4.47 (apparent t, J = 5.1 Hz, 2 H), 4.52 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (t), 21.2 (t), 71.5 (t), 74.2 (t), 88.9 (s), 182.8 (s), 194.1 (s); exact mass m/z calcd for $C_7H_8O_3$ 140.0474, found 140.0473.

(2*R*,3*S*,4*R*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-heptyltetrahydro-6-methoxy-3-methyl-2*H*-pyran-3-ol (44). A solution of **43** (13.51 g, 30.71 mmol) in Et_2O (26 mL) was added dropwise over about 40 min to a stirred and cooled (−78 °C) mixture of MeMgI (3.0 M in Et_2O, 21.0 mL) in Et_2O (100 mL). Stirring at −78 °C was continued for 2.5 h. The mixture was diluted with saturated aqueous NH_4Cl (32 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 25 cm), using 1:5 EtOAc−hexane, gave **44** (13.0 g, 93%) as a yellow oil: $[\alpha]_D$ +45.4 (c 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 3500, 3063, 3030, 2953, 2925 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 6.9 Hz, 3 H), 1.14 (s, 3 H), 1.18−1.68 (m, 12 H), 2.18 (d, J = 1.6 Hz, 1 H), 3.36 (s, 3 H), 3.47 (d, J = 10.1 Hz, 1 H), 3.56 (d, J = 9.7 Hz, 1 H), 3.81 (dd, J = 9.6, 3.7 Hz, 1 H), 4.63 (d, J = 3.2 Hz, 1 H), 4.64 (d, J = 11.3 Hz, 1 H), 4.67 (AB q, J = 12.0 Hz, $\Delta\nu_{AB}$ = 46.7 Hz, 2 H), 5.01 (d, J = 10.9 Hz, 1 H), 7.24−7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (q), 22.1 (q), 22.6 (t), 26.4 (t), 27.6 (t), 29.2 (t), 29.6 (t), 31.8 (t), 55.1(q), 72.7 (d), 73.1 (t), 74.3 (s), 76.2 (t), 78.1 (d), 80.9 (d), 98.0 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 138.3 (s); exact mass (electrospray) m/z calcd for $C_{28}H_{40}NaO_5$ (M + Na) 479.2768, found 479.2771.

Acetic Acid (2*R*,3*S*,4*R*)-3-Acetoxy-2-heptyl-3-methyl-3,4-dihydro-2*H*-pyran-4-yl Ester (48). Zn dust (9.33 g) was tipped into a stirred solution of AcONa (11 g) and AcOH (15.6 mL) in water (22 mL), and saturated aqueous $CuSO_4$ (3 mL) was then added. The blue color disappeared, and a solution of **47** (1.32 g, 2.93 mmol) in Ac_2O (6 mL) was added at a fast dropwise rate. Stirring was continued for 2 h and the mixture was diluted with CH_2Cl_2 (25 mL) and filtered. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 16 cm), using 1:6 EtOAc−hexane, gave **48** (0.76 g, 83%) as a yellow oil: $[\alpha]_D$ −106.0 (c 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 2926, 2857, 1747, 1458, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 6.9 Hz, 3 H), 1.20−1.66 [m, including a singlet (3 H) at δ 1.58, 14 H in all], 1.83−1.93 (m, 1 H), 1.99 and 2.00 (s, 6 H), 4.08 (d, J = 10.9 Hz, 1 H), 4.90 (t, J = 10.2 Hz, 1 H), 5.38 (d, J = 5.3 Hz, 1 H), 6.26 (d, J = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 20.9 (q), 21.7 (q), 21.8(q), 22.6 (t), 26.4 (t), 26.9 (t), 29.2 (t), 29.4 (t), 31.8 (t), 67.2 (d), 78.2 (s), 79.4 (d), 98.3 (d), 143.9(d), 169.5 (s), 169.9 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{28}NaO_5$ (M + Na) 335.1829, found 335.1828.

Acetic Acid (2*R*,3*S*,4*S*)-4-Acetoxy-5-bromo-2-heptyltetrahydro-6-methoxy-3-methylpyran-3-yl Ester (49). A solution of **48** (0.250 g, 0.60 mmol) in dry MeOH (6 mL) was added dropwise to a stirred and cooled (−50 °C) solution of NBS (0.106 g, 0.60 mol) in dry MeOH (4 mL). The cooling bath was left in place but not recharged and stirring was continued for 19 h. Most of the MeOH was evaporated and the residue was diluted with Et_2O (20 mL). The resulting solution was washed with 10% aqueous $Na_2S_2O_3$ (15 mL) and water (15 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 22 cm), using 20% EtOAc−hexanes, gave **49** (0.339 g, 99%) as a mixture of isomers. The more polar isomer had the following: FTIR (neat) 2956, 2927, 2857, 1749, 1466, 1370, 1236, 1129, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.0 Hz, 3 H), 1.22−1.36 (m, 10 H), 1.58−1.67 [m, including a singlet at δ 1.52 (3 H), 4 H in all], 1.75−1.83 (m, 1 H), 2.09 (s, 3 H), 2.13 (s, 3 H), 3.41 (s, 2 H), 3.58 (s, 1 H), 3.73 (dt, J = 10.7, 1.2 Hz, 1 H), 4.13 (t, J = 3.7 Hz, 1 H), 4.95 (d, J = 3.5 Hz, 1 H), 5.30 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 20.3 (q), 20.8 (q), 22.4 (q), 22.6 (t), 26.3 (t), 27.6 (t), 29.3 (t), 29.4 (t), 31.8 (t), 46.8 (d), 55.7 (q), 71.3 (d), 75.9 (d), 80.0 (s), 100.6 (d), 169.6 (s), 169.7 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{31}{}^{79}BrNaO_6$ 445.11962, found 445.11978.

Acetic Acid (2*R*,3*S*,4*S*)-4-Acetoxy-5-bromo-6-cyano-2-heptyltetrahydro-3-methylpyran-3-yl Ester (50). Me_3SiCN (2.90 mL, 20.7 mmol), followed by $BF_3\cdot OEt_2$ (2.90 mL, 20.7 mmol), was added dropwise to a stirred and cooled (−78 °C) solution of bromoacetal **49** (1.30 g, 3.07 mmol) in dry CH_2Cl_2 (12 mL). The cold bath was left in place but not recharged and stirring was continued for 35 h. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and water (2 × 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 28 cm), using 1:6 EtOAc−hexanes, gave **50** (0.636 g, 64%) as a yellow oil, which was a mixture of two isomers: FTIR ($CHCl_3$, cast) 2956, 2928, 2857, 1754, 1466, 1437, 1368, 1231, 1202, 1140, 1094, 1050, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84−0.90 (m, 3 H), 1.23−1.36 (m, 10 H), 1.40−1.51 (m, 1 H), 1.59 (s, 2 H), 1.62−1.66 (m, 1 H), 1.74 (s, 1 H), 1.98 (s, 1 H), 2.07 (s, 2 H), 2.14 (s, 3 H), 3.72 (dd, J = 9.7, 2.2 Hz, 1 H), 4.30 (dd, J = 11.1, 5.8 Hz, 1 H), 5.04 (d, J = 5.8 Hz, 1 H), 5.22 (d, J = 11.1 Hz, 1 H); exact mass m/z calcd for $C_{16}H_{25}{}^{81}BrNO_4$ (M − C_2H_3O) 376.09464, found 376.09484.

Acetic Acid (2*R*,3*S*,4*R*)-4-Acetoxy-6-cyano-2-heptyl-3,4-dihydro-3-methyl-2*H*-pyran-3-yl Ester (51). DBU (0.250 mL, 1.85 mmol) was added dropwise to a stirred and cooled (0 °C) solution of bromonitrile **50** (0.636 g, 1.24 mmol) in dry THF (20 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h, by which time the solution had reached room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 × 15 cm), using 1:6 EtOAc−hexane, gave unsaturated nitrile **51** (0.480 g, 94%) as an oil: $[\alpha]_D$ −46.3 (c 0.38, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2970, 2928, 2858, 2237, 1752, 1645, 1373, 1241, 1161, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.24−1.40 (m, 10 H), 1.60 (s, 3 H), 1.64−1.73 (m, 1 H), 1.74−1.90 (m, 1 H), 2.045 (s, 3 H), 2.054 (s, 3 H), 4.19 (dt, J = 10.7, 1.8 Hz, 1 H), 5.49 (dd, J = 5.0, 1.4 Hz, 1 H), 5.76 (d, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 20.5 (q), 21.3 (q), 21.5 (q), 22.5 (t), 25.9 (t), 26.4 (t), 29.0 (t), 29.1 (t), 31.6 (t), 66.2 (d), 81.5 (d), 112.2 (d), 113.4 (s), 129.2 (s), 169.2 (s), 169.4 (s); exact mass m/z calcd for $C_{18}H_{27}NO_5$ 337.1889, found 337.1891.

(2*R*,3*R*,4*R*)-2-Heptyl-3,4-dihydro-3,4-dihydroxy-3-methyl-2*H*-pyran-6-carboxylic Acid Methyl Ester (52). KOH (4.0 g, 71.3 mmol) was added to a stirred solution of **51** (0.429 g) in water (62 mL)

and the mixture was refluxed (oil bath at 105−110 °C), the disappearance of the starting material being monitored by TLC (silica, 1:1 EtOAc−hexane). After 24 h another portion of KOH (0.385 g, 6.86 mmol) was added and refluxing was continued for 11 h (oil bath at 120−130 °C). At this stage the reaction was complete. The mixture was cooled to room temperature and then in an ice bath, and acidified to pH 1 with hydrochloric acid (2 N). The solution was saturated with solid NaCl and extracted with Et_2O (3 × 15 mL). The combined ether extracts were treated with ethereal CH_2N_2 until a yellow color persisted. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.25 × 22 cm), using 1:1 EtOAc−hexanes, gave unsaturated ester **52** (0.366 g, 100%) as a yellow oil: $[\alpha]_D$ +130.6 (*c* 0.19, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3446, 2954, 2926, 2857, 1733, 1653, 1438, 1373, 1267, 1140, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.24−1.38 (m, including a singlet, 11 H), 1.38−1.44 (m, 1 H), 1.64−1.74 (m, 2 H), 1.76−1.86 (m, 1 H), 2.0 (s, 1 H), 2.31 (d, J = 10.4 Hz, 1 H), 3.73 (dd, J = 10.0, 1.9 Hz, 1 H), 3.80 (s, 3 H), 4.04 (dd, J = 10.3, 2.4 Hz, 1 H), 5.95 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 20.8 (q), 22.6 (t), 25.7 (t), 27.6 (t), 29.2 (t), 29.5 (t), 31.8 (t), 52.3 (q), 68.4 (s), 69.3 (d), 82.3 (d), 112.9 (d), 144.1 (s), 162.7 (s); exact mass *m*/*z* calcd for $C_{15}H_{26}O_5$ 286.1780, found 286.1783.

(2*R*,3*S*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-hydroxy-3-methyl-2*H*-pyran-6-carboxylic Acid Methyl Ester (53). *t*-$BuMe_2SiOSO_2CF_3$ (140 mL, 0.607 mmol) was added dropwise to a stirred and cooled (0 °C) solution of diol **52** (100 mg, 0.3 mmol) and 2,6-lutidine (0.180 mL, 1.55 mmol) in CH_2Cl_2 (5 mL). Stirring at 0 °C was continued for 1 h, the ice bath was removed, and stirring was continued for 4 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.75 × 20 cm), using 1:1 EtOAc−hexanes, gave **53** (140.2 mg, 100%) as a colorless oil: $[\alpha]_D$ −0.8 (*c* 0.73, $CHCl_3$); FTIR ($CHCl_3$, cast) 3546, 2954, 2929, 2858, 1734, 1653, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 3 H), 0.18 (s, 3 H), 0.86−0.94 (m, 12 H), 1.19 (s, 3 H), 1.22−1.39 (m, 9 H), 1.62−1.74 (m, 2 H), 1.84−1.97 (m, 1 H), 2.72 (s, 1 H), 3.73 (d, J = 10 Hz, 1 H), 3.8 (s, 3 H), 4.07 (dd, J = 3.0, 0.8 Hz, 1 H), 5.79 (d, J = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1 (q), −4.2 (q), 14.0 (q), 17.9 (s), 22.5 (t), 23.0 (q), 25.6 (q), 26.0 (t), 27.3 (t), 29.0 (t), 29.4 (t), 31.7 (t), 52.1 (q), 68.0 (s), 69.5 (d), 81.6 (d), 110.1 (d), 143.6 (s), 162.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{40}NaO_5Si$ (M + Na) 423.2537, found 423.2536.

(2*R*,3*S*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-methyl-3-[(triethylsilyl)oxy]-2*H*-pyran-6-carboxylic Acid Methyl Ester (54). $Et_3SiOSO_2CF_3$ (1 mL, 4.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ester **53** (269 mg, 0.78 mmol) and 2,6-lutidine (0.7 mL, 6 mmol) in CH_2Cl_2 (25 mL). The ice bath was left in place but not recharged and stirring was continued for 18 h. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 × 25 cm), using hexanes, gave **54** (345 mg, 100%) as a colorless oil: $[\alpha]_D$ −1.9 (*c* 0.76, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2930, 2875, 2858, 1745, 1656, 1462, 1438, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 6 H), 0.54−0.69 (m, 6 H), 0.86−0.95 (m, 21 H), 1.20 (s, 3 H), 1.25−1.32 (m, 9 H), 1.59−1.67 (m, 2 H), 1.80−1.91 (m, 1 H), 3.71 (d, J = 10.5 Hz, 1 H), 3.77 (s, 3 H), 4.10 (br s, 1 H), 5.76 (d, J = 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.56 (q), −4.46 (q), 4.9 (t), 6.5 (t), 6.6 (t), 6.8 (q), 7.0 (q), 14.1 (q), 18.4 (s), 22.6 (t), 23.1 (q), 26.0 (q), 26.3 (t), 27.7 (t), 29.2 (t), 29.6 (t), 31.8 (t), 52.1 (q), 71.3 (d), 71.4 (s), 82.9 (d), 112.3 (d), 142.5 (s), 163.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{54}NaO_5Si_2$ (M + Na) 537.3402, found 537.3405.

(4*S*,5*S*,6*R*)-3-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-6-heptyltetrahydro-5-methyl-2-prop-2-ynyloxy-5-[(triethylsilyl)oxy]-2*H*-pyran-2-carboxylic Acid Methyl Ester (55). A solution of **54** (24.5 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 1 h to a stirred and cooled (−40 °C) solution of NBS (0.0123 g, 0.06 mmol) and 2-propyn-1-ol (0.07 mL, 1.20 mmol) in CH_2Cl_2 (1 mL). The bath temperature was raised to −20 °C by addition of acetone and stirring was continued for 2 h at −20 °C. The cold bath was left in place but not recharged and stirring was continued for 21 h. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5% aqueous $Na_2S_2O_3$ (10 mL). The organic layer was washed with water (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 30 cm), using 1:6 EtOAc−hexanes, gave the bromo ester **55** (28.3 mg, 93%) as a single isomer: $[\alpha]_D$ +4.23 (*c* 0.31, $CHCl_3$); FTIR ($CHCl_3$, cast) 3313, 2954, 2930, 2876, 2858, 2126, 1761, 1463, 1255 1160, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 3 H), 0.24 (s, 3 H), 0.62−0.71 (m, 6 H), 0.86 (t, J = 7 Hz, 3 H), 0.93−1.00 (m, 18 H), 1.18 (s, 3 H), 1.22−1.31 (m, 10 H), 1.40−1.48 (m, 1 H), 1.511.52 (m, 1 H), 2.41 (t, J = 2.4 Hz, 1 H), 3.53 (dd, J = 10.1, 1.8 Hz, 1 H), 3.75 (s, 3 H), 3.81 (d, J = 10.3 Hz, 1 H), 4.28 (dd, J = 15.7, 2.5 Hz, 1 H), 4.59 (d, J = 10.4 Hz, 1 H), 4.63 (dd, J = 15.8, 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −3.4 (q), −2.0 (q), 6.8 (t), 7.0 (q), 14.1 (q), 19.1 (s), 22.6 (t), 22.7 (q), 26.1 (t), 27.0 (q), 28.5 (t), 29.2 (t), 29.8 (t), 31.9 (t), 52.0 (t), 52.7 (d), 53.3 (q), 74.0 (s), 76.0 (d), 78.8 (s), 79.0 (d), 100.4 (s), 167.2 (s); exact mass *m*/*z* calcd for $C_{28}H_{52}{}^{79}BrO_6Si_2$ (M − C_2H_5) 621.2465, found 621.2457.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptylhexahydro-5-methyl-3-methylene-5-[(triethylsilyl)oxy]-7a*H*-furo[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (56). Et_3B in THF (21 μL, 1 M in hexanes) was added to a stirred mixture of **55** (20 mg, 0.03 mmol) and Bu_3SnH (14 μL, 0.047 mmol) in EtOAc (1 mL) in a flask open to the air. Stirring was continued for 3.5 h, and the mixture was diluted with Et_2O (5 mL), washed with brine, and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.75 × 22 cm), using 1:6 EtOAc−hexanes, gave **56** (13 mg, 74%) as a colorless oil: $[\alpha]_D$ −12.9 (*c* 0.04, $CHCl_3$); FTIR ($CHCl_3$, cast) 2953, 2929, 2875, 2857, 1754, 1462, 1252, 1228, 1175, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3 H), 0.06 (s, 3 H), 0.63−0.73 (m, 6 H), 0.88 (t, J = 7 Hz, 3 H), 0.93−1.01 (m, 18 H), 1.13 (s, 3 H), 1.23−1.34 (m, 9 H), 1.44−1.64 (m, 3 H), 3.04 (d, J = 10 Hz, 1 H), 3.41 (d, J = 9.6 Hz, 1 H), 3.57 (dd, J = 10.0, 2.4 Hz, 1 H), 3.71 (s, 3 H), 4.37 (dt, J = 12.5, 1.7 Hz, 1 H), 4.51 (d, J = 12.5 Hz, 1 H), 5.00 (s, 1 H), 5.20 (t, J = 2.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −3.4 (q), −2.5 (q), 6.9 (q), 7.1 (t), 14.1 (q), 18.5 (s), 22.0 (q), 22.7 (t), 26.0 (t), 26.5 (q), 28.6 (t), 29.2 (t), 29.6 (t), 31.8 (t), 49.0 (d), 52.3 (q), 68.7 (t), 74.3 (s), 75.6 (d), 78.8 (d), 105.1 (s), 111.5 (s), 144.1 (s), 169.2 (s); exact mass *m*/*z* calcd for $C_{28}H_{53}O_6Si_2$ (M − C_2H_5) 541.3381, found 541.3384.

(4*R*,5*S*,6*R*)-[4-(*tert*-Butyldimethylsilyl)oxy]-6-heptylhexahydro-5-methyl-3-oxo-5-[(triethylsilyl)oxy]-7a*H*-furo[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (57). An O_3−O_2 stream was passed through a stirred and cooled (−78 °C) solution of **56** (197 mg, 0.35 mmol) in dry CH_2Cl_2 (10 mL) for 12 min. The solution was purged with O_2 for 15 min, and then Ph_3P (142 mg, 0.54 mmol) was added. The cooling bath was removed and stirring was continued for 7 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.75 × 22 cm), using 1:6 EtOAc−hexanes, gave keto ester **57** (158 mg, 80%) as a colorless oil: $[\alpha]_D$ +34.3 (*c* 0.02, $CHCl_3$); FTIR ($CHCl_3$, cast) 2954, 2929, 2876, 2857, 1770, 1739, 1463, 1258, 1231, 1141 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −0.02 (s, 3 H), 0.07 (s, 3 H), 0.58−0.68 (m, 6 H), 0.89 (t, J = 7 Hz, 3 H), 0.92−0.98 (m, 18 H), 1.17 (s, 3 H), 1.24−1.36 (m, 9 H), 1.48−1.54 (m, 1 H), 1.58−1.74 (m, 2 H), 2.76 (d, J = 9.4 Hz, 1 H), 3.61 (d, J = 9.5 Hz, 1 H), 3.64 (dd, J = 9.9, 2.5 Hz, 1 H), 3.76 (s, 3 H), 4.21 (AB q, J = 16.5 Hz, $\Delta\nu_{AB}$ = 80.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (small impurity

signals at 130−136 ppm) δ −4.6 (q), −2.7 (q), 6.9 (t), 7.0 (q), 14.1 (q), 18.5 (s), 21.6 (q), 22.7 (t), 26.0 (t), 26.4 (q), 28.5 (t), 29.2 (t), 29.5 (t), 31.8 (t), 51.9 (q), 52.7 (d), 70.6 (t), 73.6 (s), 74.6 (d), 78.9 (d), 102.7 (s), 168.5 (s), 209.4 (s); exact mass *m*/*z* calcd for $C_{27}H_{51}O_7Si_2$ (M − C_2H_5) 543.3173, found 543.3191.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-*b*]pyran-3(2*H*)-one (59). $(Bu_3Sn)_2O$ (3.5 mL, 6.8 mmol) was added to a stirred solution of **57** (158 mg, 0.28 mmol) in PhH (9 mL) and the mixture was refluxed at 85 °C for 23 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.75 × 10 cm), using 1:1 EtOAc−hexanes, gave the acid **58**, which was used immediately.

$Cu(OAc)_2 \cdot H_2O$ (0.34 g, 1.7 mmol) was added to a stirred solution of the freshly prepared acid in PhH (9.5 mL) (N_2 atmosphere). Dry pyridine (0.1 mL) was added, and stirring was continued for 50 min. The flask was then wrapped with aluminum foil, and $Pb(OAc)_4$ (0.8 g, 1.83 mmol) was tipped in. Stirring was continued for 50 min, and another portion of $Pb(OAc)_4$ (0.9 g, 2.06 mmol) was added, followed by dry DMF (0.9 mL). The flask was fitted with a reflux condenser and flushed well with N_2. The mixture was refluxed for 11 h (oil bath at 88 °C). PhH (4 mL) was added and refluxing was continued for 1 h. The resulting solution was cooled to room temperature, evaporated to a small volume, and applied directly to a flash chromatography column (27 × 2.75 cm) made up with silica gel in 1:20 EtOAc−hexane. Flash chromatography, using 1:20 to 1:6 EtOAc−hexanes, gave **59** (88 mg, 61%) as a yellow oil: $[\alpha]_D$ +6.8 (*c* 0.10, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2956, 2928, 2877, 2857, 1707, 1604, 1467, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 60 °C) δ 0.18 (s, 6 H), 0.62−0.74 (m, 6 H), 0.89−1.02 (m, 21 H), 1.26−1.37 (m, 12 H), 1.44−1.65 (m, 1 H), 2.01−2.06 (m, 2 H), 4.11 (dd, *J* = 7.1, 3.8 Hz, 1 H), 4.26 (s, 1 H), 4.50 (AB q, *J* = 15.7 Hz, $\Delta\nu_{AB}$ = 27.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.58 MHz, 50 °C) δ −4.7, 6.89, 6.99, 14.0, 18.3, 22.7, 24.8, 26.1, 27.1, 29.1, 29.4, 31.8, 67.6, 73.4, 75.6, 90.0, 92.6, 181.4, 192.8; exact mass *m*/*z* calcd for $C_{26}H_{49}O_5Si_2$ (M − CH_3) 497.3119, found 497.3128.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-2,5-dimethyl-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-*b*]pyran-3(2*H*)-one (60). *n*-BuLi (2.5 M in hexanes, 0.1 mL, 0.23 mmol) was added to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.32 mmol) in dry THF (0.8 mL) and stirring was continued for 40 min. A solution of **59** (105.0 mg, 0.21 mmol) in THF (0.2 mL) was then added dropwise and stirring at −78 °C was continued for 1 h. Freshly distilled HMPA (0.03 mL, 0.17 mmol) was added rapidly followed immediately by MeI (25 μL, 0.40 mmol), which was also added quickly, and stirring at −78 °C was continued for 18 h. Then the cold bath was removed and the solution was allowed to reach room temperature. The mixture was quenched with water (2 mL) and diluted with Et_2O (5 mL). The organic layer was washed with water, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:6 EtOAc−hexane, gave **60** (80 mg, 75%) as a yellow oil: $[\alpha]_D$ +71.2 (*c* 0.20, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2956, 2929, 2877, 2857, 1706, 1602, 1467, 1249, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.14 (s, 6 H), 0.0.56−0.71 (m, 6 H), 0.82−1.00 (m, 21 H), 1.21−1.35 (m, 13 H), 1.43 (d, *J* = 7.0 Hz, 3 H), 1.56−1.60 (m, 1 H), 1.97−2.04 (br s, 1 H), 4.08 (d, *J* = 4.9 Hz, 1 H), 4.20 (t, *J* = 4.3 Hz, 1 H), 4.63−4.67 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, 60 °C) δ −4.6, 7.0, 14.0, 16.2, 18.4, 22.7, 23.0, 26.2, 27.2, 29.1, 29.2, 29.4, 31.6, 31.8, 67.5, 73.5, 84.0, 89.9, 91.4, 179.9, 195.8; exact mass *m*/*z* calcd for $C_{26}H_{49}O_5Si_2$ (M − C_2H_5) 497.3119, found 497.3113.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-2,5-dimethyl-2-(phenylseleno)-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-*b*]pyran-3(2*H*)-one (61). *n*-BuLi (2.5 M in hexanes, 41 μL, 0.1 mmol) was added to a stirred and cooled (−0 °C) solution of *i*-Pr_2NH (0.016 g, 0.16 mmol) in dry THF (0.3 mL). After 15 min the solution was cooled to −78 °C and **60** (43 mg, 0.08 mmol) in THF (0.3 mL) was added dropwise. Stirring at −78 °C was continued for 40 min and a solution of PhSeCl (0.023 g, 0.12 mmol) in THF (0.1 mL) was then added dropwise. Stirring at −78 °C was continued for 4 h and the mixture was quenched with saturated aqueous NH_4Cl (2 mL) and diluted with Et_2O (5 mL). The organic layer was washed with water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.75 × 22 cm), using 1:8 EtOAc−hexanes, gave the unsaturated ketone **61** (39 mg, 70%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2955, 2928, 2876, 2857, 1709, 1603, 1454, 1248, 1199, 1167, 1138, 1089, 1063, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 6 H), 0.51−0.64 (m, 7 H), 0.08−0.98 (m, 22 H), 1.23−1.35 (m, 10 H), 1.50−1.60 (br s, 1 H), 1.77 (s, 3 H), 1.83−1.97 (br s, 1 H), 1.98−2.11 (m, 1 H), 3.84−4.0 (m, 2 H), 7.24−7.29 (m, 2 H), 7.34 (tt, *J* = 7.3, 1.0 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.3 MHz) δ −4.6, 6.8, 7.1, 14.1, 18.3, 22.7, 23.0, 24.7, 27.0, 27.4, 29.1, 29.3, 31.8, 66.3, 73.0, 90.6, 91.7, 94.0, 125.2, 129.0, 129.5, 137.8, 177.5, 193.1; exact mass *m*/*z* calcd for $C_{33}H_{55}O_5{}^{80}SeSi_2$ (M − CH_3) 667.27533, found 667.27426.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-2-methylene-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-*b*]pyran-3(2*H*)-one (62). H_2O_2 (30%, 0.05 mL, 0.57 mmol) was added to a stirred solution of **61** (39 mg, 0.06 mmol) in THF (1.4 mL) and water (0.3 mL) (flask open to the air). Stirring was continued for 1.5 h, and the mixture was diluted with THF (3 mL) and water (2 mL), and extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.75 × 24 cm), using 1:10 *t*-BuOMe−hexanes, gave **62** (29.6 mg, 76%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 6 H), 0.60−0.72 (m, 6 H), 0.82−1.03 (m, 21 H), 1.25−1.36 (m, 13 H), 1.55−1.60 (m, 1 H), 1.98−2.12 (m, 1 H), 4.14−4.24 (m, 1 H), 4.25−4.32 (m, 1 H), 5.08 (d, *J* = 2.4 Hz, 1 H), 5.49 (d, *J* = 2.7 Hz, 1 H).

(4*R*,5*R*,6*R*)-6-Heptyl-5,6-dihydro-4,5-dihydroxy-5-methyl-2-methylene-4*H*-furo[2,3-*b*]pyran-3(2H)-one (1). HF−pyridine (70% w/w, 34 μL) was added to a stirred and cooled (0 °C) solution of **62** (12.3 mg, 0.04 mmol) in dry THF (1 mL) (Ar atmosphere). Stirring was continued for 25 min, the ice bath was removed, and another portion of HF−pyridine (0.2 mL) was added. The progress of the reaction was monitored by TLC (silica, 1:1 EtOAc−hexanes). After 1.5 h, the reaction flask was placed in an ice bath and the mixture was diluted with Et_2O (2 mL) and quenched with saturated aqueous $NaHCO_3$ until CO_2 evolution stopped. The organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm), using 1:1 EtOAc−hexanes, gave **1** (2 mg, 29%) as a colorless oil: $[\alpha]_D$ +124.2 (*c* 0.11, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3382, 2956, 2927, 2857, 1695, 1595, 1478, 1306, 1033 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.31−1.41 (m, 7 H), 1.41−1.52 (m, 2 H), 1.66−1.80 (m, 2 H), 1.92−1.96 (m, 1 H), 4.08 (s, 1 H), 4.46 (dd, *J* = 10.9, 2.3 Hz, 1 H), 5.27 (d, *J* = 3.1 Hz, 1 H), 5.52 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR (CD_3OD, 125.3 MHz, 50 °C) δ 14.8, 22.5, 24.1, 27.0, 29.2, 30.7, 30.8, 33.4, 67.3, 72.6, 87.5, 95.0, 97.6, 155.5, 181.0, 183.3; exact mass *m*/*z* calcd for $C_{16}H_{24}O_5$ 296.1624, found 296.1612.

Acknowledgment. We thank Crompton Co. and NSERC for financial support, S. Ardelean and D. Song for assistance, and Dr. R. McDonald for the X-ray structure determination. We are extremely grateful to Professors O. Sterner (Lund University, Sweden) and H. Anke (University of Kaiserslautern, Germany) for their sample of natural benesudon.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org. The X-ray data have been deposited with the Cambridge Crystallographic Data Centre and assigned the registry number CCDC 684303.

JO801028Y