Total Synthesis of Eleutherobin (I)

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The Total Synthesis of Eleutherobin

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Abstract: The total synthesis of the title compound (**1**), starting with (*R*)-(−)-α-phellandrene (**6**), has been accomplished. The synthesis rigorously proves the relative stereochemical relationship of the diterpenoid and carbohydrate domains of eleutherobin. Key reactions included a Nozaki−Kishi ring closure to produce a furanophane (see **37** → **38**), a pyranose to furanose transposition (see **50** → **47**), and a novel oxycarbaglycosidation (cf. **58** → **87**) for joining the two domains.

The demonstration that paclitaxel (taxol) (**2**) is a valuable resource at the clinical level in the treatment of human ovarian and breast tumors has had significant consequences in medicine.[1,2] The use of paclitaxel continues to expand as there is growing evidence that it may provide patients benefit against a host of other cancers.[3] As a consequence of these life-extending advances, the clinical success of paclitaxel has inspired searches for other drugs which might operate through related modalities of action. Central to the quest for paclitaxel-inspired new agents is the seminal recognition of Horwitz and associates that the mode of action of the parent drug involves the inhibition of disassembly of microtubules.[4] In the absence of findings to the contrary, it is assumed that the in vitro mode of action established by Horwitz is also germane to the clinical efficacy of the agent. Hence, the search for other substances operating in the paclitaxel tradition involves, in the first instance, screening at the level of microtubule assembly stabilization concurrently with evaluations of cytotoxicity.

From a diverse array of natural sources, other agents have been discovered. These include discodermolide (**3**)[5] and epothilones (**4**),[6] which have subsequently been proven to display a paclitaxel-like mechanism of action. The study of these potential drugs, particularly the epothilones, has inspired an extensive, multidisciplinary research effort including fermentation, structure proof, total synthesis,[7] and pharmacology.[8]

As interest in the epothilones was growing at a variety of levels, another natural product series substantially sharing the paclitaxel mode of action was discovered.[9] Thus, several structurally related natural products, classifiable as "eleutheosides", were identified. These compounds were shown to exhibit potent antitumor properties. Two compounds, identified some time ago, which bear the eleutheside skeleton, are valdivone[10] and sarcodictyin.[11] Of the newer structures in this general family, the one which interested us the most was eleutherobin. The habitat from which eleutherobin was isolated is a rare alcynacean identified as an Eleuthorobia species in marine soft corals found in Western Australia.[9] The isolation of natural products from these coral sources is not a simple matter. This being the case, there seemed to be a possible opportunity for total synthesis to play a role in providing access not only to analogues but also to eleutherobin itself (vide infra).

Furthermore, the structure of eleutherobin, shown to be **1**, contains (as will be seen) an assortment of challenges to the science of chemical synthesis. In addition to an aglycon sector

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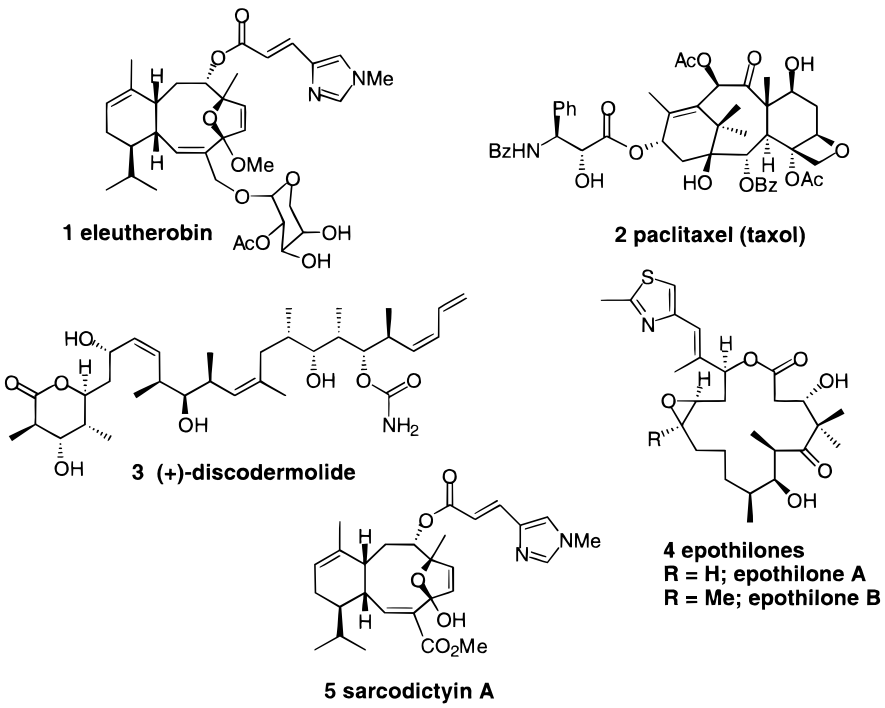


Figure 1.

which had hitherto not been assembled[12] in the laboratory, eleutherobin displays a somewhat novel urocanic ester linkage as well as an arabinose domain.

While expression **1** was suggested by Fenical and co-workers to properly represent the structure of eleutherobin, the degree of rigor in the assignment was not uniform.[9b] Thus, NMR experiments solidly defined the relative stereochemistry within the diterpenoid and carbohydrate segments. However, as the authors pointed out, there were no through space correlations to relate the stereochemistry of the aglycon and the arabinose domains. Thus, in principle, either segment might in fact be enantiomeric with that shown in expression **1**. One such possibility is considered in some detail below (see neoeleutherobin, **94**). Still another possibility could be one in which *both* sectors would be enantiomeric with those shown. In that case the issue would be that of the *absolute* configuration of eleutherobin itself. Here again, the authors did not provide fully convincing data as to the absolute configuration of the natural product.[9b]

Regardless of these unaddressed issues of structure, the biological data for eleutherobin already rendered it of considerable interest.[9c] Thus, at the level of gross cytotoxicity, eleutherobin exhibited an IC_{50} (10−15 nM) value which puts it squarely in the taxol range. Moreover, eleutherobin was competitive with paclitaxel in terms of microtubule assembly stabilization and was shown to competitively bind in the paclitaxel-binding domain.

Given the difficult availability of eleutherobin from natural sources as noted above, it would remain for chemical synthesis to generate enough of the agent for early in vivo evaluations. While more drug could eventually be amassed from its natural sources, this difficult and costly venture would most likely be undertaken only if the biological performance of eleutherobin would justify such a re-isolation. For these reasons, and in keeping with our long-standing interest in natural products which appear to owe their activity to tubulin binding, we undertook a total synthesis of eleutherobin.[13]

Synthetic Planning and Strategy. Since, as discussed above, we could not at the time be fully confident about the absolute stereochemistry of eleutherobin, a scheme which could be readily adapted to deliver either antipode of the natural agent would be desirable. Similarly, since the relative relationships of the arabinosidal and terpenoid domains were not known with acceptable rigor, we looked forward to the possibility of permuting the independently synthesized domains. Hopefully in that way we could evaluate which hybrid structure in fact corresponds to the "real" eleutherobin. Ever mindful of the goal of producing enough eleutherobin for early in vivo evaluations, we focused on schemes which held promise to be fairly concise in their execution and would lead to significant rather than symbolic amounts of final product.

To begin the total synthesis program, we started with the operational proposition that its terpenoid sector is as set forth in structure **1**. Accordingly, an intriguing choice presented itself. The starting material we came to favor was (*R*)-(−)-α-phellandrene.[14] We note that the particular choice of (*R*)-(−)-

(12) Near the end of the course of our studies (see ref 13), the total syntheses of sarcodictyins, eleutherobin, and eleuthosides were described by Professor K. C. Nicolaou and colleagues. (a) For the total synthesis of sarcodictyin A, see: Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661. (b) For the total syntheses of eleutherobin and eleuthosides, see: Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J. Y.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520. Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am.Chem. Soc.* **1998**, *120*, 8674.

(13) Some of the results contained herein were published as preliminary communications shortly after the publication of the first total synthesis of eleutherobin (ref 12b): (a) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 789. (b) Chen, X.-T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 185.

(14) The proof of the absolute configuration of (*R*)-(−)-α-phellandrene involves the convergence of several independent lines of experimentation and is secure. See: (a) Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*; Oxford University Press: New York, 1974; p 78. (b) For a crystallographic determination of a carbonylative ring-enlarged product of (*R*)-(−)-α-phellandrene complexed to $Fe(CO)_3$, see: Eilbracht, P.; Hittinger, C.; Kufferath, K.; Henkel, G. *Chem. Ber.* **1990**, *123*, 1071.

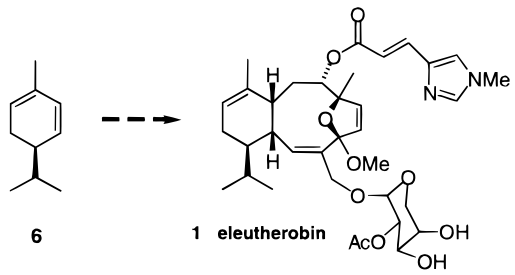


Figure 2.

α-phellandrene (**6**) would not be in keeping with our preference for a single synthesis which could accommodate the absolute configuration (to be determined eventually) of eleutherobin, by drawing upon either enantiomer of the starting material. Apparently, α-phellandrene is only available commercially in the *R*- configuration as shown in expression **6**. However, this antipode, already containing the trisubstituted double bond, seemed to be sufficiently promising in terms of our ultimate destination as to warrant special consideration. In embarking on this course, we envisioned that if the aglycon section of eleutherobin were enantiomeric with that which was formulated by Fenical,[9] it would be possible to use other entries from the chiral pool to gain access to the *ent* versions of the series that would be forthcoming from (*R*)-(−)-α-phellandrene.

Another key supposition in our planning exercise was that the disubstituted double bond of α-phellandrene, though somewhat more proximal to the potentially hindering isopropyl group, could be distinguished as the site of chemical reactivity. In this regard, we favored reaction types which would be responsive to the degree of substitution of the double bond itself and might be responsive to directing effects imposed on the double bond through its conjugation with the trisubstituted linkage. An attractive subtarget would be cyclobutanone **9**, which would have to be introduced *anti* to the proximal isopropyl function. A candidate reaction for gaining access to the desired bicyclo [4.2.0] ring system would be a 2 + 2 cycloaddition of α-phellandrene with dichloroketene (**7**).[15] It was anticipated that this type of reaction would be quite sensitive to the degree of substitution on the double bond. Furthermore, we expected the regiochemical course of the cycloaddition step to be controlled by the conjugating effects of the trisubstituted double bond. Hence it was projected that in such a cycloaddition process, initial bond formation would occur through electrophilic attack of the ketene carbonyl group at the olefinic center adjacent to the isopropyl function. Accordingly, **8** would be the expected product. Reduction of the chlorine groups would afford **9**.

From this point, we envisioned a fragmentation to produce a structure written as **10**. The vagueness implied in notations X and Y in structure **10** is deliberate. At this relatively unstructured level of planning, we avoid commitment to any particular pattern of terminal functionality in this expression. We shall address all the critical particulars encompassed in this broad conceptual framework as the plan gains coherence.

Upon studying the matter further, we considered the possibility that the 2,5-dihydrofuran sector (**14**) could arise from a formal enedione such as **13** which could in turn be derived by epoxidation of a furan moiety (**12**) and subsequent bond reorganization.[16] We were not unmindful, however, that difficulties could be encountered in distinguishing the furanoid double bonds of **12** from the trisubstituted olefin (C11−C12) (see Figure 3). The furanophane **12** could be derived from **10** via a two-stage interpolation of **11** (wherein groups W and Z are not specified). To generate the dihydrofuran sector (**14**), the plan thus called for delivery of a methyl nucleophile (possibly as a methyl Grignard or methyllithium agent) to C7 of the enedione **13**. Of course, provision to direct the desired nucleophilic methylation to this site rather than to C4 would be necessary.

Fortunately, an attractive solution, which simultaneously addressed both of the issues of chemoselectivity, presented itself. This strategy involved the prospect that the substrate for epoxidation would contain a free hydroxyl at C8 (see structure **15**). Hopefully, this hydroxyl center would direct the oxidant to the proximal unsaturation.[17] In this way, the vulnerability of the furan to oxidation relative to that of the C11−C12 olefinic linkage would be enhanced. Moreover, the C8 hydroxyl in structure **17** would be expected to engage the resulting C4 ketone in a hemiacetal linkage thereby accomplishing chemodifferentiation between carbons 4 and 7 (see structure **18**). We hoped that at a strategic point, the pyranose resulting from this site specific nucleophilic methylation could be opened (cf. **19**) and re-closed to provide furanose **20**. The latter might eventually be converted to **1**. Undefined, for the moment, is the functionality at C3 as the synthesis unfolds. The key point is that C3 be maintained in a form where it would not compete with the important directing effect, discussed above, which would be confined to the C8 hydroxyl group (see structure **15**). Integration of these considerations led us to the program for synthesis contemplated in Figure 4, wherein R′ is not specifically defined. We now describe the translation of these conjectures to practice in the context of a total synthesis of eleutherobin.

Our synthesis commenced (Scheme 1), as projected, with the reaction of dichloroketene (**7**) (generated as shown by zinc induced reductive elimination of trichloroacetyl chloride) with the commercially available (*R*)-(−)-α-phellandrene (**6**).[15] In our early experiments we utilized pure samples of **6**. Under these conditions we could readily identify two products which were the desired **8** and, surprisingly, its stereoisomer **21** in an 8:1 ratio. Apparently, no regioisomers of these products were produced. Compounds **21** and **8** were separated by silica gel chromatography and the structures assigned through spectroscopic means.[18]

As the projected route gained continuing experimental validation, we had need for substantial quantities of **8**. Accordingly, we took recourse to relatively inexpensive bulk commercial offerings of crude phellandrenes.[19] Purification was deferred to the stage of compound **9**, obtained by reductive bisdechlorination of **8**.

Considerable thought was given to the way in which the cyclobutanone could be exploited. We were committed at the outset to the concept generalized in the expression **10** + **11** → **12**. Of course, it would be critical to obtain the equivalent of

(15) (a) For a ketene cycloaddition with a cyclohexadiene, see the following: Greenlee, M. L. *J. Am. Chem. Soc.* **1981**, *103*, 2425. (b) For a diastereoselective ketene cycloaddition, see: Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, *13*, 1911.

(16) (a) Adger, B. M.; Barett, C.; Brennan, J.; McKervey, M. A.; Murray, R. W. *Chem. Commun.* **1991**, 1553. Lefebvre, Y. *Tetrahedron Lett.* **1972**, 133. (b) Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. (c) Cavill, G. W.; Laing, D. G.; Williams, P. J. *Aust. J. Chem.* **1969**, *22*, 2145.

(17) (a) Henbest, H. B., Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958. (b) For a previous instance of hydroxyl-directed epoxidation utilizing dimethyldioxirane, see: Chow, K.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 4211.

(18) The fact the two isomers in question were indeed stereoisomers and not regioisomers was proven by HMBC assignments on both **8** and **21**.

(19) (*R*)-(−)-α-Phellandrene, 50% purity, is available from Fluka Chemical Corp., 1001 West St. Paul Ave., Milwaukee, WI 53233.

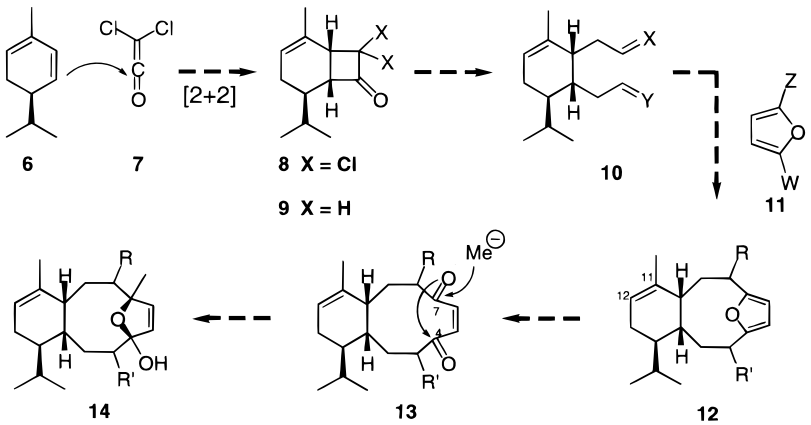


Figure 3.

10 in a fashion where the terminii symbolized as X and Y were cleanly differentiated in their chemical proclivities. Furthermore, access to the specific version of **10** had to be uncomplicated. It was from these perspectives that we turned to the elegant chemistry of Trost[20] involving the dimethylaminomethylenation of a cyclobutanone with a Bredereck reagent.[21] This reaction accomplishes the functional equivalent of α-formylation of a strained ketone. In the case at hand, subjection of **9** to the action of Bredereck reagent (**22**) afforded **23** in 75% yield. Pursuing the "formyl" equivalency still further, compound **23** was treated under conditions (*p*-TsOH·H_2O−MeOH at 60 °C) which were expected to favor methanolysis. This step was followed by an exchange reaction with acetone which accomplished de-acetalization of the first formed **24**, providing **25** in 60% overall yield from **23**.

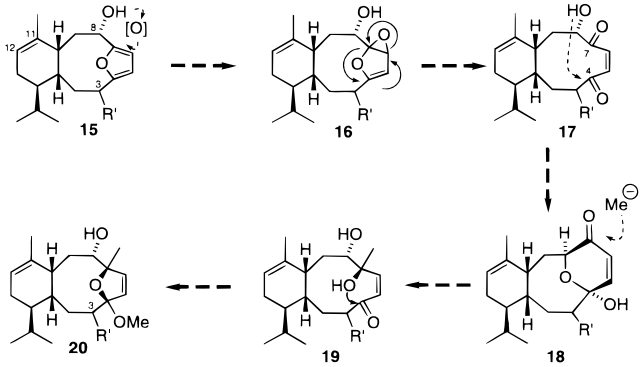


Figure 4.

As a specific version of the generalized system **11**, we studied the usefulness of readily available 2,5-dibromofuran (**26**).[22] Monometalation of this compound was accomplished via reaction with *n*-BuLi in THF. Lithio derivative **27**, thus generated, reacted with aldehyde ester **25**. This coupling step turned out to be the worst phase of the total synthesis undertaking. From the beginning we had no clear rationale for predicting the stereochemical outcome of this coupling. Least predictable was the conformation of the aldehyde group entering in the reaction. While some rotamers held out the prospect of face selectivity in the addition step, in other hypothetical conformers, factors favoring the two possible diastereotopic modalities of attack seemed to be quite balanced. In a "worst case" scenario, it was hoped that the wrong (8*R*) facial stereoisomer could be rehabilitated in the scheme through direct inversion or via oxidation followed by reduction to provide the desired (8*S*) alcohol.

In the event, coupling did occur giving rise to a 1.3:1 mixture of diastereomers.[23] The "major" product, isolated in 57% yield, was shown to be the required **28** on the basis of arguments discussed below (vide infra). Its hydroxyl function could be protected as a *tert*-butyl diphenylsilyl ether derivative (**31**) (97% yield). Small and variable amounts of another isomer formulated as the undesired **29** were also obtained. However, the bulk of the (8*R*) product suffered lactonization, emerging as **30** (30−40%). Unlike the situations with **28** and **29**, the stereochemistry of this compound could be rigorously assigned.[24] When the lactone **30** was subjected to the action of Triton-B and the resultant salt treated with methyl iodide, the "minor" hydroxy ester was obtained. It was in this way that we confirmed that the latter has the stereochemistry shown in **29**. By inference, the major hydroxy ester is shown to be **28**. The rigorous but somewhat indirect structural assignment of **28** was subsequently supported by a crystallographic determination of advanced intermediate **45** (vide infra) in which the stereochemistry at C8 had been encoded.[25] Though the configurational assignments were secure, the synthesis suffered badly from a lack of stereocontrol in the first stage of connecting the phellandrene-derived domain with the furan-derived nucleophile (cf. **10** + **11**).

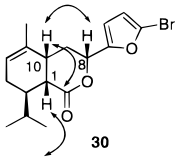
(20) Trost, B. M.; Preckel, M.; Leichter, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 2224.

(21) (a) Bredereck, H.; Effenberger, F.; Simchen, G. *Chem. Ber.* **1963**, *96*, 1350. (b) For a review, see: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

(22) (a) For preparation, see: Keegstra, M. A.; Klomp, A. J. A.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3371. (b) For use, see: Wellmar, U.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 1159. (c) For 5-iodo-2-furylmagnesium iodide see: Gilman, H.; Mallory, H. E.; Wright, G. F. *J. Am. Chem. Soc.* **1932**, *54*, 733. (d) For 5-bromo-2-thienyllithium, see: Shiao, M.-J.; Shih, L.-H.; Chia, W.-L.; Chau, T.-Y. *Heterocycles* **1991**, *32*, 2111.

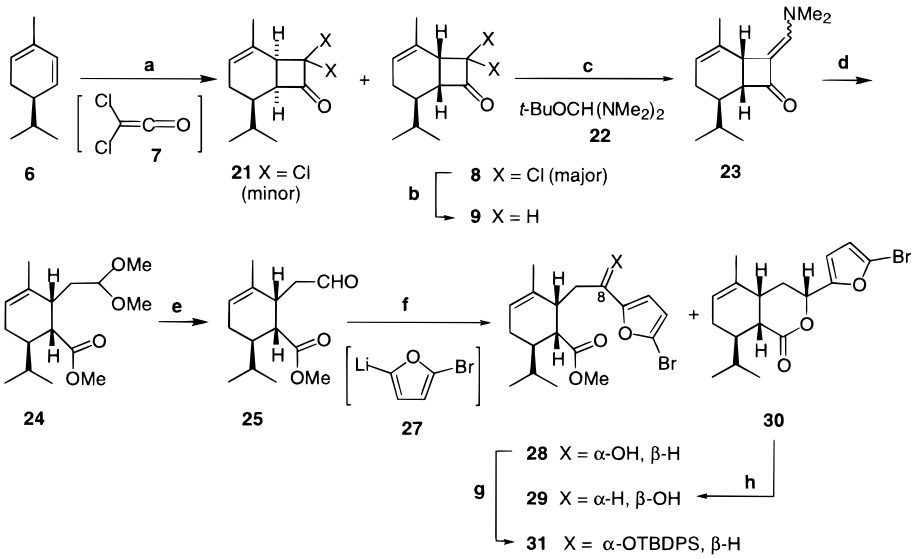
(23) The 1.3:1 ratio reflects a ratio of **28**:[**29** + **30**].

(24) 1D-selective NOESY on the lactone, **30**, led to the assignment of the critical C8 center. The C8, C10, and C1 H's showed mutual NOE enhancement upon irradiation of each individual one. Furthermore, the C1 H and the isopropyl methyls showed enhancement, thus proving that the C1 H and therefore C10 and C8 as well were all *β*.



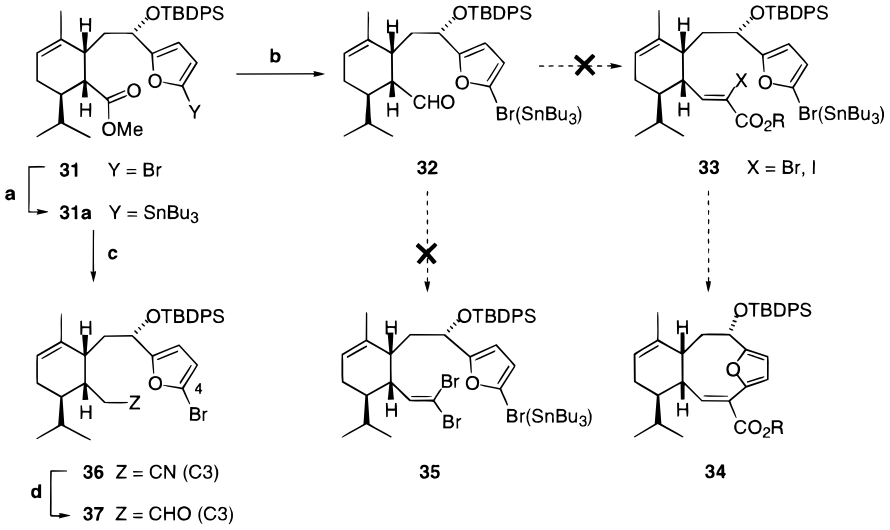
(25) We considered the possibility of integrating the C8-*R* products (**29** and **30**) into the main synthetic stream. As shown in Scheme 1, **30** could be converted to **29**. Indeed the oxidation of **29** could be conducted but the resultant ketone gave a mixture of streosiomers at C8 upon attempted reduction under several conditions.

Scheme 1[a]



[a] (**a**) trichloroacetyl chloride, Zn, Et_2O, sonication, 0 °C, 65%; (**b**) Zn, MeOH, NH_4Cl, 87%; (**c**) **22**, 60 °C, 75%; (**d**) *p*-TsOH·H_2O, MeOH, 60 °C; (**e**) *p*-TsOH·H_2O, acetone, 60% for (**d** and **e**); (**f**) 2,5-dibromofuran (**26**) + *n*-BuLi, THF, −78 °C → (**27**), **27** + **25** in THF → **28**, 57%; (**g**) TBDPSCl, imidazole, DMAP, 0 °C, 97%; (**h**) Triton B, THF; MeI.

Scheme 2[a]



[a] (**a**) *t*-BuLi, THF:pentane:Et_2O (4:1:1), −110 °C; Bu_3SnCl, ∼80%; (**b**) **i** DIBAL−toluene, CH_2Cl_2, −78 °C, >95%; **ii** Dess-Martin periodinane, ∼90%; (**c**) **i** DIBAL−toluene CH_2Cl_2 −78 °C, >95%; **ii** MsCl, pyridine, DMAP, 0 °C, >95%; **iii** KCN, 18-c-6 ether, CH_3CN, 80 °C, 96%; (**d**) DIBAL−toluene, toluene, −78 to 0 °C, 84%.

Similarly frustrating were the results of a series of attempted olefination reactions conducted on aldehdye **32**, derived from ester **31**, as shown (Scheme 2).[26] Our original plan contemplated extension of this aldehyde through hetero-branched olefination to give rise to a system of the type **33**. The thought was that the tri-*n*-butylstannyl function in **33** would facilitate formation of a furanocycle corresponding to **12** (see **32** → **33** → **34**). Unfortunately, the Wittig olefination phase failed. Another failure was sustained in the attempted olefination of aldehyde **32** with a view to reaching **35**, which also seemed to be of some potential.[27] Once again, this modified Wittig reaction failed. A series of such projected olefinations using compounds **32** itself or closely related congeners on related systems where the functionality on the furan was somewhat different were equally unsuccessful. Depending on the phosphorus-based reagent used, reactions failed either for a lack of reactivity of the aldehyde or due to surprising vulnerability of the furan. A listing of these failed reactions is given in the Supporting Information.

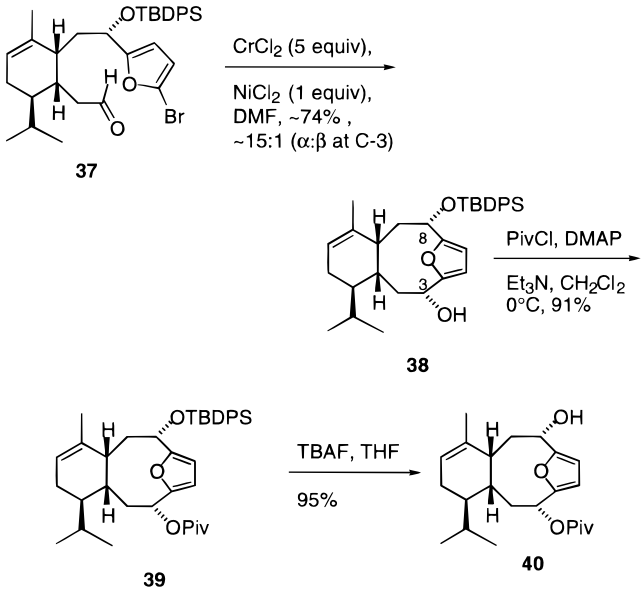
At this stage, we returned to ester **31** and successfully carried out a one-carbon extension to reach nitrile **36** and thence the aldehyde **37**, as shown. In keeping with the governing conception of **10** + **11** → **12**, all efforts were now directed to achieving carbon−carbon bond formation between the bromine-bearing carbon of the furan (C4) and C3 of the elongated constructs **36** or **37**.

Among the possibilities which were investigated were (i) free radical cyclization, (ii) attempted lithiation induced cyclization, and (iii) samarium(II) iodide mediated reductive cyclization.

(26) The bromo ester **31** was converted to the stannylated ester **31a**, as shown in Scheme 2 by the action of *t*-BuLi at −110 °C followed by immediate quenching with Bu_3SnCl. A 6:1 ratio of the stannylated and the debrominated compound resulted. These could be separated by chromatography.

(27) For instance, Stille couplings of a 1,1-disubstituted vinylidene dibromide have been carried out: Shen, W.; Li, W., private communication.

Scheme 3



These attempts were all unsuccessful. Presumably, these and related failures listed in the Supporting Information reflect the highly strained character of the target.

Fortunately one workable ring closure method was discovered (Scheme 3). This thrust involved formation of a *m*-cyclophane derivative from a Nozaki−Kishi[28] reductive cyclization of bromoaldehyde **37**, thus enabling the C3−C4 bond construction (see compound **38**). Moreover, the reaction occurred with excellent selection in the formation of the stereogenic center at C3.[29] While this carbon was destined to become a ketone as the synthesis unfolded, it was certainly a considerable convenience to be able to obtain **38** as a single entity from the mixture in which it was highly enriched. That the configuration at C3 is, in fact, *R* was rigorously proven only after crystallographic analysis at a later point in the synthesis.

With this critical step accomplished, the next consideration was to maintain a clear-cut chemical differentiation between the C8 and C3 oxygen substituents such that a free hydroxyl is uniquely exposed at C8. Toward this end, the C3 hydroxyl was protected as a pivaloate (see compound **39**). At this stage, we could achieve deprotection of the alcohol at C8 (see compound **40**). The stage for studying the viability of the program implied in expression **15** → **18** was at hand.

Several attempts were initiated to achieve clean oxidation of the furan sector. The most successful involved the reaction of compound **40** with dimethyldioxirane (DMDO) (ca. 1 equiv) in acetone at −78 °C.[30,31] Under these conditions, there was isolated a 94% yield of the desired hydroxypyranone **41** (Scheme 4). In retrospect, the advantage of keeping the C8 hydroxyl free had been demonstrated. Thus, attempts to achieve site specific oxidation of the furan when the C8 hydroxyl was protected, either with *m*-chloroperoxybenzoic acid or with DMDO, were unsuccessful. There were encountered significant interferences arising from the oxidation of the trisubstituted double bond. However, with **40** in which the C8 hydroxyl is free and DMDO as the oxidizing agent, this competition was avoided.

We next turned to the nucleophilic methylation at C7. In our original published approach,[13] compound **41** itself was subjected to action of methyllithium. This reaction, indeed, provided a 42% yield of **42**. Although the yield was somewhat disappointing, the process was apparently stereoselective as expected. The nucleophile approached unhindered from the α-face of the carbonyl group as shown in the Chem 3D representation of **41** in Scheme 4.

We now had to address the matter of converting the pyranose to the furanose. Our scheme contemplated opening of the hemiacetal engagement between C8 and C4. The liberated C8 hydroxyl would be trapped (with the trapping electrophile, P^+). A new hemiacetal joining the tertiary alcohol at C7 and the newly unveiled ketone function at C4 would be established (see **42** → **43** → **44**). If such a valence tautomerization could be accomplished, it would then be necessary to methylate the hemiacetal like hydroxyl at C4 (see compound **46**, Scheme 5).

Indeed, as described in our previous report,[13] these steps could be reduced to practice (Scheme 5). We elected to explore the possibility of acetylation as a reaction to differentiate the secondary hydroxyl at C8 and the tertiary hydroxyl at C7 in hypothetical intermediate **43**. In the event, this reaction was successful leading to acetate **45** (**44**, P = acetyl) presumably via **43** (*P* = acetyl). *Fortuitously, the acetate derived from this reaction was solid and an X-ray crystallographic determination performed on crystals of* ***45*** *provided unambiguous proof of structure as well as all the stereochemical assignments posited thus far.*

Remarkably, it proved possible to methylate the tertiary hydroxyl in this potentially labile system through the action of silver oxide−methyl iodide (see compound **46**). At this stage we had need to modify the protection pattern at the C8 oxygen to correspond to a stable arrangement that would ensure its survival in the future reactions which were contemplated. Toward this end, de-acylation was selectively accomplished at C8 of **46** and the hydroxyl group in the resultant **47** was converted to its *tert*-butyldimethylsilyl derivative **48**.

Though a great deal of progress had been achieved, the cumbersome and mediocre yielding nature of our route came to be of increasing concern as we sought to bring through substantial quantities of material in anticipation of in vivo biological evaluation. With these concerns in mind, we investigated a bolder strategy for the pyranose → furanose interconversion. Toward this end, we returned to the action of DMDO on compound **40**. The purified product (cf. **41**) was converted to its trimethylsilyl derivative **49**. Reaction of this compound with methyllithium provided, as expected, compound **50** in excellent yields (unlike the poor yields encountered in substrate **41** bearing the C4 free hydroxyl group). Remarkably, treatment of this product with methanol in the presence of catalytic *p*-TsOH·H_2O afforded the previously encountered **47**. The overall yield from **41** → **47** was ca. 80%. A mechanism to account for the siloxy-mediated valence isomerization is implied in Scheme 6.

At the time of our initial report,[13] we could advance no rigorous evidence concerning the stereochemistry of **41** or **49**. In this uncertainty, we tentatively represented the relationship of the bridgehead substituents as *out-out*.[32] This arrangement corresponds to the presumed thermodynamically most stable

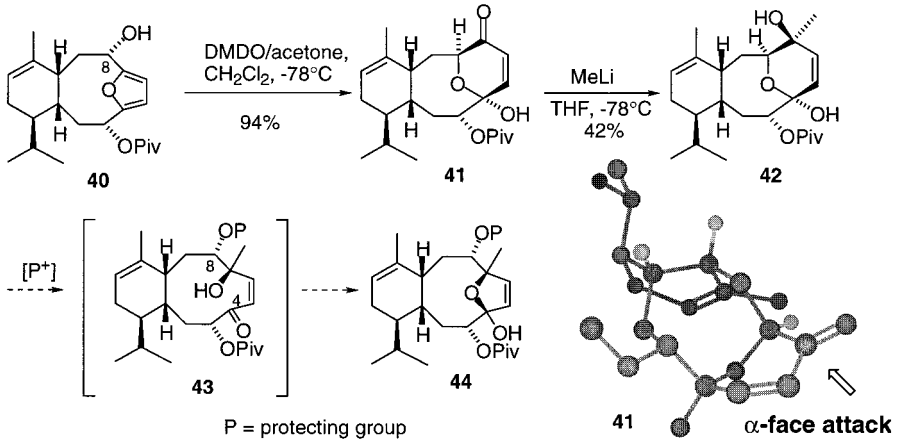
(28) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. Kishi, Y. *Pure Appl. Chem.* ***1992***, *64*, 343. (c) For a review of the Nozaki−Kishi reaction, see: Cintas, P. *Synthesis* **1992**, 248. (d) See also: Eckhardt, M.; Brückner, R. *Liebigs Ann. Chem.* **1996**, 473.

(29) A 15:1 mixture of isomers at C3 favoring the 3*R* isomer was obtained.

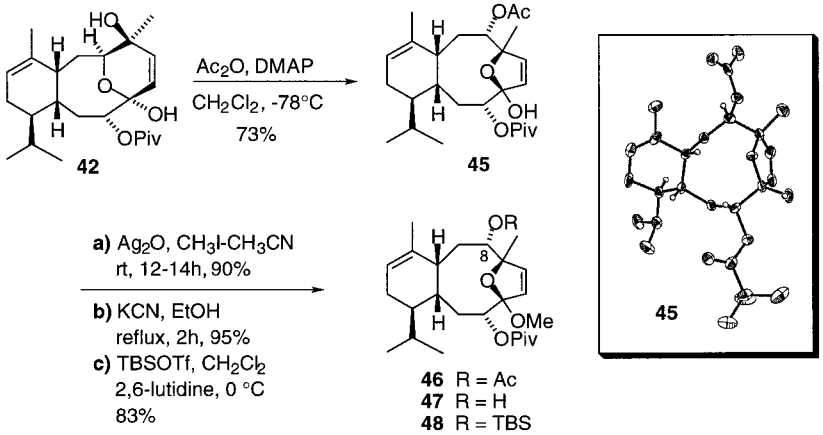
(30) (a) See ref 17b. (b) Sharpless directed epoxidation conditions (Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136) using catalytic $VO(acac)_2$ and *t*-BuOOH were also tried but DMDO[31] proved much superior.

(31) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

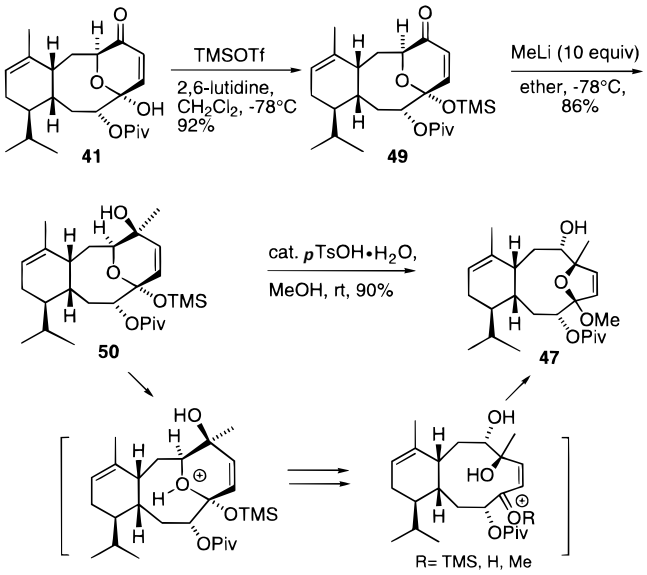
Scheme 4



Scheme 5



Scheme 6



configuration (Macromodel v 5.5 calculations).[33] Spectroscopically, however, it was difficult to obtain persuasive proof regarding this stereochemical question due to the conformational fluxionality of the ring system. This resulted in broadening of signals in the proton NMR spectrum. Sharpening of peaks could be observed only at temperatures around 220 K. In the first level of analysis, low-temperature COSY and 1D NOESY experiments might have been construed to suggest an *in-out* assignment for the TMS-protected compound **49**. However, the matter was unclear. Eventually, some crystals of the lactol enone were obtained. Crystallographic analysis (Figure 5) indeed established the *out-out* formulation shown in **41**. [Although very good diffraction patterns were obtained from crystals of **41**, the structure could not be refined beyond an *R* factor of 0.15].

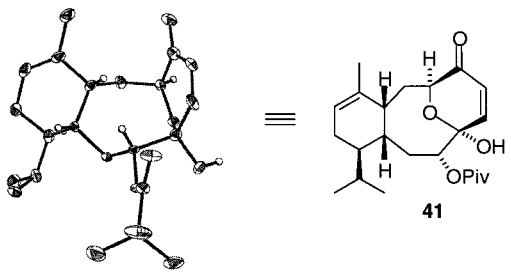


Figure 5.

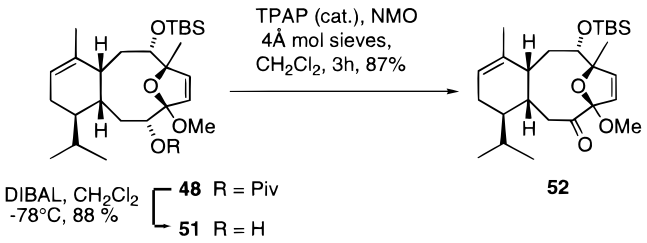
With an excellent route to **47** and thence **48** now in hand, we focused on reaching ketone **52**. This subgoal was readily accomplished by reductive de-pivaloylation of **48** through the agency of diisobutylaluminum hydride (see compound **51**), followed by oxidation with TPAP as shown (Scheme 7).

Several options for proceeding from ketone **52** to eleutherobin (**1**) were considered. Conceptually, the most straightforward pathway would be to accomplish a homologation at C3 (Scheme

(32) For a discussion on *out-out* and *in-out* arrangements in bridged compounds, see: Eliel, E. L.; Wilen S. H. *Stereochemistry of Organic compounds*; Wiley: New York, 1994; pp 791−793.

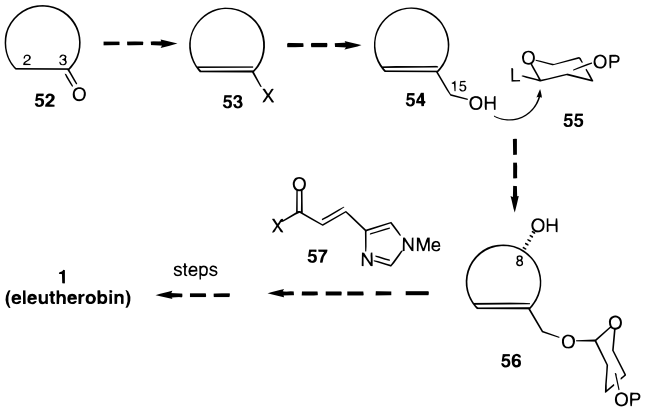
(33) Macromodel v 5.5 calculations on **49**: E_{rel} (kcal/mol) = 0 (*out-out*), 12.35 (H *in*-OTMS *out*); 14.33 (H *out*-OTMS *in*).

Scheme 7



8). This one-carbon fragment would correspond to C15 of eleutherobin. It would eventually be presented as a hydroxymethyl group. Clearly, the homologation must be coordinated with introduction of the C2−C3 double bond (see system **54**). Glycosylation of acceptor **54** with a suitable arabinosyl donor (**55**) followed by deprotection at C8 would establish **56**. Thereafter, the properly methylated urocanic acid acylating agent (cf. **57**) would be installed. Total deprotection (either concurrently or in phases) would be required to reach **1**.

Scheme 8



Focusing at the outset on the problem of reaching a version of **53**, we came to favor the intermediacy of a vinyl triflate (**58**). With the C2−C3 double bond in place, a variety of reaction types for introducing the one-carbon C15 fragment could be explored. In the event, the triflate **58** was synthesized from the ketone **52**. In this way, the C2−C3 double bond problem, implied in formalism **53**, had been accommodated.[34]

The possibility of introducing the one-carbon fragment by palladium-induced methoxycarbonylation[35] of the vinyl triflate function was considered and briefly explored. In the event, this reaction attempted under standard conditions (see Scheme 9) led to unworkably low yields of **59**. Certainly, we might have pursued this reaction in much greater detail and, perhaps, reached the α,β-unsaturated ester in serviceable yields. Clearly, even if methoxycarbonylation were accomplished, it would be necessary to reduce the ester linkage to a primary alcohol to reach **54**.

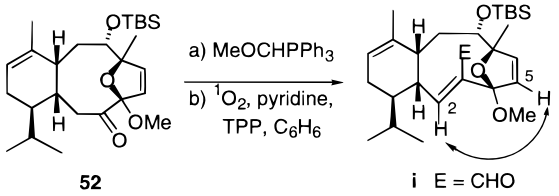
Before embarking on such a yield enhancement course, it seemed appropriate to investigate another option. The palladium-mediated coupling of vinyl triflates with vinylstannanes is well-known as a route to conjugate dienes.[36] Hence, we came to wonder whether a one-carbon homologation could be achieved via a relatively rare sp^3 version of the Stille coupling.[37,38] Toward this end we synthesized *p*-methoxybenzyl tri-*n*-butylstannane following Buchwald's procedure.[39] Remarkably, coupling was accomplished in 55% yield using tetrakis(triphenylphosphine)-palladium(0) in the presence of lithium chloride (Scheme 9). Since the vinyl triflate has the *E* configuration (the C2−C3 double bond shown in **58**), it is not surprising that the structure of the sp^3 Stille cross-coupling product is as shown in **59**. In principle, the next phase would involve deprotection at C15 to liberate the required allylic alcohol function (see system **61**). The alcohol group would serve as the glycosyl acceptor site for attachment of a suitable arabinosyl donor (cf. coupling of **54** and **55**).

Of course, for this scheme to be successful in terms of reaching eleutherobin, it would be necessary to achieve differential deprotection at C15 while retaining the methyl glycoside at C4. A few probes in this regard (see Scheme 9) failed to lead to the desired **61** and seemed to underscore the vulnerability of this methyl glycoside.

Additional serious concerns as to embarking on this otherwise logical course of deprotection of **60** and arabinosylation of **61** arose from a concurrent investigation dedicated to probing the likely stereoselectivity margins of the impending classical glycosylation phase of the synthesis. In anticipation of such an approach, we had begun to cope with the synthesis of a suitable arabinosyl donor. It would be necessary to protect the oxygens at C3′ and C4′ of such an arabinosyl donor. While several approaches for generating a suitable glycosyl coupling candidate with appropriate protection patterns at the oxygens connected to carbons 2′, 3′, and 4′ were considered and explored, we eventually settled on the sequence shown below in Scheme 10.[40]

The route started with D-arabinose (**62**). Following peracetylation (see compound **63**), an ethylthio group was introduced at the anomeric position, as shown in structure **64**. Cleavage of the acetates through the action of sodium methoxide in methanol gave rise to **65**, in which the *cis*-related hydroxyl groups at C3′ and C4′ were engaged as an isopropylidene linkage (see compound **66**). The uniquely exposed hydroxyl group at C2′ was protected as a TBS ether (see compound **67**) or as a SEM derivative (**68**). Anticipating some experiments to be described later, L-arabinose **69** was converted in an identical fashion to enantiomeric arabinosyl donors **70** and **71** as well as the *p*-methoxybenzyl derivative **72**.

(34) At this stage we inferred that the geometry of the vinyl triflate to be *E* as shown in **58**. A key point in the argument was the comparison of the C2−H in the NMR spectrum of the vinyl triflate with that of the corresponding H in the α,β-unsaturated aldehyde **i** (derived from the ketone **52**, see Supporting Information for details). This was accomplished in a two-step procedure consisting of methoxymethylenation and a subsequent Conia reaction with singlet oxygen, see: Rousseau, G.; LePerchec, P.; Conia, J. M. *Synthesis* **1978**, 67. Thus, an NOE enhancement between C2−H and C5−H was observed in **i** but not in the vinyl triflate **58**, implying that the C2−C3 double bond in **i** is *Z* and by inference *E* in the vinyl triflate (see structure **58**). Rigorous proof as to the correctness of the assignment was achieved when the total synthesis of eleutherobin was accomplished.



(35) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

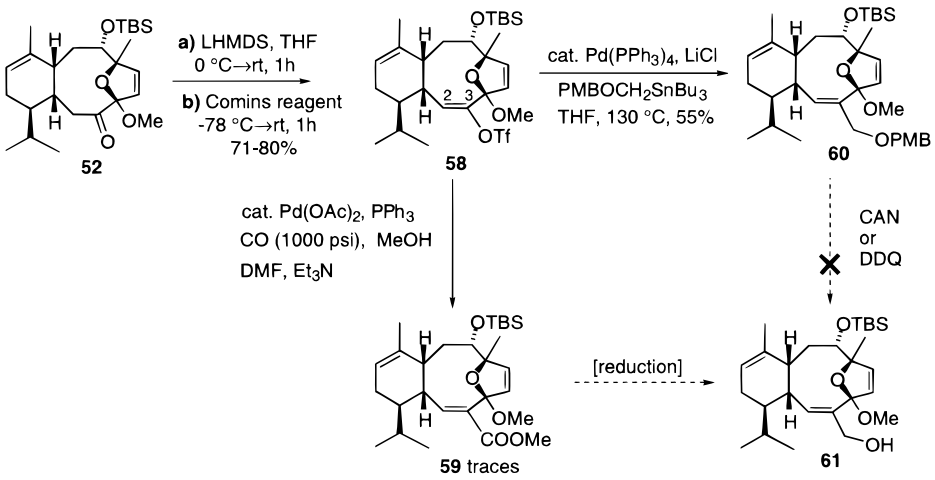
(36) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(37) (a) Kosugi, M.; Sumiya, T.; Ogata, T.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1225. (b) Majeed, A.; Antonsen, Ø.; Benneche, T.;Undheim, K. *Tetrahedron* **1989**, *45*, 993. (c) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H., III; Munroe, J. E. *J. Org. Chem.* **1989**, *54*, 5828. (d) Férézou, J. P.; Julia, M.; Li, Y.; Liu, W.; Pancrazi, A. *Synlett* **1991**, 53.

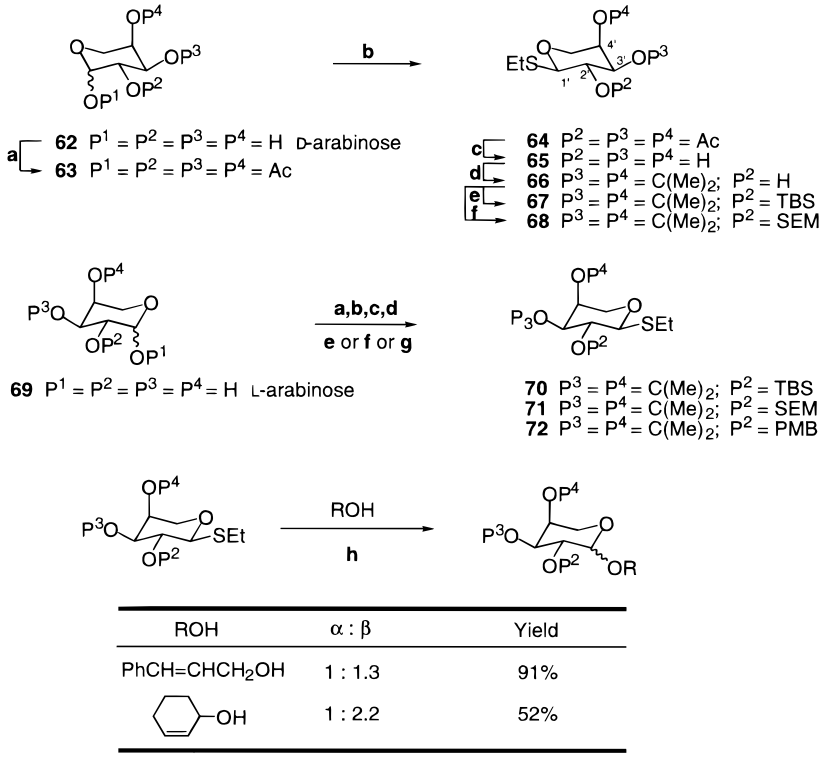
(38) For selective alkyl transfer to a vinyl iodide using internal coordination at tin, see: Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.

(39) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1989**, *8*, 1593.

Scheme 9



Scheme 10[a]



ROH	α : β	Yield
PhCH=CHCH$_2$OH	1 : 1.3	91%
	1 : 2.2	52%

[a] (**a**) Ac_2O, pyridine, DMAP, 0 °C → rt, 100%; (**b**) EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 76% [α:β = 10:1]; (**c**) NaOMe, MeOH, rt, 100%; (**d**) 2,2-dimethoxypropane, *p*-TsOH·H_2O, rt, 96%; (**e**) (*t*-Bu)Me_2SiCl, imidazole, DMAP, CH_2Cl_2, rt, 93%; (**f**) $Me_3SiCH_2CH_2OCH_2Cl$ (SEM-Cl), (*i*-Pr)$_2$NEt, CH_2Cl_2, rt, 82%; (**g**) *p*-$MeOC_6H_4CH_2Cl$ (PMBCl), NaH, DMSO, 91%; (**h**) MeOTf (3 equiv), 2,6-di-*tert*-butylpyridine (3.5 equiv), CH_2Cl_2:Et_2O [1:2], 4 Å molecular sieves, 0 °C.

Our earliest studies aimed at introducing an axial arabinose function were actually conducted with the L-system **72** (see Scheme 10). Two model alcohols were evaluated as L-arabinosyl acceptors. They were cyclohexenol and cinnamyl alcohol. A variety of conditions were screened, and representative conditions are shown in Scheme 10. As these results show, we were unable to develop a glycosidation procedure which would provide the required β-glycoside,[41] with usable stereoselectivity employing a thioethyl donor.

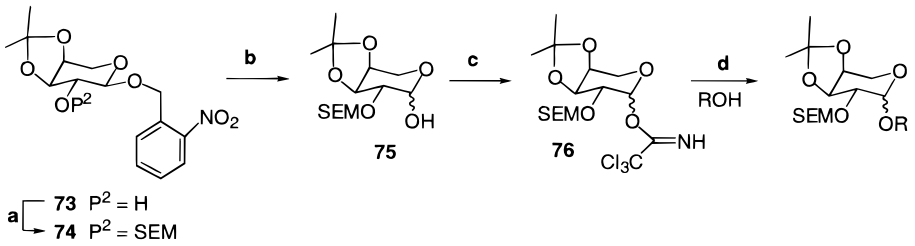
We then turned to the possibility of utilizing a trichloroacetimidate as an arabinosyl donor. For this purpose we started with compound **73** bearing an *o*-nitro benzyl group at the anomeric center of the L-arabinose system.[42] Alkylation at the C2′ hydroxyl with SEM chloride afforded **74** which was photolytically deprotected to provide **75**. Activation of the

(40) (a) Tri-*O*-acetyl thioethyl L-arabinoside has been described before: Pakulski, Z.; Pierozynski, D.; Zamojski, A. *Tetrahedron* **1994**, *50*, 2975. (b) For a suitably protected thiophenyl arabinoside, see: Nicolaou, K. C.; Trujillo, J. I.; Chibale, K. *Tetrahedron* **1997**, *53*, 8751. (c) Also see ref 12b.

(41) By conventions of carbohydrate nomenclature, descriptors α and β in the arabinose series define the configurational relationship between C1 and C4 of the pyranoside. For the nomenclature of carbohydrates, see: McNaught, A. D. *Carbohydr. Res.* **1997**, *297*, 1. In terms of the structures presented here, α would correspond to the equatorial anomer and β to the axial one.

(42) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625.

Scheme 11[a]



ROH	76	T (°C)	α : β	Yield
$PhCH_2OH$	α:β (1:2) mixture	-10	only β	14%
$PhCH{=}CHCH_2OH$	β	-40	1 : 2.3	48%

[a] (**a**) $Me_3SiCH_2CH_2OCH_2Cl$ (SEM-Cl), (*i*-Pr)$_2$NEt, CH_2Cl_2, rt, 92%; (**b**) *hν*, THF:H_2O [9:1], 0 °C, 50%; (**c**) Cl_3CCN, K_2CO_3, CH_2Cl_2, 0 °C → rt, 81%, α:*β* [1:2]; (**d**) TMSOTf (0.1−0.4 equiv), CH_2Cl_2, 4 Å molecular sieves.

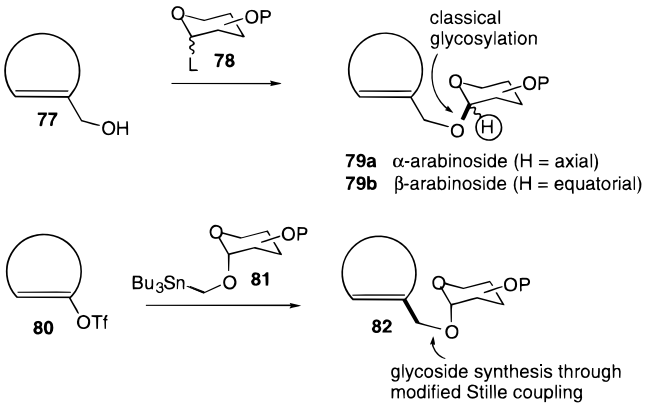
anomeric hydroxyl group through the reaction of potassium carbonate and trichloroacetonitrile gave rise to **76** as a 1:2 [α:*β*] mixture. To evaluate the donor system **76**, we screened benzyl alcohol and cinnamyl alcohol as potential arabinosyl acceptors. In the event, these couplings led to semienriched ratios (favoring the desired *β*-anomer) of the glycosides albeit in poor yields (see table in Scheme 11).

At this stage we had several layers of concern. First, it was not at all certain that a conventional glycosylation would be possible on an aglycon (cf. **61**) bearing a potentially vulnerable allylic methyl glycoside. Moreover, if we were to pursue the pathway adumbrated in Scheme 8, we faced the prospect of obtaining serious anomeric mixtures in the glycosylation reaction. Further complicating matters was that the separation of these compounds tended to be quite difficult. The attendant consequences on material throughput would be particularly damaging.

It was from the context of these apprehensions that a new possibility for reaching eleutherobin presented itself. In reaching compound **60**, we had already shown that the vinyl triflate **58** is a viable substrate to undergo a novel variation of Stille coupling with an organostannane bound to an sp^3 carbon (cf. **60**). Accordingly, we posed the question as to whether the carbon to which the tin is attached could, itself, carry an *entire glycosyloxy function*, in particular, the arabinose sector of eleutherobin. In essence, we were asking whether it would be possible to introduce a glycoside domain not to the fully functional aglycon **61** but rather to the vinyl triflate itself. The question is framed in more general terms in Scheme 12.

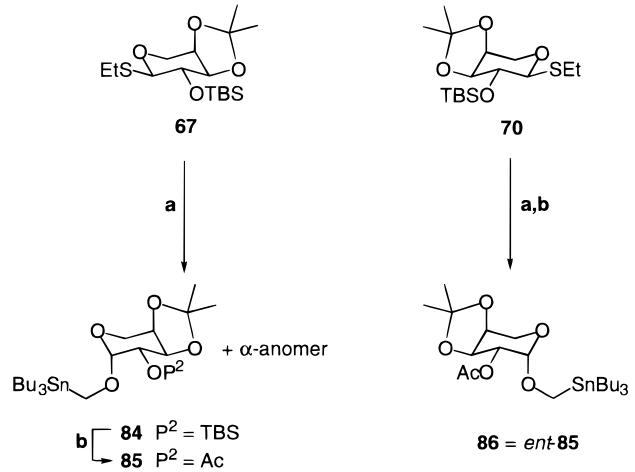
To address this issue in the context of our total synthesis, it would be necessary to assemble glycosyloxymethyl stannanes

Scheme 12



with both D- and L-arabinose sectors. We initially approached the problem of appending the stannyloxymethyl functionality to a suitable arabinose sector via a Schmidt-type alkylation of the anomeric hydroxyl with tributylstannylmethyl iodide.[43] This route was abandoned in the face of poor conversions and unacceptably low yields. We then envisaged a glycosylation of a suitable arabinosyl donor with tri-*n*-butylstannylmethanol (**83**).[44] Given the glycosylation results previously described in Schemes 10 and 11, we certainly had no grounds to anticipate significant stereoselection in the arabinosylation of **83**. Of course, we could afford the consequences of stereorandom glycosylation since the precious aglycon was not at risk at this stage.

Scheme 13[a]



[a] (**a**) Bu_3SnCH_2OH (**83**), MeOTf, DTBP, CH_2Cl_2:Et_2O [1:2], 4 Å molecular sieves, 0 °C, [α:*β* = ∼1:1], 93%; (**b**) **i** TBAF−THF, rt, ∼98%; **ii** Ac_2O, DMAP, CH_2Cl_2, rt, ∼99% [DMAP = 4-dimethylaminopyridine; DTBP = 2,6-di-*tert*-butylpyridine].

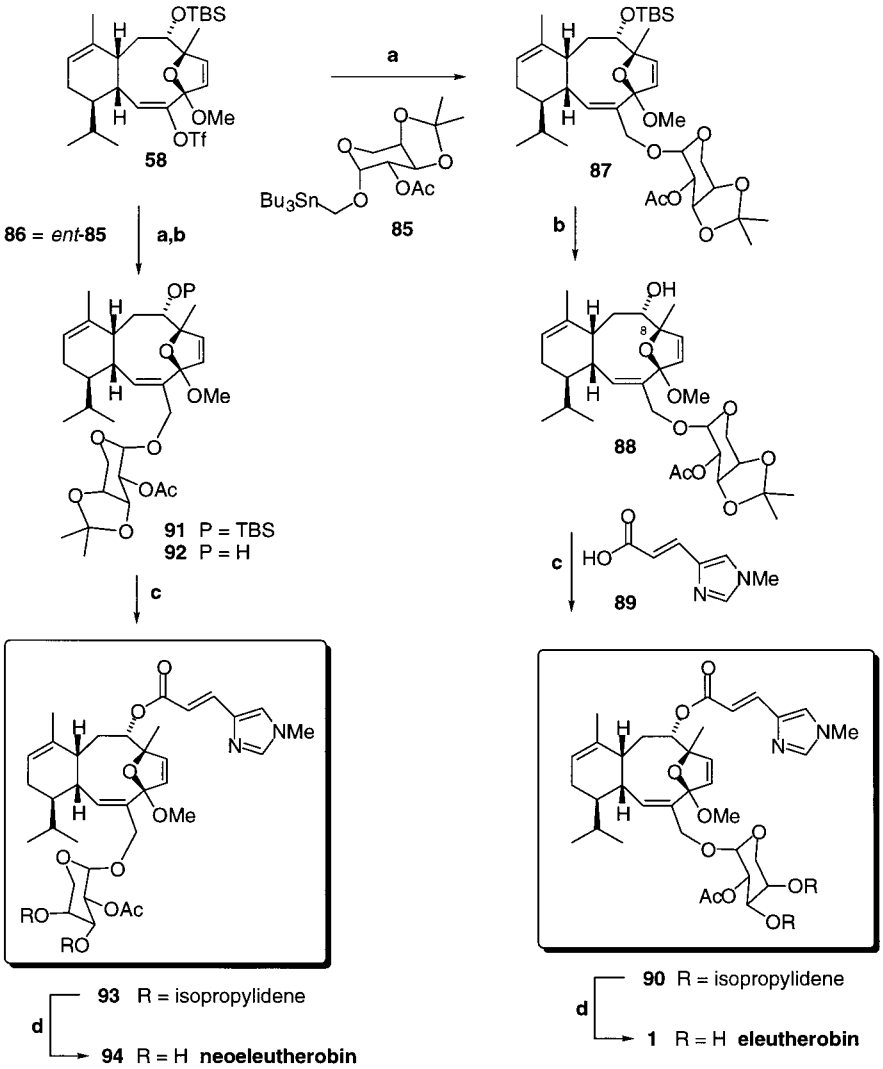
In the event, a Lönn−Garegg[45] glycosylation of the ethylthio donor **67** was carried out with **83** to give a 93% yield of a ∼1:1 mixture of glycosides (**84**) followed by removal of the silyl group. The components were then readily separated. For the moment, only the axial (*β*) anomer[41] was of interest. Installation

(43) (a) Schmidt, R. R.; Reichrath, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 466. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (b) Seitz, D. E.; Carroll, J. J.; Cartaya, M. C. P.; Lee, S.-H.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129.

(44) Seebach, D.; Meyer, N. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 438.

(45) (a) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973**, *27*, 5. (b) Garegg, P. J.; Henrichson, C.; Norberg, T. *Carbohydr. Res.* **1983**, *116*, 162. (c) Lönn, H. *Carbohydr. Res.* **1985**, *139*, 105, 115.

Scheme 14[a]



[a] (**a**) $Pd(PPh_3)_4$ (cat.), LiCl (40 equiv), THF, 130 °C, ~40−50%; (**b**) TBAF, THF, rt, 67%; (**c**) **89**, DCC, DMAP, $CHCl_3$, 50 °C, ~80%; (**d**) PPTS, MeOH, Δ, ~70%.

of an acetate led to **85**. In a similar way, the enantiomeric ethylthio donor, **70** (vide supra), served to glycosylate **83** affording as expected, a 1:1 mixture of separable glycosides. As before, the TBS group at the C2′ hydroxyl center was removed. Again only the axial (β) anomer was carried forward. The C2′ hydroxyl group was acetylated furnishing the potential *ent*-"oxycarba" donor **86** (Scheme 13).

The stage was now set to test the oxycarbaglycosidation concept set forth in Scheme 12. In the event, it turned out to be possible to effect a union of the domains in this way. Thus, reaction of vinyl triflate (**58**) with "oxycarbadonor" **85** gave rise to a Stille coupling product formulated as **87** (Scheme 14). It was assumed that nothing had occurred to affect the stereochemistry of the C2−C3 double bond. Proof was secured when compound **87** was eventually converted to eleutherobin (vide infra).

In the earliest stages of this oxycarbaglycosylation, the yields of the coupling were particularly modest. However, as developmental work went forward, some of the experimental parameters were defined. In particular, significant concentrations of lithium chloride were helpful.[46] Careful maintenance of the temperature and solvent conditions which are described in the Experimental Section are critical. Happily the yields seemed to be improving as the scale of the reaction was increased.

With this critical merger step accomplished, a clear route to eleutherobin could now be identified for the first time. Thus, the hydroxyl group at C8 in compound **87** was liberated by desilylation (see compound **88**). Several attempts were made to achieve acylation of the C8-hydroxyl with the acid chlorides derived from *N*-methyl urocanic acid **89**.[47] All of these methods were unsuccessful though it was never fully clarified if the failures resulted from failure to synthesize the acid chloride or, perhaps less likely, failure to achieve coupling of the C8 hydroxyl group to the acid chloride. In the end, success was achieved by coupling of the free acid to the C8 alcohol through the agency of dicyclohexylcarbodiimide in the presence of DMAP. This reaction afforded an 80% yield of compound **90**. At this stage there remained to be accomplished only the deprotection of the oxygens at C3′ and C4′ of the arabinose unit. This goal was attained through the action of PPTs in methanol as shown. The acetonide was cleaved as the last step

(46) For discussions on role of LiCl as an additive in Stille reactions, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 54. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (c) Reference 33b.

(47) (a) See ref 10a. (b) Mawlawi, H.; Monje, M. C.; Lattes, A.; Riviére, M. *J. Heterocycl. Chem.* **1992**, *29*, 1621. (c) Viguerie, N. L.; Sergueeva, N.; Damiot, M.; Mawlawi, H.; Riviére, M.; Lattes, A. *Heterocycles* **1994**, *37*, 1561.

of the synthesis, and the product was presumed to be fully synthetic eleutherobin.

Unfortunately, we did not have an "authentic" sample of eleutherobin available to us. While extensive representative spectra of eleutherobin were provided by Professor Fenical, a direct material comparison was not possible. The comparisons were quite encouraging in terms of their virtual spectral congruence.

It was at this stage that we had to face an important issue of intellectual rigor in using the total synthesis to support the Fenical structure of eleutherobin. *Implicit in such an application would be the assumption that were the real eleutherobin not to correspond to structure **1**, its spectral properties would be materially different from those of fully synthetic **1** of unambiguous structure*. It must be recognized that this type of surmise is inherent in all "proofs of structure" which accrue from apparent congruence of spectra of "authentic" and "synthetic" material. Given the sophisticated resolving power of modern spectroscopic measurements, this kind of assumption would seem to be warranted. However, in the case at hand, there were two sources of apprehension. First, we could not make a direct comparison. We were comparing in house measurements on our synthetic sample with data accrued elsewhere—necessarily under nonidentical conditions.

Furthermore, there was additional concern arising from the bidomainal nature of the structure. Our primary focus was that of differentiating between formulations **1** and **94** (neoeleutherobin, vide infra). The assumption that the spectroscopic properties of synthetic eleutherobin of unambiguous structure **1** would be materially different from those of **94** in which the aglycon sector is identical with **1** but the carbohydrate is enantiomeric implies the presumption that the two domains are measurably interactive at the level of spectroscopic readout. This need not necessarily be the case. If each sector is fully autonomous, the overall spectroscopic displays of eleutherobin and neoeleutherobin might very well be quite similar. Given the absence of authentic material, it seemed well to pursue this matter to a rigorous conclusion. We were well prepared to do so since, as described above, we had already assembled the L-arabinose donor construct **86**.

In the event, reaction of compound **58** with *ent*-donor **86** proceeded, as was described for the D-series donor **85** (see compound **91**). The coupling yields were quite comparable. The protocol for further progress had now been well established. Once again, cleavage of the TBS group at position 8 liberated the required hydroxyl group (**92**). Carbodiimide-mediated acylation with urocanic acid derivative **89** produced **93**. Finally, the acetonide group was cleaved as before with PPTs producing **94**. Needless to say, the pertinent spectra for compound **94** were eagerly measured and the readouts carefully scrutinized. These measurements on the L-arabinose-derived synthetic product revealed small, but unmistakable differences with the exhibited data provided by Fenical for "authentic" eleutherobin. The differences, while subtle, were far more substantive than the very slight differences between the data of the fully synthetic compound and that reported by Fenical for authentic **1**.

Moreover, with the two pure compounds in hand we could conduct an important polarimetric measurement. Thus, $[\alpha]^{23}_{D}$ of fully synthetic **1** was -73.2 ($c = 0.17$, MeOH). By contrast, the fully synthetic neoeleutherobin (**94**) has an $[\alpha]^{23}_{D}$ under comparable conditions of $+44.5$. It was previously reported that $[\alpha]^{25}_{D}$ for authentic eleutherobin was -49.3 ($c = 3.0$, MeOH).[9a] An $[\alpha]^{25}_{D}$ of -67.0 ($c = 0.2$, MeOH) had been registered for the fully synthetic eleutherobin arising from the laboratories of Professor K. C. Nicolaou.[12b] We can therefore confidently assert that the relative and absolute stereochemistry of eleutherobin is as implied in structure **1**. Furthermore, the total synthesis of this compound has thus been accomplished. Similarly, the total synthesis of neoeleutherobin, **94**, has been accomplished.

Summary

Several key facets of the venture merit recapitulation. The use of the readily available (*R*)-(−)-α-phellandrene (**6**) turned out to be a profitable one in that it provided a properly configured and fortuitously functionalized matrix for extensive investigations. The use of the Nozaki−Kishi ring closure to furanophane **38** provided a productive step in paving the way for the critical oxidative furfuryl alcohol → pyranose transposition **40** → **41**. The pyranose system served as a reliable platform for nucleophilic methylation **41** → **42** followed by controlled valence isomerization to a furanose (see **50** → **47**). Finally, the basis for a new method (oxycarbaglycosidation) for merging carbohydrate and lipid domains has been demonstrated (see **58** → **87**). In the course of these studies, the full structure of eleutherobin was clarified in detail.

As discussed earlier, one of the goals of our program in this total synthesis was to secure enough eleutherobin for biological investigation in xenografts. This was indeed accomplished. The results of both in vitro and in vivo studies with eleutherobin as well as SAR profiles will be disclosed soon.

Experimental Section

General Methods. All commercial materials were used without purification unless otherwise noted. The following solvents were distilled under positive pressure of dry argon: tetrahydrofuran (THF), diethyl ether (Et_2O) from sodium−benzophenone ketyl, methylene chloride (CH_2Cl_2) from CaH_2. All the reactions were performed under an inert (Ar) atmosphere. Spectra (^1H, ^{13}C) were recorded on AMX-300 MHz, AMX-400 MHz, and DRX-500 MHz Bruker instruments referenced to $CDCl_3$ (^1H NMR = δ 7.24 and ^{13}C NMR = δ 77.0) peaks unless stated otherwise. Line broadening = 1.0 Hz was used before Fourier transformation in ^{13}C NMR spectra. Infrared spectra were recorded with a Perkin-Elmer Paragon 1000 FTIR spectrometer, and optical rotations were measured with a Jasco DIP-30 instrument using a 10 cm length cell. Mass spectral analyses were performed with JEOL JMS-DX-303 and NERMAG R10-10 spectrometers. X-ray crystallographic analysis was performed on a Bruker P4 diffractometer using a SMART CCD detector. Analytical thin-layer chromatography was performed using E. Merck silica gel 60 F_{254} coated 0.25 mm plates. Compounds were visualized by dipping the plates in a cerium sulfate−ammonium molybdate solution followed by heating. Flash column chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40−63 μm). Unless otherwise indicated all isolated intermediates were >98% pure according to ^1H and ^{13}C NMR analysis.

Dichlorocyclobutanones 8 and 21. In a 250 mL three-necked flask, equipped with a mechanical stirrer and an addition funnel, were placed ether (50 mL), (*R*)-(−)-α-phellandrene **6** (3.5 mL, 100% purity, 21.6 mmol), and acid-washed zinc (2.82 g, 43.2 mmol) forming a gray suspension. The apparatus was placed in a sonication bath at 0 °C. The addition funnel was charged with a mixture of trichloroacetyl chloride (2.89 mL, 25.89 mmol) and ether (17 mL). The contents of the additional funnel were added in a dropwise fashion to the suspension over 2 h with stirring and sonication. After an additional hour of agitation at 0 °C, the reaction mixture was filtered through Celite 545 to reveal a clear pale yellow solution. The organics were concentrated in vacuo, and the residue was taken up in ether, refiltered, and washed with saturated solutions of $NaHCO_3$ and NaCl. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated, and chromatographed (99:1 hexanes:ether) to furnish the dichlorocyclobutanones **8** (3.4 g, 65%) and **21** (425 mg, 8%). In a similar manner the reaction was performed on larger scales (~100 mL of (*R*)-(−)-α-phellandrene, 50% purity) to yield the cyclobutanone in 60−83% yields.

The following data describe the major isomer **8**: ^{1}H NMR [300 MHz, $CDCl_3$] δ 5.73 (br m, 1H), 3.69 (dd, J = 10.1, 7.8 Hz, 1H), 3.25 (d, J = 10.4 Hz, 1H), 2.06 (m, 1H), 1.90−1.70 (m, 5H), 1.67 (m, 1H), 0.95 (d, J = 5.7 Hz, 3H), 0.88 (d, J = 5.7 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 197.1, 129.6, 125.7, 87.3, 56.9, 49.7, 38.4, 30.4, 24.7, 22.4, 20.7, 19.3; IR [ν max cm^{-1}] 3020, 2965, 1803, 1523; $[\alpha]^{23}_D = -18.4°$ (c 1.00, $CHCl_3$); HRMS (EI) calcd for $[C_{12}H_{16}Cl_2O]^+$ 246.0579, found 246.0590.

Data for the minor isomer **21**: ^{1}H NMR [300 MHz, $CDCl_3$] δ 5.83 (d, J = 7.3 Hz, 1H), 4.29 (ddd, J = 10.4, 5.5, 1.6 Hz, 1H), 3.40 (d, J = 10 Hz, 1H), 2.25 (m, 1H), 1.91 (d, J = 1.6 Hz, 3H and overlapping m, 1H), 1.70 (m, 1H), 1.22 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 197.5, 131.1, 127.8, 86.4, 56.9, 51.4, 40.9, 30.7, 27.3, 24.2, 21.5, 21.4; IR [ν max cm^{-1}] 2964, 2870, 1799, 1473.

Dechlorinated Cyclobutanone 9. To a suspension of zinc (24 g, 367 mmol) and ammonium chloride (20 g, 374 mmol) in methanol (100 mL) at 0 °C was added a solution of the dichlorocyclobutanone **8** (17.3 g, 70.0 mmol) in methanol (100 mL). The gray suspension was permitted to warm to room temperature (~25 °C), stirred for about 8 h, and then filtered to remove solids. After the solvent was concentrated in vacuo, the residue was taken up in ether and washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was again removed, and the residue was chromatographed (99:1 hexanes:ether) to furnish the cyclobutanone **9** (10.8 g, 87%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 5.55 (br s, 1H), 3.39 (m, 1H), 3.25 (m, 1H), 2.71 (m, 2H), 2.10 (m, 1H), 1.81 (m, 1H), 1.67 (m, 2H), 1.65 (s, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 211.3, 134.4, 122.3, 60.7, 51.0, 37.7, 30.5, 27.5, 24.9, 21.1, 20.8, 19.6; IR [ν max cm^{-1}] 2963, 1769; $[\alpha]^{23}_D = -159.2°$ (c 0.96, $CHCl_3$); MS (EI) 178 [M$^+$], 136.

Vinylogous Amide 23 via Bredereck Condensation. To a round-bottom flask equipped with a stir bar were added the cyclobutanone **9** (6.72 g, 37.7 mmol) and (t-BuO)(Me_2N)$_2$CH (50 mL, 242 mmol). The mixture was warmed to 60 °C for 3 h, before the excess reagent was recovered by distillation and the residue chromatographed (70:30 hexanes:EtOAc) on Florisil to furnish the vinylogous amide **23** (5.78 g, 66%) as a 2.5:1 mixture (based on integration of vinyl protons) of geometric isomers which was taken through to the next step. Selected ^{1}H NMR [500 MHz, $CDCl_3$] δ 6.94 (d, J = 1.2 Hz, 0.29H), 5.9 (d, J = 0.6 Hz, 0.71H), 5.47 (br unresolved m, 0.29H), 5.40 (br unresolved m, 0.71H), 3.16 (br unresolved m, 4.3H), 2.99 (s, 1.7H), 1.81 (d, J = 1.6 Hz, 0.87H), 1.72 (d, J = 1.4 Hz, 2.13H).

Aldehyde Ester 25. The vinylogous amide **23** (12.8 g, 54.9 mmol) and methanol (90 mL) were added to a round-bottom flask, and p-TsOH·H_2O (10.5 g, 55.2 mmol) was added. The mixture was stirred for 4 h at 60 °C and cooled to room temperature, and the solvent removed in vacuo. The residue was dissolved in acetone (120 mL), and an additional portion of p-TsOH·H_2O (10.5 g, 55.2 mmol) was added. After stirring for 1 h, the contents were concentrated in vacuo and the residue was dissolved in ether and washed sequentially with saturated solutions of $NaHCO_3$ and brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, concentrated, and chromatographed (96:4 → 94:6 hexanes:ether) to yield the aldehyde ester **25** (7.8 g, 60%): ^{1}H NMR [400 MHz, $CDCl_3$] δ 9.68 (s, 1H), 5.41 (br s, 1H), 3.57 (s, 3H), 2.99 (m, 2H), 2.65 (m, 1H), 2.33 (m, 1H), 1.85 (m, 4H), 1.62 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 201.1, 175.7, 134.1, 122.3, 51.5, 46.3, 44.5, 34.9, 34.8, 27.6, 23.2, 21.7, 20.9, 15.2; IR [ν max cm^{-1}] 2958, 1727; $[\alpha]^{23}_D = +59.3°$ (c 0.50, $CHCl_3$); HRMS (FAB) calcd for $[C_{14}H_{22}O_3]^+$ 238.1569, found 238.1562.

Lithiofuran Addition. A dry round-bottom flask (100 mL), equipped with a stir bar, was charged with tetrahydrofuran (10 mL). The aldehyde **25** (1.31 g, 5.5 mmol) was added, and the mixture was cooled to −78 °C. A separate flask (100 mL), equipped with a stir bar, was charged with tetrahydrofuran (20 mL). The dibromomofuran **26** (3.72 g, 16.5 mmol) was added and the mixture cooled to −78 °C. n-BuLi (2.5 M, 1 equiv, 6.2 mL) was added in a dropwise fashion, and after stirring for 10 min, the contents of this flask were cannulated in dropwise into the flask that contained the aldehyde. The resulting mixture was allowed to stir for ~1 h at −78 °C, then the reaction was quenched with methanol followed by pH 7 buffer, and the reaction was permitted to slowly warm to room temperature. After regular extractions with ether, the organic layer was washed with brine and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the residue was immediately chromatographed (95:5 → 90:10 hexanes:ether) to furnish the following compounds and some recovered aldehyde **25**, which was recycled. The yields are based on recovered starting material and varied (38−57% for **28**) with the scale of the reaction.

Alcohol 28 (0.88 g, 57%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 6.21 (d, J = 3.3 Hz, 1H), 6.18 (d, J = 3.3 Hz, 1H), 5.38 (br s, 1H), 4.44 (m, 1H), 3.67 (s, 3H), 2.65 (m, 1H), 2.41 (m, 1H), 2.25 (m, 2H), 1.9 (m, 5H), 1.55 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 175.6, 158.9, 135.3, 121.6, 120.9, 111.8, 108.4, 66.3, 51.5, 46.8, 37.4, 35.9, 35.3, 27.7, 23.4, 22.0, 20.9, 15.7; IR [ν max cm^{-1}] 3721, 3580, 1725; $[\alpha]^{23}_D = +53.9°$ (c 1.5, $CHCl_3$); HRMS (EI) calcd for $[C_{18}H_{25}BrO_4]^+$ 384.0937, found 384.0929.

Alcohol 29 (0.38 g, 24%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 6.25 (m, 2H), 5.47 (br s, 1H), 4.51 (m, 1H), 3.68 (s, 3H), 2.67 (m, 1H), 2.31 (m, 2H), 1.96 (m, 4H), 1.83 (m, 2H), 1.71 (s, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 175.6, 158.4, 136.2, 121.2, 121.1, 111.8, 108.9, 67.8, 51.4, 47.2, 38.2, 36.5, 35.2, 27.7, 23.4, 22.2, 20.9, 15.5; IR [ν max cm^{-1}] 3424, 2959, 1725; $[\alpha]^{23}_D = +71.5°$ (c 0.41, $CHCl_3$).

Lactone 30 (0.25 g, 18%): ^{1}H NMR [400 MHz, $CDCl_3$] δ 6.35 (d, J = 3.3 Hz, 1H), 6.27 (d, J = 3.3 Hz, 1H), 5.43 (br s, 1H), 5.25 (dd, J = 12.1, 2.7 Hz, 1H), 2.80 (t, J = 7.3 Hz, 1H), 2.63 (m, 1H), 2.35 (ddd, J = 14.2, 6.3, 2.7 Hz, 1H), 2.18 (m, 1H), 1.82 (m, 3H), 1.69 (m, 1H), 1.65 (s, 3H), 0.93 (d, J = 4.2 Hz, 3H), 0.91 (d, J = 4.2 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 172.7, 153.3, 132.9, 122.6, 122.0, 112.1, 111.0, 72.6, 41.4, 37.2, 34.6, 30.7, 27.4, 23.7, 21.2, 21.0, 18.5; IR [ν max cm^{-1}] 1732; $[\alpha]^{23}_D = +33.8°$ (c 0.50, $CHCl_3$); HRMS (FAB) calcd for $[C_{17}H_{22}BrO_3]^+$ 353.0753, found 353.0755.

Silylated Alcohol 31. A solution of alcohol **28** (8.66 g, 22.5 mmol) in methylene chloride (50 mL) at 0 °C was treated with imidazole (9.17 g, 134.7 mmol) and TBDPSCl (17.5 mL, 67.3 mmol), and the mixture was stirred at 25 °C for 4 h. The reaction mixture was diluted with methylene chloride (200 mL), washed successively with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Chromatography (99:1 hexanes:ether) provided the TBDPS ether **31** (12.0 g, 97%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.66 (m, 2H), 7.46 (m, 2H), 7.38 (m, 4H), 7.27 (m, 2H), 5.91 (d, J = 3.2 Hz, 1H), 5.59 (d, J = 3.2 Hz, 1H), 5.31 (br s, 1H), 4.37 (dd, J = 8.4, 5.2 Hz, 1H), 3.44 (s, 3H), 2.56 (dd, J = 10.6, 4.4 Hz, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 2.03 (m, 1H), 1.87 (m, 3H), 1.78 (m, 1H), 1.70 (s, 3H), 1.02 (s, 9H), 0.85 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 174.7, 157.6, 136.2, 136.0, 135.4, 133.4, 133.1, 129.6, 129.1, 127.6, 127.1, 120.8, 120.4, 111.3, 109.6, 68.2, 51.2, 47.2, 37.5, 37.4, 34.8, 27.6, 26.8, 23.2, 22.3, 20.8, 19.3, 15.4 (6 unresolved); IR [ν max cm^{-1}] 2959, 1732; $[\alpha]^{20}_D = -30.1°$ (c 0.84, $CHCl_3$); HRMS (FAB) calcd for $[C_{34}H_{42}BrO_4Si]^+$ 621.2036, found 621.2029.

Alcohol. To a solution of the ester **31** (11.4 g, 18.3 mmol) in toluene (anhydrous, 100 mL) at −78 °C was added dropwise DIBAL (1.0 M in hexane solution, 54.9 mL). After ~1 h, acetone (3 mL), ethyl acetate (3 mL), and aqueous buffer (pH 7, 3 mL) were sequentially added, the cooling bath was removed, and the solution was stirred vigorously. After 20 min, anhydrous Na_2SO_4 was added and the reaction mixture was stirred vigorously for a further 30 min. The mixture was then filtered through a pad of anhydrous Na_2SO_4 in a sintered glass funnel (medium) and the solvent removed under reduced pressure. Chromatography (95:5 hexanes:ether) provided the primary alcohol (10.8 g, 99%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.68 (dd, J = 7.9, 1.3 Hz, 2H), 7.49 (dd, J = 7.9, 1.3 Hz, 2H), 7.41 (m, 1H), 7.37 (m, 3H), 7.29 (t, J = 7.5 Hz, 2H), 5.99 (d, J = 3.3 Hz, 1H), 5.65 (d, J = 3.3 Hz, 1H), 5.23 (br s, 1H), 4.78 (t, J = 7.0 Hz, 1H), 3.65 (dt, J = 11.1, 5.6 Hz, 1H), 3.47 (dt, J = 10.7, 4.5 Hz, 1H), 2.12 (m, 1H), 2.06 (m, 1H), 1.86 (m, 2H), 1.70 (m, 3H), 1.49 (d, J = 1.3 Hz, 3H), 1.43 (m, 1H), 1.28 (t, J = 5.4 Hz, 1H), 1.04 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 157.7, 137.3, 136.0, 135.6, 133.3, 129.7, 129.3, 127.5, 127.2, 121.1, 120.5, 111.5, 110.2, 68.6, 62.0, 41.7, 37.0, 36.0, 34.6, 26.9, 24.1, 22.8, 21.0, 19.2, 16.0 (8

unresolved); IR [ν max cm^{-1}] 3429, 2954, 2858; $[\alpha]^{20}_D = -5.3°$ (*c* 1.34, $CHCl_3$); HRMS (FAB) calcd for $[C_{33}H_{42}BrO_3Si]^+$ 593.2086, found 593.2070.

Mesylation. A solution of alcohol (12.2 g, 20.48 mmol) in pyridine (50 mL) was cooled to 0 °C prior to sequential addition of DMAP (300 mg) and CH_3SO_2Cl (4.75 mL, 61.37 mmol). The cooling bath was removed after 5 min, and the mixture was stirred at 25 °C for 4 h. The reaction was quenched with the addition of saturated aqueous $CuSO_4$ and diluted with EtOAc, and the layers were separated. The aqueous portion was extracted with EtOAc, and the combined organic portions were dried over anhydrous Na_2SO_4, filtered, and concentrated. Chromatography (95:5 → 90:10 hexanes:EtOAc) furnished the mesylate (12.68 g, 92%) as a colorless oil: ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.65 (dd, J = 7.8, 1.3 Hz, 2H), 7.46 (dd, J = 7.8, 1.3 Hz, 2H), 7.40 (m, 1H), 7.36 (m, 3H), 7.28 (t, J = 7.6 Hz, 2H), 6.00 (d, J = 3.3 Hz, 1H), 5.76 (d, J = 3.3 Hz, 1H), 5.22 (br s, 1H), 4.67 (dd, J = 7.7, 6.6 Hz, 1H), 4.21 (dd, J = 10.1, 6.2 Hz, 1H), 4.00 (dd, J = 10.1, 8.0 Hz, 1H), 2.85 (s, 3H), 2.05 (m, 1H), 1.94 (m, 4H), 1.82 (m, 1H), 1.57 (m, 1H), 1.47 (d, J = 0.9 Hz, 3H), 1.42 (m, 1H), 1.00 (s, 9H), 0.78 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 157.3, 135.8, 135.7, 135.5, 133.3, 133.2, 129.7, 129.4, 127.6, 127.3, 121.4, 120.7, 111.5, 110.4, 69.9, 68.1, 39.1, 37.2, 37.0, 36.6, 34.7, 31.4, 27.2, 26.8, 23.8, 22.7, 22.6, 20.6, 19.1, 17.1, 14.1 (3 unresolved); IR [ν max cm^{-1}] 2960, 2858, 1590; $[\alpha]^{20}_D = -14.0°$ (*c* 0.95, $CHCl_3$); HRMS (FAB) calcd for $[C_{34}H_{44}BrO_5SSi]^+$ 671.1862, found 671.1869.

Cyanide 36. To a solution of the mesylate (12.86 g, 18.82 mmol) and 18-crown-6 (12.4 g, 46.91 mmol) in CH_3CN (anhydrous, 85 mL) was added potassium cyanide (6.13 g, 94.13 mmol), and the reaction mixture was heated to 60 °C for 2.5 h. The mixture was then quenched with ice−water and extracted with ether. The crude product was chromatographed (97:3 hexanes:EtOAc) to give the nitrile **36** (10.87 g, 96%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.65 (dd, J = 7.8, 1.3 Hz, 2H), 7.43 (m, 3H), 7.37 (m, 3H), 7.28 (t, J = 7.4 Hz, 2H), 6.04 (d, J = 3.2 Hz, 1H), 5.80 (d, J = 3.2 Hz, 1H), 5.20 (br s, 1H), 4.65 (t, J = 7.1 Hz, 1H), 2.17 (m, 2H), 1.96 (m, 1H), 1.87 (m, 4H), 1.81 (m, 1H), 1.50 (m, 1H), 1.42 (s, 3H), 1.40 (m, 1H), 1.00 (s, 9H), 0.76 (d, J = 7.7 Hz, 3H), 0.75 (d, J = 7.7 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ156.8, 135.8, 135.5, 134.8, 133.2, 133.0, 129.8, 129.4, 127.6, 127.3, 121.2, 121.0, 119.3, 111.6, 110.7, 77.2, 68.3, 38.5, 36.6, 35.6, 27.2, 26.8, 23.6, 22.3, 20.4, 19.1, 17.9, 17.5 (6 unresolved); IR [ν max cm^{-1}] 2960, 2894, 2248; $[\alpha]^{20}_D = -17.5°$ (*c* 1.05, $CHCl_3$); HRMS (FAB) calcd for $[C_{34}H_{41}BrNO_2Si]^+$ 602.2090, found 602.2090.

Aldehyde 37. To a solution of the nitrile **36** (9.75 g, 16.2 mmol) in toluene (200 mL) at −78 °C was added dropwise DIBAL (1.0 M in hexane solution, 32.3 mL). The reaction mixture was warmed to room temperature over 1 h before acetone (3 mL), ethyl acetate (3 mL), and aqueous buffer (pH 7, 3 mL) were sequentially added and the solution stirred vigorously. After 20 min, anhydrous Na_2SO_4 was added and the reaction mixture stirred vigorously for a further 30 min. The mixture was then filtered through a pad of anhydrous Na_2SO_4 in a sintered glass funnel (medium). The solvents were removed under reduced pressure. Chromatography (96:4 hexanes:ether) provided the aldehyde **37** (8.44 g, 86%): ^{1}H NMR [500 MHz, $CDCl_3$] 9.54 (t, J = 1.9 Hz, 1H), 7.64 (dd, J = 7.9, 1.3 Hz, 2H), 7.45 (dd, J = 7.9, 1.3 Hz, 2H), 7.41 (m, 1H), 7.34 (m, 3H), 7.27 (t, J = 7.4 Hz, 2H), 6.01 (d, J = 3.2 Hz, 1H), 5.71(d, J = 3.2 Hz, 1H), 5.19 (br s, 1H), 4.59 (dd, J = 8.9, 5.7 Hz, 1H), 2.29 (ddd, J = 16.6, 6.6, 2.5 Hz, 1H), 2.21 (ddd, J = 16.6, 7.1, 1.5 Hz, 1H), 2.13 (m, 1H), 1.96 (m, 1H), 1.87 (m, 2H), 1.80 (m, 2H), 1.53 (m 1H), 1.41 (d, J = 1.0 Hz, 3H), 1.23 (m, 1H), 0.99 (s, 9H), 0.77 (d, J = 6.8 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 202.4, 157.1, 136.2, 135.8, 135.5, 133.3, 133.2, 129.7, 129.4, 127.6, 127.3, 121.0, 120.8, 111.5, 110.6, 68.5, 43.6, 38.8, 37.4, 36.2, 34.3, 27.2, 26.8, 23.9, 22.6, 20.8, 19.1, 17.2 (6 unresolved); IR [ν max cm^{-1}] 2959, 1724; $[\alpha]^{20}_D = -6.2°$ (*c* 3.05, $CHCl_3$); HRMS (FAB) calcd for $[C_{34}H_{43}BrO_3SiNa]^+$ 629.2063, found 629.2077.

Nozaki−Kishi Cyclization. Anhydrous chromium dichloride (5.94 g, 48.33 mmol) and anhydrous nickel chloride (1.3 g, 10.03 mmol) were placed in a dry 1 L flask and cooled to −60 °C. Anhydrous DMF (475 mL) was added slowly to the stirred mixture of solids. Thereafter, the mixture was degassed (via freeze−thaw, 3 cycles). Separately, the aldehyde **37** (6.16 g, 10.14 mmol) was taken up in DMF (150 mL) and degassed as well. This solution was then added via a cannula to the mixture of $CrCl_2$ and $NiCl_2$ in DMF at −60 °C. After completion of addition, the cooling bath was removed and the reaction mixture allowed to stir at room temperature. After 6−8 h, water was added and the reaction mixture partitioned between ether and water. The aqueous phase was extracted three times with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resultant oil was purified by chromatography (95:5 → 80:20 hexanes:ether) to afford the furanophane **38** (3.77 g, 70%) and the C3-β epimer (215 mg, 4%).

Data for the major isomer, **alcohol 38**: ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.71 (m, 4H), 7.38 (m, 6H), 6.04 (d, J = 3.0 Hz, 1H), 5.95 (d, J = 3.0 Hz, 1H), 5.01 (br s, 1H), 4.60 (dd, J = 9.9, 5.6 Hz, 1H), 4.46 (m, 1H), 2.56 (ddd, J = 12.5, 9.9, 2.0 Hz, 1H), 2.39 (q, J = 12.2 Hz, 1H), 2.10 (dt, J = 13.2, 3.4 Hz, 1H), 2.02 (m, 1H), 1.95 (d, J = 6.0 Hz, 1H), 1.82 (m, 1H), 1.63 (m, 1H), 1.45 (dt, J = 13.1, 5.3 Hz, 1H), 1.34 (m, 1H), 1.23 (m, 1H), 1.08 (s, 12H), 0.88 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H), −0.56 (br s, 1H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 160.5, 159.7, 139.1, 135.9, 135.7, 133.7, 133.6, 129.7, 129.6, 127.5, 127.4, 118.5, 116.5, 110.6, 70.6, 68.1, 43.3, 39.7, 38.4, 37.2, 36.8, 26.9, 26.8, 24.8, 22.0, 21.4, 19.1, 15.0 (6 unresolved); IR [ν max cm^{-1}] 3336, 2955; $[\alpha]^{20}_D = +28.7°$ (*c* 0.94, $CHCl_3$); HRMS (FAB) calcd for $[C_{34}H_{44}O_3Si]^+$ 528.3060, found 528.3050.

Data for the minor isomer: ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.71 (m, 4H), 7.40 (m, 6H), 6.00 (dd, J = 3.0, 1.3 Hz, 1H), 5.97 (d, J = 3.0 Hz, 1H), 5.17 (d, J = 9.4 Hz, 1H), 5.03 (br s, 1H), 4.58 (dd, J = 9.8, 5.6 Hz, 1H), 2.48 (ddd, J = 11.5, 9.9, 2.1 Hz, 1H), 2.33 (m, 1H), 1.99 (m, 2H), 1.84 (m, 1H), 1.66 (m, 1H), 1.60 (d, J = 9.5 Hz, 1H), 1.46 (dt, J = 13.1, 5.4 Hz, 1H), 1.38 (m, 2H), 1.07 (s, 12H), 0.88 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H), −0.43 (br s, 1H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 163.8, 159.4, 139.2, 136.0, 135.8, 133.9, 133.8, 129.7, 129.6, 127.6, 127.5, 118.6, 116.9, 106.4, 69.9, 69.6, 43.0, 38.0, 36.6, 36.4, 35.1, 27.0, 26.8, 25.0, 22.1, 21.5, 19.2, 14.8 (6 unresolved); IR [ν max cm^{-1}] 3330, 2955; $[\alpha]^{20}_D = -17.9°$ (*c* 0.64, $CHCl_3$); HRMS (FAB) calcd for $[C_{34}H_{44}O_3Si]^+$ 528.3060, found 528.3050.

Pivaloate 39. The alcohol **38** (3.77 g, 7.13 mmol) and DMAP (518 mg, 4.24 mmol) were dissolved in CH_2Cl_2 (50 mL), and the mixture was cooled to 0 °C. Triethylamine (5.92 mL, 4.25 mmol) and pivaloyl chloride (2.65 mL, 21.98 mmol) were sequentially added, and the mixture was stirred for 5 h. The reaction mixture was then diluted with CH_2Cl_2 (200 mL) and washed with aqueous buffer (pH 7, 30 mL) followed by brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by chromatography (96:4 hexanes:ether) to give the ester **39** (3.97 g, 91%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.71 (m, 4H), 7.39 (m, 6H), 6.16 (d, J = 3.0 Hz, 1H), 5.96 (d, J = 3.0 Hz, 1H), 5.40 (dd, J = 11.0, 3.7 Hz, 1H), 5.01 (br s, 1H), 4.59 (dd, J = 9.9, 5.6 Hz, 1H), 2.58 (ddd, J = 12.7, 10.1, 2.2 Hz, 1H), 2.51 (q, J = 12.5 Hz, 1H), 1.96 (m, 2H), 1.83 (m, 1H), 1.65 (m, 1H), 1.45 (dt, J = 13.0, 5.3 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.23 (m, 9H), 1.08 (s, 9H), 1.06 (s, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H), −0.54 (br s, 1H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 178.0, 160.9, 156.7, 139.0, 135.9, 135.8, 133.7, 133.6, 129.7, 129.6, 127.6, 127.5, 118.5, 116.8, 113.2, 70.6, 69.5, 43.3, 39.7, 38.7, 38.4, 37.0, 32.9, 27.1, 27.0, 24.9, 22.1, 21.4, 19.1, 15.0 (9 unresolved); IR [ν max cm^{-1}] 2955, 1723; $[\alpha]^{20}_D = +74.0°$ (*c* 0.90, $CHCl_3$); HRMS (FAB) calcd for $[C_{39}H_{52}O_4SiNa]^+$ 635.3533, found 635.3514.

Alcohol 40. A mixture of the silyl ether **39** (353 mg, 0.57 mmol) was taken up in THF (5 mL), TBAF (1.0 M THF, 2.87 mL) was added, and the reaction was stirred at room temperature for 10−12 h. The reaction mixture was diluted with ethyl acetate and aqueous buffer (pH 7) added. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was chromatographed (85:15 hexanes:ether) to give alcohol **40** (235 mg, 95%): ^{1}H NMR [400 MHz, $CDCl_3$] δ 6.44 (d, J = 3.0 Hz, 1H), 6.29 (d, J = 3.0 Hz, 1H), 5.43 (dd, J = 11.0, 4.0 Hz, 1H), 5.11 (br s, 1H), 4.73 (dd, J = 9.9, 5.7 Hz, 1H), 2.42 (m, 2H), 2.17 (br s, 1H), 1.92 (m, 3H), 1.68 (m, 2H), 1.43 (d, J = 1.5 Hz, 3H), 1.35 (m, 1H), 1.26 (m, 1H), 1.19 (s, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H), −0.31 (br s, 1H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 178.0, 160.7, 157.0, 138.5, 118.8, 116.7, 113.4, 69.3, 69.2, 42.9, 39.3, 38.6, 38.5, 37.0, 32.9, 27.0, 26.9, 24.8, 22.3, 21.2, 15.0 (2

unresolved); IR [ν max cm^{-1}] 3424, 2955, 1723, 1475; $[\alpha]^{20}_D = +29.3°$ (*c* 0.92, $CHCl_3$); HRMS (EI) calcd for $[C_{23}H_{34}O_4]^+$ 374.2457, found 374.2453.

Enone Lactol 41. To a round-bottom flask were added the hydroxy furan **40** (191 mg, 2.45 mmol) and CH_2Cl_2 (20 mL), and the mixture was cooled to −78 °C. Dimethyldioxirane (20.3 mL, 0.116 M in acetone, 2.35 mmol) was then syringed in slowly and the reaction mixture stirred for 10 min. The solvent was then removed by a strong flow of Ar. The residue was chromatographed (95:5 → 90:10 hexanes:EtOAc) to furnish the enone **41** (903 mg, 94%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 7.08 (d, J = 10.5 Hz, 1H), 6.19 (d, J = 10.5 Hz, 1H), 5.35 (br s, 1H), 4.89 (d, J = 7.6 Hz, 1H), 4.67 (t, J = 4.4 Hz, 1H), 3.29 (br s, 1H), 2.50−2.32 (m, 1H), 2.12−1.71 (m, 7H), 1.63−1.38 (m, 2H), 1.58 (s, 3H), 1.26 (s, 9H), 0.92 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 196, 178, 152, 127, 123, 93, 79, 78, 40, 38, 33, 27, 27, 25, 22, 22; IR [ν max cm^{-1}] 3442, 2960, 1711, 1691, 1479; $[\alpha]^{20}_D = -60.3°$ (*c* 0.69, $CHCl_3$); HRMS (EI) calcd for $[C_{23}H_{34}O_5]^+$ 390.2406, found 390.2399.

Alcohol Lactol 42. The crude lactol enone **41** (110 mg, 0.28 mmol) was dissolved in THF (5 mL). The solution was cooled to −78 °C, and a solution of CH_3Li (1.4 M, 0.76 mL, 1.07 mmol) was added slowly. The reaction was stirred at −78 °C for 30 min before it was quenched by methanol and pH 7.0 buffer. The aqueous solution was extracted with EtOAc (3 times). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude material was purified by chromatography (85:15 → 80:20 hexanes:EtOAc) to give the desired product **42** (46 mg, 42%): ^{1}H NMR [400 MHz, $CDCl_3$] δ 6.22 (d, J = 6.0 Hz, 1H), 5.91 (d, J = 6.0 Hz, 1H), 5.18 (br s, 1H), 4.88 (d, J = 8.6 Hz, 1H), 3.85 (d, J = 9.6 Hz, 1H), 3.26 (br s, 1H), 2.54 (br s, 1H), 1.69 (s, 3H), 1.51 (s, 3H), 1.56−1.84 (m, 8H), 1.18 (s, 9H), 1.17−1.24 (m, 2H), 0.82 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 178.8, 138.7, 136.2, 128.5, 119.3, 111.4, 93.6, 77.1, 76.8, 39.2, 38.7, 38.0, 37.9, 36.8, 31.8, 29.7, 27.1, 26.9, 26.6, 24.3, 23.0, 21.2 (2 unresolved); IR [ν max cm^{-1}] 3438, 2959, 1709; $[\alpha]^{20}_D = +31.2°$ (*c* 2.09, $CHCl_3$); MS (CI, NH_3) 389 $[M + H - H_2O]^+$.

Enone Silylated Lactol 49. A round-bottom flask (equipped with a stir bar) was charged with the enone **41** (997 mg, 2.55 mmol). CH_2Cl_2 (80 mL) was added and the solution cooled to −78 °C following which 2,6-lutidine (0.89 mL, 7.65 mmol) and trimethylsilyl triflate (0.68 mL, 3.76 mmol) were added slowly and the mixture was stirred for 10 min whence TLC analysis showed disappearance of the starting material. The cooling bath was then removed and aqueous buffer (pH 7) added. The reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the crude material was chromatographed [94:5:1 hexanes:ether:triethylamine] to furnish the protected enone **49** (1.08 g, 92%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 7.14 (d, J = 10.5 Hz, 1H), 6.10 (d, J = 10.5 Hz, 1H), 5.32 (br s, 1H), 4.71 (d, J = 7.1 Hz, 1H), 4.60 (t, J = 4.4 Hz, 1H), 2.41−2.27 (m, 1H), 2.10−1.68 (m, 7H), 1.62−1.38 (m, 5H), 1.23 (s, 9H), 0.93 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 196, 179, 154, 125, 122, 94, 78, 39, 39, 27, 27, 25, 22, 22, 2; IR [ν max cm^{-1}] 2959, 1727, 1691, 1480; $[\alpha]^{23}_D = +14.2°$ (*c* 0.45, $CHCl_3$); HRMS (EI) calcd for $[C_{26}H_{42}O_5Si]^+$ 462.2802, found 462.2801.

Alcohol 50. To a round-bottom flask, equipped with a stir bar, were added the enone **49** (1.08 g, 2.33 mmol) and ether (70 mL), and the mixture was cooled to −78 °C. Methyllithium (1.4 M in ether, 16.6 mL, 23.24 mmol) was added slowly and the mixture stirred for 10 min whence TLC analysis showed very little starting material left. The reaction mixture was quenched at −78 °C with methanol and aqueous buffer (pH 7) and the cooling bath removed. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was chromatographed [90:10:1 hexanes:EtOAc:Et_3N] to furnish the alcohol **50** (963 mg, 86%; 99% based on recovered starting material): ^{1}H NMR [300 MHz, $CDCl_3$] δ 5.74 (d, J = 10.4 Hz, 1H), 5.62 (dd, J = 10.4, 1.0 Hz, 1H), 5.40 (br s, 1H), 4.88 (d, J = 7.3 Hz, 1H), 4.10 (dd, J = 12.1, 4.2 Hz, 1H), 2.69−2.55 (m, 3H), 2.38−2.33 (m, 1H), 2.19−2.05 (m, 2H), 1.96−1.82 (m, 1H), 1.82−1.70 (m, 4H), 1.62 (s, 1H), 1.55−1.42 (m, 2H), 1.49 (s, 3H), 1.23 (s, 9H), 0.94 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 179, 134, 132, 131, 122, 94, 80, 79, 78, 68, 47, 39, 39, 36, 35, 30, 28, 28, 24, 22, 22, 21, 3 (4 unresolved); IR [ν max cm^{-1}] 3474, 2959, 1725, 1479; $[\alpha]^{22}_D = -31.1°$ (*c* 0.46, $CHCl_3$); HRMS (EI) calcd for $[C_{27}H_{46}O_5Si]^+$ 478.3115, found 478.3120.

Acid-Mediated Pyranose−Furanose Rearrangement. The alcohol **50** (936 mg, 1.96 mmol) was taken up in methanol (70 mL). *p*-TsOH·H_2O (56 mg, 0.29 mmol) was added and the solution allowed to stir at room temperature. TLC analysis after ∼30 min indicated disappearance of starting material. Et_3N (a few drops) was added to quench the reaction, and after concentration in vacuo, the crude material was chromatographed with (90:9:1 hexanes:EtOAc:Et_3N) to give the desired **47** (742 mg, 90%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 6.25 (d, J = 6.0 Hz, 1H), 5.88 (d, J = 6.0 Hz, 1H), 5.19 (br s, 1H), 4.98 (d, J = 9.2 Hz, 1H), 3.85 (d, J = 10.2 Hz, 1H), 3.18 (s, 3H), 2.53 (br s, 1H), 1.82−1.86 (m, 2H), 1.73 (s, 3H), 1.64−1.74 (m, 4H), 1.50 (s, 3H), 1.45 (dd, J = 15.1, 3.1 Hz, 1H), 1.17 (s, 9H), 1.14−1.23 (m, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 177.1, 138.7, 136.5, 127.9, 119.4, 114.3, 93.4, 77.2, 73.6, 49.9, 38.9, 38.6, 38.1, 37.8, 36.9, 32.0, 26.9, 26.7, 26.0, 24.3, 23.0, 22.2, 15.1 (2 unresolved); IR [ν max cm^{-1}] 3491, 2962, 1723, 1455, 1361, 1281; $[\alpha]^{20}_D = +22.9°$ (*c* 1.50, $CHCl_3$); HRMS (FAB) calcd for $[C_{25}H_{40}O_5Na]^+$ 443.2773, found 443.2763.

Silylated Alcohol 48. To a round-bottom flask, equipped with a stir bar, was added the alcohol **47** (715 mg, 1.70 mmol). Methylene chloride (50 mL) was added and the solution cooled to 0 °C. Thereafter, 2,6-lutidine (1.15 mL, 9.87 mmol) was added followed by TBSOTf (1.13 mL, 4.92 mmol). The cooling bath was then removed and the mixture stirred for 10 min before aqueous buffer (pH 7) was added. The reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed (99:1 → 96:4 hexanes:ether) to furnish the silylated compound **48** (754 mg, 83%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 6.25 (d, J = 6.0 Hz, 1H), 5.88 (d, J = 6.0 Hz, 1H), 5.22 (br s, 1H), 5.03 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 9.6 Hz, 1H), 3.22 (s, 3H), 2.57 (br s, 1H), 1.95−1.40 (m, 9H), 1.76 (s, 3H), 1.46 (s, 3H), 1.21 (s, 9H), 0.91 (s, 9H), 0.87 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H), 0.11 (s, 3H) 0.10 (s, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 178, 139, 138, 128, 120, 115, 94, 78, 74, 50, 40, 39, 38, 38, 37, 32, 27, 27, 27, 26, 25, 24, 22, 18, 16, −3, −4 (4 unresolved); IR [ν max cm^{-1}] 2957, 1728; $[\alpha]^{23}_D = +25.3°$ (*c* 1.21, $CHCl_3$); HRMS (FAB) calcd for $[C_{31}H_{54}O_5Si]^+$ 534.3741, found 534.3761.

Alcohol 51. To a round-bottom flask, equipped with a stir bar, were added the pivaloate **48** (812 mg, 1.52 mmol) and methylene chloride (40 mL), and the mixture was cooled to −78 °C. DIBAL (1.0 M in hexane, 4.44 mL) was added slowly, and the mixture was stirred for 10 min before acetone (3 mL), ethyl acetate (3 mL), and aqueous buffer (pH 7, 3 mL) were sequentially added. The cooling bath was removed and the resulting solution stirred vigorously for 20 min. Thereafter, anhydrous Na_2SO_4 was added and the reaction mixture was stirred vigorously for a further 30 min. The mixture was then filtered through a pad of anhydrous Na_2SO_4 in a sintered glass funnel (medium), and the solvents were removed under reduced pressure. The residue was chromatographed (90:10 → 85:15 hexanes:ether) to furnish the alcohol **51** (600 mg, 88%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 6.26 (d, J = 6.1 Hz, 1H), 5.84 (d, J = 6.0 Hz, 1H), 5.19 (br s, 1H), 3.88 (d, J = 11.4 Hz, 1H), 3.72 (d, J = 7.6 Hz, 1H), 3.28 (s, 3H), 2.95 (s, 1H), 2.49 (br s, 1H), 2.00−1.52 (m, 7H), 1.75 (s, 3H), 1.50 (s, 3H), 1.30−1.24 (m, 1H), 1.24−1.13 (m, 1H), 0.89 (s, 9H), 0.86 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 140, 139, 130, 120, 117, 94, 78, 76, 51, 40, 38, 38, 37, 32, 27, 26, 26, 25, 24, 22, 18, 15, −3, −5 (2 unresolved); IR [ν max cm^{-1}] 3568, 2957, 2859, 1461; $[\alpha]^{22}_D = +50.4°$ (*c* 0.55, $CHCl_3$); HRMS (FAB) calcd for $[C_{26}H_{45}O_4Si]^+$ 449.3087, found 449.3090.

Ketone 52. The alcohol **51** (1.09 g, 2.42 mmol) was taken up in CH_2Cl_2 (60 mL) and stirred at room temperature under Ar. Ground 4 Å molecular sieves (1.3 g) were added, and the solution was stirred for ∼30 min before addition of NMO (528 mg, 4.51 mmol) followed by TPAP (266 mg, 0.76 mmol). TLC after 3 h showed disappearance

of starting material. The solution was then filtered through a short plug of SiO_2. Evaporation of solvents furnished the ketone **52** (949 mg, 87%) which was good enough to be used for the next step or could be chromatographed: ^{1}H NMR [500 MHz, $CDCl_3$] δ 6.42 (br s, 0.7H), 6.2−5.82 (br unresolved m, 1.3H), 5.16 (br s, 1H), 3.92 (d, J = 10.7 Hz, 1H), 3.3 (br s, 3H), 2.66 (br m, 1H), 2.5−2.0 (br unresolved m, 2.6H), 1.92−1.83 (br unresolved m, 1.4H), 1.7 (br unresolved m, 5H), 1.55 (s, 0.7H), 1.51 (s, 3.3H), 1.23 (br unresolved m, 2H), 0.87 (s, 12H), 0.76 (br unresolved m, 3H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 145.4, 138.1, 133.2, 126.5, 125.6, 121.7, 112.4, 93.7, 80.4, 50.2, 41.4, 38.4, 34.2, 33.3, 28.8, 25.7, 25.0, 24.3, 22.2, 22.1, 20.1, 17.7, −3.7, −4.9 (2 unresolved); IR [ν max cm^{-1}] 2957, 2931, 1721, 1464; $[\alpha]^{23}_D = +36.2°$ (c 1.03, $CHCl_3$); HRMS (CI, NH_3) calcd for $[C_{26}H_{44}O_4Si]^+$ 448.3009, found 448.3000.

Triflate 58. To a round-bottom flask, equipped with a stir bar, were added the ketone **52** (465 mg, 1.04 mmol) and THF (20 mL), and the mixture was cooled to 0 °C. LHMDS (1.0 M in THF, 1.10 mL) was added slowly, and the mixture was stirred for 1 h. After removal of the cooling bath, the mixture was stirred for a further 1 h and then cooled to −78 °C. In a separate flask 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (2.16 g, 5.50 mmol) was dissolved in THF (20 mL), and this solution was added via cannula to the reaction flask. After 30 min, the cooling bath was removed and the mixture allowed to stir for 30 min before aqueous buffer (pH 7) was added. The reaction mixture was extracted with ether, the organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was chromatographed (98:2 → 96:4 hexanes:ether) to furnish the triflate **58** (426 mg, 71%): ^{1}H NMR [300 MHz, $CDCl_3$] δ 6.26 (d, J = 5.9 Hz, 1H,), 5.88 (d, 1H, J = 5.9 Hz), 5.52 (d, J = 10.2 Hz, 1H), 5.29 (br unresolved m, 1H), 3.82 (ddd, J = 10.2,4.0, 3.4 Hz, 1H), 3.59 (d, J = 7.2 Hz, 1H), 3.25 (s, 3H), 2.35 (m, 1H), 2.1 (m, 2H), 1.70 (dd, J = 13.4, 2 Hz, 1H), 1.59 (s, 3H), 1.56−1.35 (m, 2H), 1.45 (s, 3H), 1.33−1.21 (m, 2H), 1.27 (s, 3H), 1.24 (s, 3H), 1.18 (s, 9H), 0.11(s, 3H), 0.1 (s, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 145.4, 138.1, 133.2, 126.5, 125.6, 121.7, 112.4, 93.7, 80.4, 50.2, 41.4, 38.4, 34.2, 33.3, 28.8, 25.7, 25.0, 24.3, 22.2, 22.1, 20.1, 17.7, −3.7, −4.9 (3 unresolved); IR [ν max cm^{-1}] 2961, 2860, 1419; $[\alpha]^{23}_D = -5.64°$ (c 1.21, $CHCl_3$).

Thioglycoside 67. To a solution of the thioglycoside **64** (730 mg, 2.3 mmol) in MeOH (10 mL) was added NaOMe (12 mg, 0.23 mmol). The solution was stirred for 3 h and then neutralized with Dowex-50 (H^+) resin and filtered. The filtrate was concentrated in vacuo. The solid residue **65** was then dissolved in acetone (5 mL), and *p*-TsOH·H_2O (47.3 mg, 0.23 mmol) and 2,2-dimethoxypropane (2 mL) were added. This mixture was stirred for 1 h before being quenched with saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was extracted with EtOAc, and the organic layer washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvents, the crude material was purified by chromatography (50:50 hexanes:EtOAc) to afford the acetonide **66** (515 mg, 96%). The acetonide **66** (515 mg, 2.2 mmol) was taken up in methylene chloride (20 mL). Imidazole (748 mg, 11 mmol) and DMAP (27 mg, 0.22 mmol) were added to it. TBSCl (663 mg, 4.4 mmol) was then added and the reaction mixture allowed to stir for ∼5 h. Water was then added to the reaction mixture and extracted with EtOAc (3 times). The organic layer was washed with brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed (95:5 → 90:10 hexanes:EtOAc) to furnish the silyl ether **67** (718 mg, 94%): ^{1}H NMR [400 MHz, $CDCl_3$] δ 4.33 (d, J = 8.0 Hz, 1H), 4.23 (m, 1H), 4.19 (dt, J = 3.4, 2.5 Hz, 1H), 3.93 (t, J = 5.9 Hz, 1H), 3.66 (dd, J = 9.4, 3.5 Hz, 1H), 3.60 (dt, J = 6.1, 1.8 Hz, 1H), 2.60 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H), 0.85 (s, 9H), 0.083 (s, 6H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 109.9, 85.7, 79.7, 73.9, 73.3, 65.3, 28.3, 26.6, 26.3, 24.9, 18.6, 15.4, −3.9, −4.3 (2 unresolved); $[\alpha]^{20}_D = +33.86°$ (c 1.06, $CHCl_3$); HRMS (CI, NH_3) calcd for $[C_{16}H_{32}O_4SSi+1]^+$ 349.1869, found 349.1884.

For the *ent*-thioglycoside **70**, $[\alpha]^{20}_D = -24.7°$ (c 0.94, $CHCl_3$).

Alcohol. To a stirred mixture of the thioglycoside **67** (241 mg, 0.692 mmol) in dry CH_2Cl_2/Et_2O (1/2, v/v, 2 mL) at 0 °C were added tributylstannylmethyl alcohol (**83**) (444 mg, 1.38 mmol), 2,6-di-*tert*-butylpyridine (544 mg, 2.4 mmol), and molecular sieves (4 Å, 100 mg). Methyl triflate (343 mg, 2.1 mmol) was added subsequently, and after 12 h of stirring at 0 °C, the reaction mixture was concentrated in vacuo. Purification of the residue by chromatography (98:2 hexanes:EtOAc) furnished the stannylmethyl glycosides **84** as a 1:1 mixture (417 mg, ∼93%) which was difficult to separate. This mixture was dissolved in THF (1 mL), and TBAF (1 M, 1.4 mL) was added. The resulting yellow solution was stirred for 2 h at room temperature, the solvent was removed under reduced pressure, the crude material was chromatographed (80:20 hexanes:EtOAc), and the mixture of anomers could be easily separated at this stage furnishing the desired β-stannylmethoxy anomer (155 mg, 45%): ^{1}H NMR [400 MHz, $CDCl_3$] δ 4.58 (d, J = 3.5 Hz, 1H), 4.16 (d, J = 3.1 Hz, 1H), 4.07 (t, J = 6.3 Hz, 1H), 4.02 (dd, J = 16.6, 8.6 Hz, 1H), 3.85 (dt, J = 13.4, 2.4 Hz, 2H), 3.71 (dd, J = 3, 6.6 Hz, 1H), 3.57 (dd, J = 16.3, 8 Hz, 1H), 2.02 (s, 1H), 1.54−1.40 (m, 9H), 1.30 (s, 3H), 1.29−1.24 (m, 6H), 0.97−0.83 (m, 15H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 109.6, 101.2, 76.7, 73.4, 70.5, 59.9, 59.0, 29.5, 28.3, 27.7, 26.3, 14.1, 9.5, (8 unresolved); $[\alpha]^{20}_D = -91.4°$ (c 1.0, $CHCl_3$); HRMS (FAB) calcd for $[C_{21}H_{42}O_5Sn + K]^+$ 533.1694, found 533.1692.

For the *ent*-stannylmethyloxy glycoside, $[\alpha]^{25}_D = +92.3°$ (c 1.04, $CHCl_3$).

Data for the α-anomer: ^{1}H NMR [400 MHz, $CDCl_3$] δ 4.19 (m, 1H), 4.09 (m, 3H), 3.95 (d, J = 6.3 Hz, 1H), 4.02 (dd, J = 16.6, 8.6 Hz, 1H), 3.85 (dt, J = 13.4, 2.4 Hz, 1H), 3.71 (dd, J = 7.6 Hz, 1H), 3.73 (dd, J = 13.2, 3.3 Hz, 1H), 3.65 (d, J = 8 Hz, 1H), 3.50 (t, J = 7.6 Hz, 1H), 2.29 (br s, 1H), 1.49 (m, 9H), 1.32 (s, 3H), 1.32 (s, 3H), 1.24 (m, 6H), 0.87 (m, 9H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 110.5, 105.5, 78.5, 74,3, 73.5, 63.5, 60.3, 29.6, 29.5, 29.4, 29.3, 28.4, 28.0, 27.7, 27.6, 27.3, 26.4, 14.1, 9.5, 7.3; $[\alpha]^{20}_D = -14.7°$ (c 1.0, $CHCl_3$); HRMS (FAB) calcd for $[C_{21}H_{42}O_5Sn + K]^+$ 533.1694, found 533.1677.

Acetate 85. The β-stannylmethoxy glycoside (135 mg, 0.27 mmol), obtained from the desilylation step above, was taken up in methylene chloride (2 mL) at 0 °C. Acetic anhydride (140 mg, 1.37 mmol) and DMAP (149 mg, 1.2 mmol) were then added. The reaction mixture was stirred for 2 h, the contents were concentrated, and the residue was purified by chromatography (90:10 hexanes:EtOAc) to afford the acetate **85** (146 mg, 99%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 4.83 (dd, J = 8, 4.8 Hz, 1H), 4.66 (d, J = 3.3 Hz, 1H), 4.23−4.17 (m, 2H), 4.02−3.89 (m, 2H), 3.82 (dd, J = 10.5, 2.8 Hz, 1H), 3.48 (dd, J = 19, 8.5 Hz, 1H), 2.06 (s, 3H), 1.54−1.40 (m, 9H), 1.32−1.23 (m, 9H), 0.95−0.81 (m, 15H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 170.9, 109.7, 99.4, 74.0, 73.5, 73.0, 58.9, 58.7, 29.6, 28.4, 26.7, 21.3, 14.1, 9.4 (9 unresolved); IR [ν max cm^{-1}] 1731; $[\alpha]^{20}_D = -133.7°$ (c 0.50, $CHCl_3$); HRMS (FAB) calcd for $[C_{23}H_{44}O_6Sn + K]^+$ 575.1800, found 575.1815.

For the *ent*-stannylmethyloxy glycoside **86**, $[\alpha]^{20}_D = +179.2°$ (c 1.15, $CHCl_3$).

Stille Reaction. The triflate **58** (283 mg, 0.49 mmol), stannane **85** (2.00 g, 3.74 mmol), $Pd(PPh_3)_4$ (117 mg, 0.10 mmol), and LiCl (861 mg, 20.35 mmol) were placed in a vial and suspended in THF (1.4 mL). This mixture was degassed (via freeze−thaw, 3 cycles) and the contents sealed. This was then heated to 130 °C until the mixture had turned black (40 min) and then cooled to room temperature. The mixture was subjected to chromatography (93:7 → 88:12 hexanes:ether), yielding the coupling product **87** (170 mg, 52%) as a pale-yellow oil. Although not completely pure, this was taken forward for the next step.

Alcohol 88. The silyl ether **87** (270 mg, 0.40 mmol) was taken up in THF (5 mL), and TBAF (1 M THF solution, 1.6 mL) was added to it. The reaction mixture was stirred at 0 °C for 2 h. Aqueous buffer (pH 7) was added followed by methylene chloride. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was chromatographed (85:15 → 80:20 hexanes−EtOAc) to give the alcohol **88** (161 mg, 67%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 6.07 (d, J = 5.9 Hz, 1H), 6.01 (d, J = 5.9 Hz, 1H), 5.49 (d, J = 9.4 Hz, 1H), 5.28 (br s, 1H), 4.88 (dd, J = 8.1, 3.2 Hz, 1H), 4.82 (d, J = 3.2 Hz, 1H), 4.26−4.30 (m, 2H), 4.21 (m, 1H), 3.80−3.96 (m, 4H), 3.66 (d, J = 7.4 Hz, 1H), 3.18 (s, 3H), 2.32 (m, 2H), 2.08 (s, 3H), 1.98 (m, 1H), 1.71 (br s, 1H), 1.61 (m, 1H), 1.57 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H), 1.40−1.47 (m, 2H), 1.33 (s, 3H), 1.18 (m, 1H), 0.89 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 170.3, 136.9, 134.0, 133.7, 132.8, 130.5, 121.6, 115.5, 109.3, 92.8, 91.3, 80.6, 77.2, 73.6, 73.1, 72.0, 69.1,

58.8, 49.5, 42.3, 39.2, 34.4, 34.0, 29.2, 28.0, 26.3, 24.5, 22.2, 22.1, 21.1, 20.4; IR [ν max cm^{-1}] 3484, 2964, 1754; $[\alpha]^{20}_D = -76.0°$ (*c* 1.36, $CHCl_3$); HRMS (FAB) calcd for $C_{31}H_{46}O_9K$ [M + K^+] 601.2779, found 601.2777.

Urocanic Acylation. The alcohol **88** (131 mg, 0.23 mmol), *N*-methylurocanic acid[47] (152 mg, 0.92 mmol), 1,3-dicyclohexylcarbodiimide (262 mg, 1.27 mmol), and DMAP (253 mg, 2.07 mmol) were dissolved in chloroform (20 mL). This mixture was warmed to 50 °C for 2 h. Aqueous buffer (pH 7) was added followed by methylene chloride. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The residue was subjected to chromatography (99:1 CH_2Cl_2:MeOH), yielding the coupling product **90** (128 mg, 80%) which was slightly impure and was taken forward for the next step without further purification.

Eleutherobin 1. The acetonide **90** (70 mg, 0.10 mmol) was dissolved in methanol (15 mL), and PPTS (50 mg, 0.20 mmol) was added. This mixture was warmed to 50 °C for 36 h. After cooling to room temperature, aqueous buffer (pH 7) was added followed by methylene chloride. The organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The residue was subjected to chromatography (95:5 CH_2Cl_2:MeOH) yielding eleutherobin **1** (60 mg, 91%): ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.52 (d, J = 15.6 Hz, 1H), 7.45 (s, 1H), 7.08 (s, 1H), 6.55 (d, J = 15.6 Hz, 1H), 6.10 (d, J = 5.8 Hz, 1H), 6.07 (d, J = 5.8 Hz, 1H), 5.54 (d, J = 9.4 Hz, 1H), 5.26 (br s, 1H), 4.96 (dd, J = 9.8, 3.5 Hz, 1H), 4.90 (d, J = 3.5 Hz, 1H), 4.80 (d, J = 7.4 Hz, 1H), 4.28 (d, J = 12.2 Hz, 1H), 4.01 (dd, J = 9.8, 3.5 Hz, 1H), 3.97 (m, 1H), 3.86 (d, J = 12.2 Hz, 1H), 3.82 (d, J = 12.5 Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.60 (m, 1H), 2.28 (m, 1H), 2.10 (s, 3H), 1.97 (m, 1H), 1.52−1.61 (m, 4H), 1.51 (s, 3H), 1.43 (s, 3H), 1.35−1.42 (m, 1H), 1.22−1.31 (m, 4H), 0.96 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR [75 MHz, $CDCl_3$] δ 171.4, 166.7, 139.2, 138.4, 137.4, 136.5, 134.1, 133.7, 132.8, 131.0, 122.8, 121.3, 115.9, 115.9, 93.4, 89.9, 81.5, 71.7, 69.4, 69.1, 68.1, 62.1, 49.7, 42.3, 38.7, 34.2, 33.6, 31.4, 29.0, 24.5, 24.2, 22.2, 22.0, 21.0, 20.5; IR [ν max cm^{-1}] 3545, 3124, 2913, 2852, 1731, 1697, 1650; $[\alpha]^{20}_D = -73.2°$ (*c* 0.17, $CHCl_3$); HRMS (FAB) calcd for $[C_{35}H_{49}O_{10}N_2]^+$ 657.3387, found 657.3388.

Neoeleutherobin 94: ^{1}H NMR [500 MHz, $CDCl_3$] δ 7.53 (d, J = 15.6 Hz, 1H), 7.45 (s, 1H), 7.08 (s, 1H), 6.56 (d, J = 15.7 Hz, 1H), 6.14 (d, J = 5.9 Hz, 1H), 6.11 (d, J = 5.9 Hz, 1H), 5.59 (d, J = 9.4 Hz, 1H), 5.26 (br s, 1H), 4.97 (m, 2H), 4.80 (d, J = 7.3 Hz, 1H), 4.28 (d, J = 12.2 Hz, 1H), 4.03 (s, 3H), 3.97 (m, 2H), 3.81 (d, 12.8 Hz, 1H), 3.70 (s and overlapping m, 3 + 1H), 3.19 (s, 3H), 2.60 (m, 1H), 2.29 (m, 1H), 2.13 (s, 3H), 1.97 (m, 1H), 1.7−1.15 (m, 6H), 1.52 (s, 3H), 1.44 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); $[\alpha]^{20}_D = +44.5°$ (*c* 0.09, MeOH); MS (CI, CH_4) for $[C_{35}H_{49}O_{10}N_2]^+$ 657.

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Supporting Information Available: Schemes for attempted Wittig reactions on **32** and attempted cyclizations on **36** and **37** and experimental procedures and spectroscopic data for compound **45**, **46**, **63**, **64**, **72**, **76** and **i** and intermediates in glycosylation reactions on model substrates. In addition, experimental copies of ^{1}H and ^{13}C of all new compounds described in the Experimental Section and full crystallographic details of **41** and **45**, including crystal data and structure refinement, atomic coordinates, and bond lengths and angles and anisotropic displacement coefficients of crystal structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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