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On the synthesis of cepacin A

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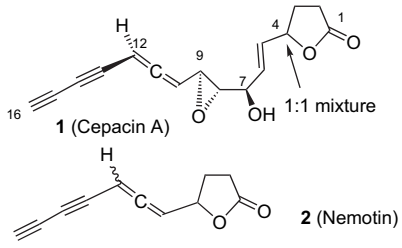
Abstract—Efforts directed toward a total synthesis of cepacin A is presented in full detail. The C-7, C-8, and C-9 stereogenic centers in the target molecule were derived from D-arabinose. The configuration of the allene axis was controlled at the bromoallenation step by the C-10 configuration of the precursor. An unexpected yet very interesting phenomenon was observed with the bromoallenation, where the α-isomer of the propargylic alcohol **31** was entirely resistant to the conditions that worked so well for its β-counterpart. The problem was eventually solved by careful tuning of the size of the neighboring groups based on the clue obtained from conformational analysis. The diyne moiety was incorporated into the molecular framework through a coupling of the TMS protected diyne with a proper bromoallene under the Sonogashira conditions with EtOAc as the solvent. Use of other solvents at this step led to complete failure.

1. Introduction

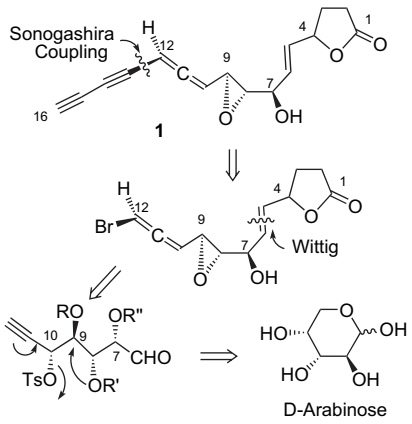
Cepacin A (**1**), a potent antibacterial substance produced by *Pseudomonas cepacia* SC 11,783, was isolated by Parker and co-workers in the 1980s.[1] By comparison of the UV and IR data with those of nemotin[2] (**2**) along with ^{1}H NMR analysis and chemical derivatization/degradation, the structure of cepacin A was proposed to be **1**. The absolute allene configuration was assigned on the basis of the optical rotation according to the rules of Lowe and Brewster.[3]



As cepacin A represents a novel type of antibacterials with an interesting structure containing a tightly packed challenging array of diyne–allene–epoxide–allylic alcohol–lactone functionalities, it makes a very attractive target for synthetic studies. Here in this article we wish to detail[4] our efforts toward synthesis of cepacin A in a hope to confirm the natural structure and find an entry to the chiral diyne–allene system.

2. Results and discussions

Our general strategy is shown in Scheme 1. Three of the four stereogenic centers (C-7, C-8, and C-9) were derived from D-arabinose, while the remainder (C-10) was intended to be created by a substrate-controlled asymmetric addition of acetylene to aldehyde. Installation of the diyne fragment was arranged at a late stage through a coupling reaction with a proper bromoallene. The stereochemistry of the allene axis was controlled by the configuration of the leaving group at the propargylic position (C-10). The lactone part was introduced through a Wittig reaction in connection with construction of the trans C=C double bond.



Scheme 1.

As in essentially all carbohydrate chiron-based syntheses, a major task in our endeavor is to differentiate the hydroxyl

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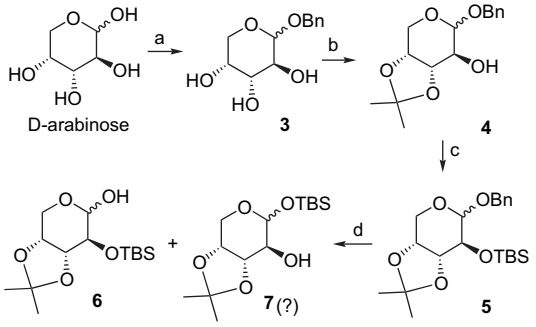
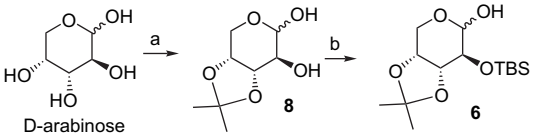
groups in the starting material. An approach (Scheme 2) in the literature[5] seemingly suitable for our purpose was then attempted.



Scheme 2. (a) $PhCH_2OH$/AcCl (cat), 84%; (b) $Me_2CO/CuSO_4$ (7.0 equiv)/concd H_2SO_4 (cat), 81%; (c) TBSCl (2.0 equiv)/imidazole/DMF/rt, 91%; (d) see the text.

Following a more recent literature procedure,[6] the hemiacetal OH in D-arabinose was replaced with a benzyl group. The resultant **3** was treated with acetone in the presence of $CuSO_4/H_2SO_4$ to yield the corresponding acetonide **4**. Protection of the hydroxyl group with TBSCl afforded **5**[5] smoothly. The final cleavage of the benzyl mixed acetal, however, did not proceed so well as expected. Catalytic hydrogenolysis over 10% Pd/C completely failed despite repeated tries. Li/naphthalene[7] system gave only a low yield (25%) of the desired **6** along with some unexpected products (seemed to be an α/β mixture of the TBS migrated product **7**).

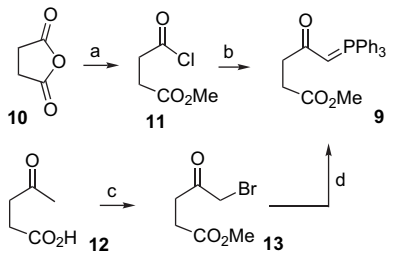
Through a more careful search of literature we then found that Kiso and Hasegawa[8] had developed a convenient procedure for making **8**. By using conventional silylation conditions we easily obtained the desired **6** (Scheme 3).



Scheme 3. (a) *p*-TsOH (cat)/$Me_2C(OMe)_2$/DMF/rt, 69%; (b) TBSCl/imidazole/DMF/rt, 60%.

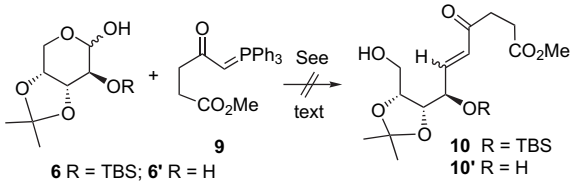
The Wittig reagent **9** needed for construction of the lactone moiety was then attempted using combinations of some known reactions (Scheme 4). We first tried to use the acid halide **11**[9] to react with $Ph_3P{=}CH_2$ as reported by Ronald and Wheeler[10] without success. Then we turned to the second route, making **9** through reaction of **13** with PPh_3.[11] Although preparation of **13** was somewhat tedious because of concurrent formation of over-brominated side products, enough amounts of **9** indeed could be obtained this way.

With both **6** and **9** in our hands, we proceeded to examine the Wittig reaction shown in Scheme 5. This was expected to be facile in the beginning as similar reactions[12] of **6** with $Ph_3P{=}CHCO_2Me$ were quite successful. However, to our surprise neither **6** nor its desilyl analogue **6′** led to the anticipated product(s). We tried many sets of reaction conditions (in CH_2Cl_2, DMF or toluene, at ambient or elevated temperatures, with or without added benzoic acid[12]) and always got



Scheme 4. (a) (i) MeOH/reflux; (ii) $SOCl_2$, 50% over two steps; (b) $Ph_3P{=}CH_2$/−78 °C to rt; (c) Br_2/MeOH/rt to reflux, 34%; (d) (i) Ph_3P/PhH/reflux; (ii) Na_2CO_3/H_2O, 59% over two steps.

either only recovered starting materials or a complicated product mixture.

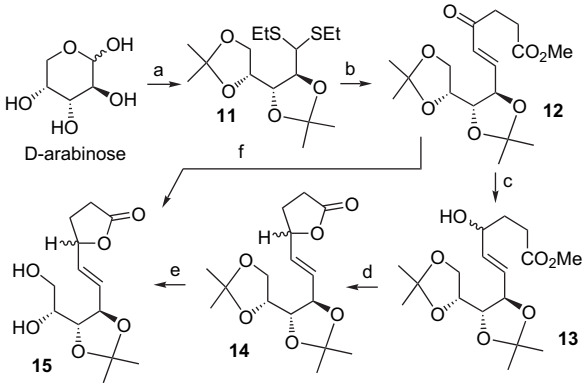


Scheme 5.

As the above failures were most likely caused by the great tendency of the aldehyde functionality to form a hemiacetal, we decided to modify our strategy of manipulating the carbohydrate chiron to avoid any possibility of cyclization to form a cyclic hemiacetal.

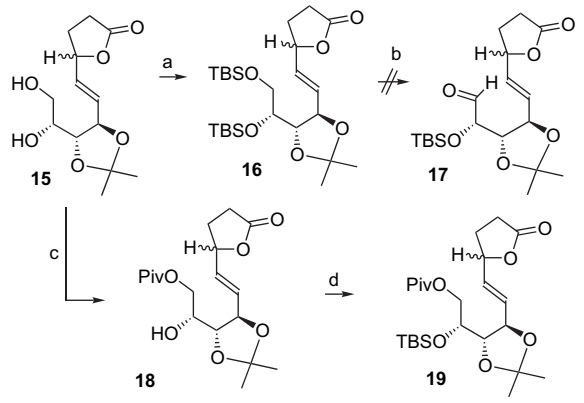
To this end, D-arabinose was treated sequentially with EtSH/6 N HCl and acetone/H_2SO_4 to yield **11** using a literature[13] procedure. The thioacetal protecting group was then removed with $HgCl_2/HgO$[14] (red) to free the aldehyde group. Further treatment with **9** afforded α,β-unsaturated ester **12** in 91% yield.

The ketone carbonyl group in **12** was reduced under the Luche[15] conditions ($CeCl_3/NaBH_4$), giving alcohol **13** as a mixture of the C-4 (cepacin numbering) epimers. As the epimers in this case were inseparable on silica gel, the mixture was used as such in the next step to give lactone **14**. The terminal acetonide was then selectively hydrolyzed with $CeCl_3\cdot 7H_2O/(CO_2H)_2/MeCN$[16] (Scheme 6) to yield diol **15**, paving the way for further elaborations.



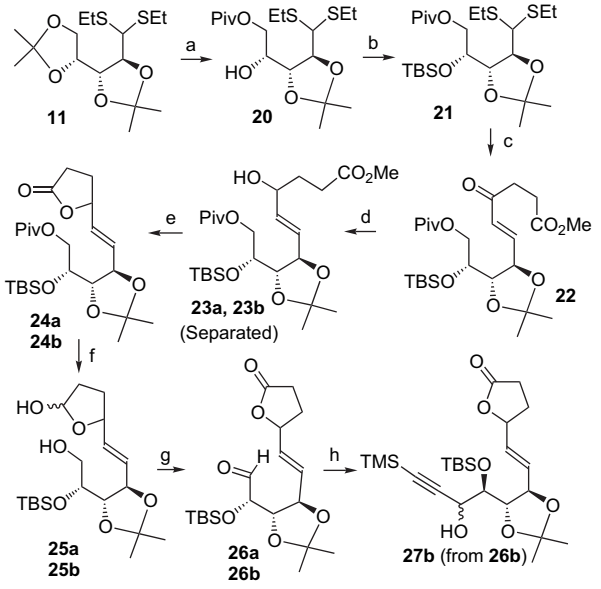
Scheme 6. (a) (i) EtSH/6 N HCl, 78%; (ii) Me_2CO/concd H_2SO_4, 92%; (b) (i) $HgCl_2/HgO$ (red)/MeCN/H_2O, 80%; (ii) **9**/toluene/reflux, 91%; (c) $NaBH_4/CeCl_3\cdot 7H_2O$/MeOH, 80%; (d) *p*-TsOH/Me_2CO/reflux, 70%; (e) $CeCl_3\cdot 7H_2O/(CO_2H)_2$/MeCN, 40%; (f) *p*-TsOH/MeOH/reflux, 64%.

Murugensan and Pandurangan[17] reported that quinolinium fluorochromate (QFC) could oxidize TBS ether directly into the corresponding aldehyde. Such a procedure would offer an expeditious access to aldehyde **17**, the precursor we needed for introducing an acetylene moiety. Hence we prepared **16** and attempted the oxidation with QFC (Scheme 7). Unfortunately, the anticipated oxidation did not[18] occur at all, which forced us to take a round-about strategy to achieve desired transformations—to mask the primary hydroxyl group before protecting the secondary hydroxyl group as a TBS ether and then to re-free the primary hydroxyl group for oxidation.



Scheme 7. (a) TBSCl/imidazole/DMAP/DMF, 54%; (b) QFC (cf. the text); (c) PivCl/Et_3N/CH_2Cl_2, 58%; (d) TBSCl/imidazole/DMF, 52%.

These steps were indeed executable. However, the corresponding yields were not high enough to ensure facile accumulation of the intermediates required for going through the many remaining steps along the synthetic sequence. Therefore, instead of proceeding further, we explored an alternative route shown in Scheme 8, where the two previously low-yielding steps were placed at an early stage of the synthesis.



Scheme 8. (a) (i) $CeCl_3 \cdot 7H_2O$/$(CO_2H)_2$/MeCN, 82%, or 80% AcOH/60 °C/2 h, 75%; (ii) PivCl/Et_3N/CH_2Cl_2, 77%; (b) TBSCl/imidazole/DMF, 95%; (c) (i) $HgCl_2$/HgO (yellow)/MeCN/H_2O; (ii) **9**/toluene/reflux, 94% from **21**; (d) $NaBH_4$/MeOH, 71%; (e) PPTS/PhH/reflux, 100%; (f) DIBAL-H/CH_2Cl_2/−78 °C, 95%; (g) IBX/DMSO, 78%, or PCC/NaOAc/CH_2Cl_2, 50%, or Dess–Martin oxidation, 41%; (h) TMSC≡CLi/THF/−78 °C, 40%.

The modified route emerged from the known **11**. Interestingly, under the same[16] conditions as utilized in the hydrolysis of **14** to **15** (40% yield), the intermediate diol in this case could be obtained in 92% yield. However, when running the reaction on preparative scales, the solid reagents tended to clog and thus hampered efficient stirring. The workup was also tedious. For these reasons, the 80% AcOH/60 °C[19] conditions were preferred in large-scale runs.

The primary and secondary hydroxyl groups were converted to a Piv (pivaloyl) ester and a TBS ether, respectively. The carbonyl group was released using an Hg(II)-mediated hydrolysis and the intermediate aldehyde was treated with **9** to afford α,β-unsaturated ester **22**. The ketone carbonyl group was reduced with $NaBH_4$, leading to a 1:1 mixture of the epimers. The isomers (**23a** and **23b**) in this case could be separated on silica gel under carefully chosen conditions. The subsequent steps were therefore performed using a single epimer as the starting material (cf. Section 4).

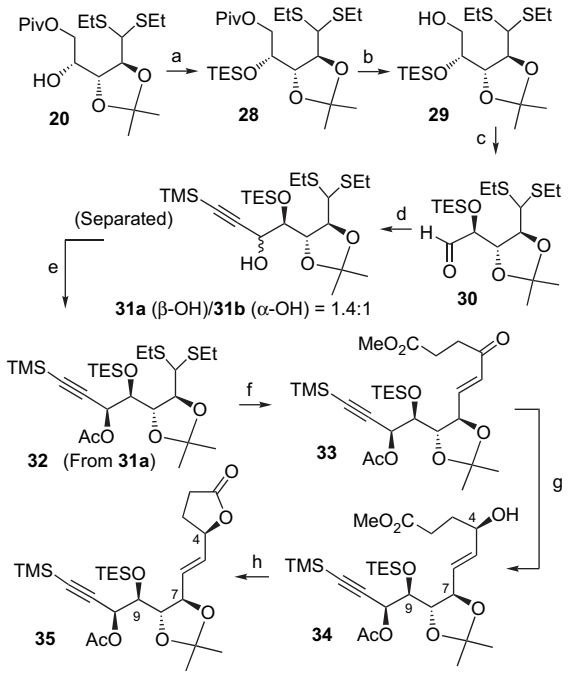
Lactonization was achieved by exposure of either **23a** or **23b** to PPTS[20] (pyridinium *p*-toluenesulfonate) in refluxing benzene. The Piv protecting group was cleaved with DIBAL-H with concurrent reduction of the lactone to a lactol. Subsequent oxidation of **25a** or **25b** with IBX[21] (*o*-iodoxybenzoic acid) gave the corresponding aldehyde (**26a** or **26b**) in 78% yield. PCC[22] (pyridium chlorochromate) or Dess–Martin periodinane[23] could also fulfill the same task, but the yields were significantly lower.

Addition of TMS protected acetylenide to the aldehyde group in **26b** was not so smooth as we expected. Despite excess amounts of the added acetylenide, the reaction did not go to completion. And the addition appeared to be totally non-selective, which meant complete loss of control over the allene configuration in a later stage. We reasoned that the sluggish reaction might result from too much steric crowding around the aldehyde group. Presence of the lactone functionality could also contribute. Therefore, the synthetic plan was modified one more time, with introduction of the acetylene moiety shifted to an earlier stage preceding incorporation of the lactone part.

As shown in Scheme 9, sequential TES protection and reductive removal of the Piv protecting group gave alcohol **29**, which on treatment with $SO_3 \cdot Py$[24] followed by addition of TMS/acetylenide resulted in a 1.4:1 mixture of **31a** (β-OH, the more polar component) and **31b** (α-OH, the less polar component). The two epimers were separable on silica gel. However, because the configurations of these compounds were unknown at that moment, we selected **31a** by chance to perform the remaining steps.

At this point, we once considered the alternative of converting the propargylic alcohol **31** into bromoallene before incorporation of the lactone moiety at the other end of the array of the arabinose-derived stereogenic centers. However, as we could not rule out the possibility of undesired sulfur alkylation (leading to formation of sulfonium salts), to be on the safe side we decided to build the lactone moiety first.

Thus, the hydroxyl group in **31a** was masked as an acetate to pave the way for the following transformations. The



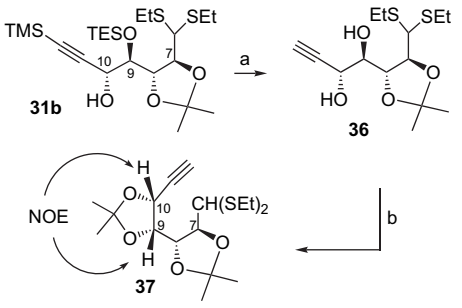
Scheme 9. (a) TESCl/imidazole/DMF/rt, 90%; (b) DIBAL-H/CH_2Cl_2/−78 °C, 91%; (c) SO_3·Py/*i*-Pr_2NEt/DMSO–CH_2Cl_2 (1:1)/0 °C to rt, 82%; (d) TMSC≡CLi/THF/−78 °C, 81%; (e) Ac_2O/Et_3N/CH_2Cl_2/rt, 82%; (f) I_2/$NaHCO_3$/Me_2CO–H_2O (5:1)/0 °C, 79%; (ii) **9**/toluene/reflux, 83%; (g) BH_3/(*S*)-2-methyl-CBS-oxazaborolidine/0 °C, 61%; (h) PPTS/PhH/40 °C, 59%.

subsequent hydrolysis of the thioacetal was not as smooth as observed with other substrates. Many conventional conditions such as $HgCl_2$/HgO, NCS/$AgNO_3$,[25] NBS,[26] $PhI(AcO)_2$,[27] and $PhI(TFA)_2$[28] all failed to give the desired aldehyde. Finally, the deprotection was realized using I_2[29] in the presence of powdered $NaHCO_3$. Once the deprotection problem was solved, the chain extension from the aldehyde group was readily achieved by treatment with **9**.

Reduction of the ketone group in this case was performed under the CBS[30] conditions. The configuration of the major isomer at the C-4 was not experimentally determined yet, but by comparison with similar substrates in the literature it is expected to be as drawn in the scheme.[31] The alcohol **34** was then readily transformed into lactone **35** using the conventional PPTS conditions.

The C-10 (cepacin numbering) configuration of **32** drawn in Scheme 9 was actually established only after completion of most of the syntheses disclosed here, through derivatization of **31b** using the sequence shown in Scheme 10. As distinct NOE was observed between the H-9 and H-10 of **37**, these two Hs must be cis to each other. Therefore, the configuration of **31b** must be as drawn (the α-isomer). Consequently, **31a** should have the configuration at the C-10 position as drawn for **32** in Scheme 9.

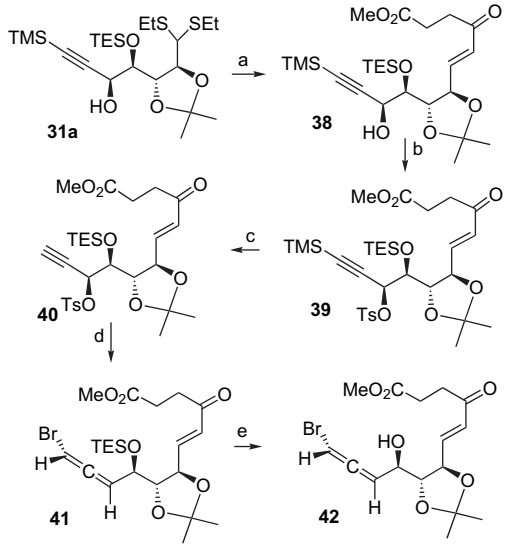
Successful arrival at **35** seemingly left only a few steps to be done before completing the whole synthesis—construction of a bromoallene terminal, introduction of a diyne moiety, and elaboration of the diol at C-8/C-9 into an epoxide. As we planned to employ Mann's[32] method to construct the bromoallene moiety, which required a good leaving group at the



Scheme 10. (a) K_2CO_3 (1.1 equiv)/MeOH–THF (2:1), 94%; (b) *p*-TsOH (cat)/$Me_2C(OMe)_2$, 95%.

propargylic position, the acetyl group must be removed first. Unfortunately, such a simple operation turned out to be extremely difficult in the presence of the silyl protecting groups and the lactone functionality. To get around this problem we decided to put a tosyl group there in the first place.

By then we also found out that by using the I_2 conditions, the thioacetal in **31a** could be hydrolyzed satisfactorily (Scheme 11). The intermediate aldehyde was readily converted into **38** by reaction with **9**. Unlike in the previous cases, the C=C double bond formed in this reaction was no longer trans only. Instead, a 4:1 mixture of trans/cis isomers was formed. The isomers were separated and only the trans one was utilized in the subsequent steps.

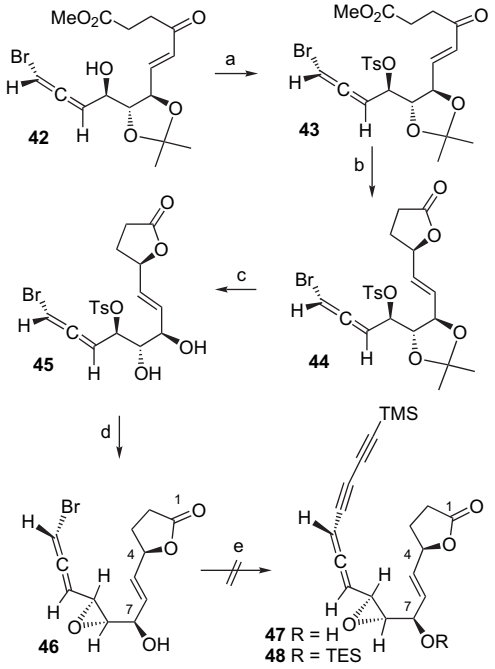


Scheme 11. (a) (i) I_2/$NaHCO_3$/Me_2CO–H_2O (5:1)/0 °C; (ii) **9**/toluene/70–80 °C, 73% from **31a**; (b) *p*-TsCl/NEt_3/DMAP/CH_2Cl_2/0 °C to rt, 74%; (c) K_2CO_3/MeOH–THF (2:1)/0 °C, 92%; (d) LiBr/CuBr·SMe_2/THF/reflux, 61% (or 84% based on the consumed **40**); (e) Bu_4NF/THF, 97%.

The hydroxyl group was then tosylated. The product was treated with LiBr/CuBr·SMe_2 in a hope to obtain the corresponding bromoallene. However, the bromide attack did not occur at the triple bond. Instead, a simple tosylate to bromide substitution at the propargylic position was observed. We reasoned that the TMS protecting group might obstruct the entry of the bromide. To circumvent this factor, the TMS protecting group was then removed with K_2CO_3 in MeOH/THF giving **40** for further transformation. Now starting from the unprotected acetylene the desired bromoallene **41**

was indeed formed smoothly, which on treatment with TBAF gave alcohol **42** in 97% yield.

Tosylation of **42** under conventional conditions followed by the CBS reduction and lactonization afforded **43**. The acetonide protecting group was then removed with $HS(CH_2)_3SH/BF_3\cdot OEt_2$ in CH_2Cl_2 to free the two hydroxyl groups. Further treatment with K_2CO_3 in 50:1 Et_2O/H_2O provided the epoxide **46** in 77% yield (Scheme 12).

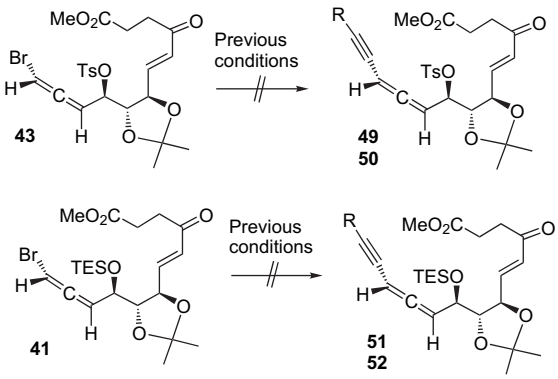


Scheme 12. (a) *p*-TsCl/NEt_3/DMAP/CH_2Cl_2/0 °C to rt, 72%; (b) (i) $BH_3\cdot SMe_2$/(*S*)-2-methyl-CBS-oxazaborolidine/0 °C, 77% (93% based on the consumed ketone); (ii) PPTS/PhH/40 °C, 85%; (c) $HS(CH_2)_3SH/BF_3\cdot OEt_2/CH_2Cl_2$, 69%; (d) $K_2CO_3/Et_2O–H_2O$ (50:1), 77%; (e) see text.

Up to this point, we were seemingly only one step away from the target structure (but with an allene of wrong configuration as revealed by a later structural establishment of **31b**)—to install a diyne fragment onto the allene. However, this turned out to be an impossible task. Direct treatment of **46** with TMSC≡C–C≡CH[33] (prepared from TMSC≡C–C≡CTMS[34]) under the Sonogashira[35] conditions ($Pd(Ph_3P)_4$ or $Pd(Ph_3P)_2Cl_2$/CuI, with different base (Et_2NH, Et_3N or *i*-Pr_2NEt) and/or solvent (THF or toluene, DMF)). Masking the C-7 hydroxyl group as a TES ether did not lead to any discernible improvements.

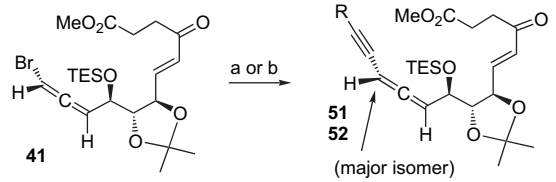
All the negative results with the epoxy-containing substrates seemingly suggested that a labile epoxy functionality in the coupling reaction might be the culprit. However, the coupling reaction of **41** and **43** also completely failed under the same conditions (Scheme 13). Although **43** does have a TsO– group at the propargylic position and is therefore similar to the epoxides **46** in a sense, the TESO– group in **41** is definitely not a good leaving group. Since this compound also failed to deliver the coupling product, the failures could not be attributed simply to the presence of a good leaving group.

When we almost completely lost the direction of further exploration a dramatic solvent effect in a similar coupling



Scheme 13.

reaction discovered by Andrus[36] came to our view, where replacing THF (or toluene or DMF) with EtOAc turned a failure to success. Encouraged by that work, we re-examined the coupling of **41** with first TMSC≡CH and then TMSC≡C–C≡CH under otherwise the same conditions. To our satisfaction, this time we also obtained the coupling products (Scheme 14). However, such a change in the solvent still did not lead to any discernible improvements in the coupling of epoxide **46**.

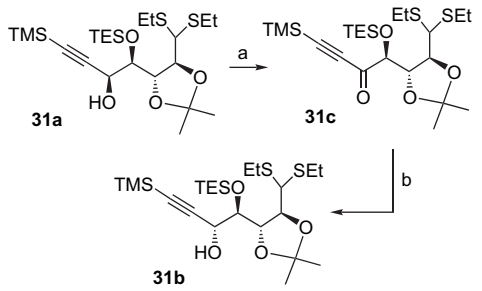


Scheme 14. (a) TMSC≡CH/$Pd(Ph_3P)_2Cl_2$/CuI/*i*-Pr_2NEt/EtOAc/−20 °C to rt, 77% for **51** (R=TMS–); (b) TMSC≡C–C≡CH/$Pd(Ph_3P)_2Cl_2$/CuI/*i*-Pr_2NEt/EtOAc/−20 °C to rt, 59% for **52** (R=TMSC≡C–).

The ^1H NMR spectrum of **51** and **52** suggested that in neither case the coupling reaction proceeded with complete allene configuration retention, although one of the isomers did predominate. The optical rotation was determined to be +50 and +45 for **51** and **52**, respectively. As the sign of the optical rotation of diyne–allene containing compounds was dominated[1] by the contribution of allene moiety, the configuration of the major isomer of **52** (and **51** a priori) is expected to be opposite to that of cepacin A (as drawn in Scheme 14). This is in line with the prediction of the bromoallene configuration derived from **31a**. Considering that **52** would not lead to natural cepacin A and the amount of **52** we had was not enough to go forward any further, we discontinued the work along this line.

In parallel to the work described above derived from **31a**, we also utilized **31b** to perform the subsequent steps (after establishing the configuration of **31b** experimentally as shown in Scheme 10) in a hope to arrive at a bromoallene of correct configuration. To make full use of **31a** we still had, we tried to oxidize it into the corresponding ketone **31c** and then reduce the carbonyl group into alcohol again as shown in Scheme 15.

Because **31a** contained sulfur ether linkage partial structures, oxidation was more difficult than otherwise. We first attempted to use mild MnO_2 as the oxidant. However, the



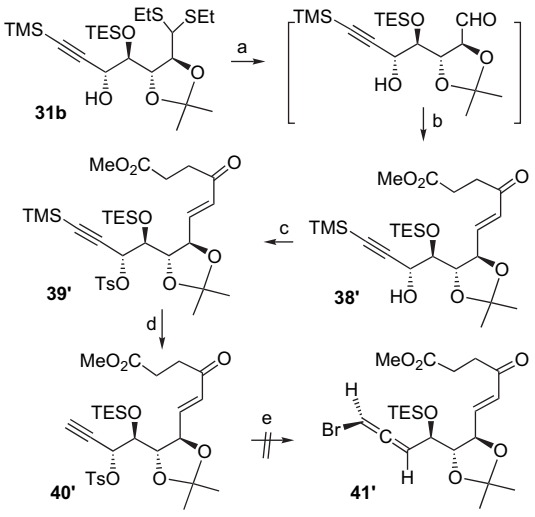
Scheme 15. (a) MnO_2/CH_2Cl_2/reflux, 50% or Dess–Martin oxidation, 72%; (b) DIBAL-H/CH_2Cl_2/−78 °C, 80%.

yield was only 50% and a large excess of the oxidant was required. These unfavorable factors made us to seek other alternatives. The $SO_3\cdot$Py protocol, which was quite effective on e.g. **29**, did not work here. Finally, we gratifyingly found that Dess–Martin oxidation could give 70% yield of the desired ketone **31c**.

Reduction of **31c** was best achieved with DIBAL-H, which delivered a 10:1 mixture of **31b/31a**. The results with L-Selectride or K-Selectride were much less satisfactory, although they were even bulkier than DIBAL-H. As we had already developed a means to separate **31a** and **31b**, with the help of the oxidation–reduction sequence we could obtain enough amounts of **31b** to perform the following steps.

As shown in Scheme 16, **31b** was subjected to the same series of transformations as in converting **31a** to **40**, giving **40′** smoothly as expected. However, in contrast to the smooth transformation of **40** to **41**, the α-epimer **40′** was surprisingly resistant to the same LiBr/CuBr·SMe_2/THF reflux conditions. We also tried to use some other leaving groups such as 2,4,6-triisopropyl-benzenesulfonate (TPS) or triflate to replace the tosyl group, but the results were all the same. No traces of **41′** could be detected.

At first sight this outcome seems ridiculous, because the structural difference between **40** and **40′** is almost negligible. However, a detailed conformational analysis of the two isomers provided us with a possible clue to the drastic change in



Scheme 16. (a) $I_2/NaHCO_3/Me_2CO–H_2O$ (5:1)/0 °C/20 min; (b) **9**/toluene/70 to 80 °C, 73% over two steps, cis/trans=1:4; (c) *p*-TsCl/DMAP/Et_3N–CH_2Cl_2/0 °C to rt, 74%; (d) K_2CO_3/MeOH–THF (2:1)/0 °C, 92%; (e) LiBr/CuBr·SMe_2/THF/reflux.

the results of the bromoallenation—the bromide attack in the case of **40′** appears to be significantly more hindered than that with **40** (Fig. 1).

The conformational analysis revealed that to overcome the doubly hindered situation encountered with **40′** a smaller protecting group must be used in place of the TES. Acetyl group is substantially smaller than TES and was therefore chosen. However, by then we already ran out of both **39′** and **40′**. Further testing could start only from **38′**.

Removal of the silyl groups in **38′** with *n*-Bu_4NF resulted in diol **53** without any complications. The subsequent task was to activate the hydroxyl group at the propargylic position and mask the other hydroxyl group as an acetate. As the difference in steric crowding between the two hydroxyl groups is not so large, a bulky sulfonating reagent is expected to be beneficial. Indeed, treatment of **53** with TPSCl (2,4,6-triisopropyl-benzenesulfonyl chloride, a reagent much bulkier than tosyl chloride) led nicely to the desired regio-selective

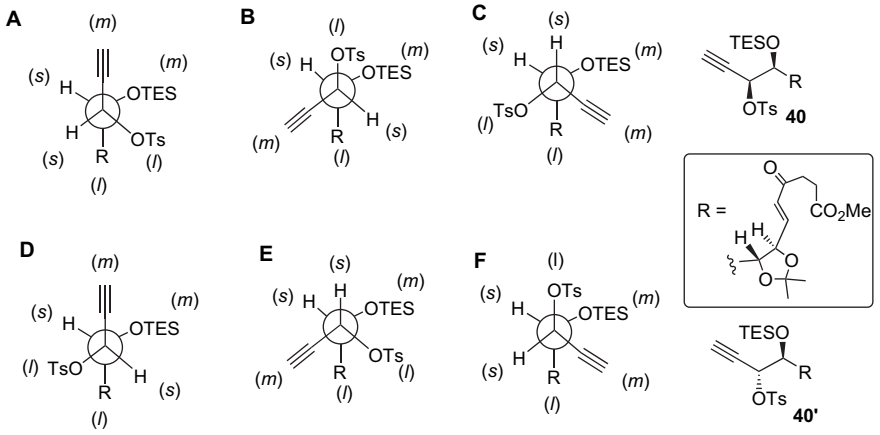
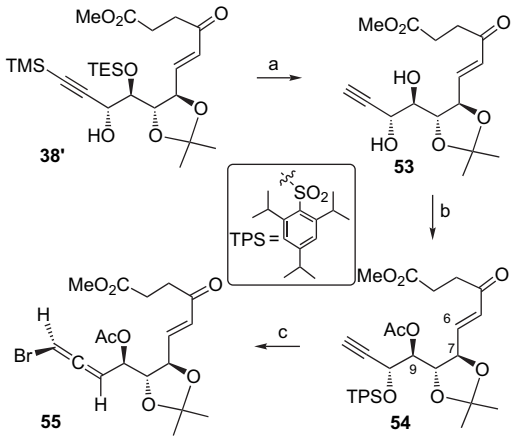


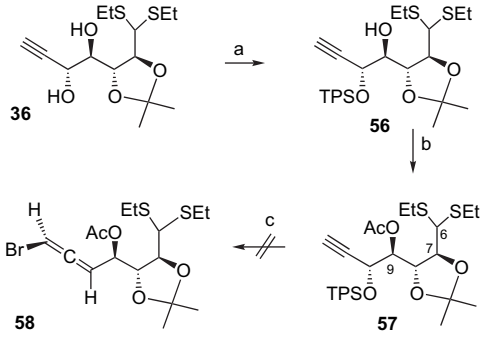
Figure 1. The Newman presentations of the conformers of **40** (**A**–**C**) and **40′** (**D**–**F**). The relative size of the substituents on each of the two central carbons of the Newman projections is shown by (*s*), (*m*), and (*l*) (standing for small, medium, and large, respectively). The conformation with (*l*)–(*l*) interaction is of the highest internal energy and thus is least stable. Consequently, the most stable conformation for **40** is **B**, while that for **40′** should be **F**. Note that in conformer **B** the attack of Br^- at the alkyne is mainly hindered by the R, whereas in **F** it is hindered by both the OTES and the R.

sulfonylation at the propargylic position as expected. The remaining free hydroxyl group at the C-9 was then readily acylated with Ac_2O. The resultant **54** underwent the bromoallenation smoothly, giving the long anticipated **55** in 86% yield (Scheme 17).



Scheme 17. (a) *n*-Bu_4NF/THF/0 °C, 85%; (b) TPSCl/DMAP/CH_2Cl_2/40 °C, then Ac_2O/DMAP, 64% from **53**; (c) CuBr·SMe_2/LiBr/THF/reflux, 86%.

It is interesting to note that another substrate **57**, which was derived from **36** through the route in Scheme 18 and very similar to **54** as far as the reaction centers are concerned, completely failed to give the corresponding bromoallene under the otherwise identical conditions. As these two compounds (**54** and **57**) differ only at the substituents on the C-6, at first sight this seems to be very difficult to understand. However, if one looks into the conformation details, some substantial difference still can be spotted.



Scheme 18. (a) TPSCl/DMAP/CH_2Cl_2/50 °C; (b) Ac_2O/DMAP/CH_2Cl_2, 94% from **36**; (c) CuBr·SMe_2/LiBr/THF/reflux.

As shown in Figure 2, the most stable conformer for both compounds is expected to be **C**, where the interaction between the two largest substituents is avoided. The relevant structural difference between **54** and **57** is highlighted with boxes in the two lower partial structures. For the former, the substituent on the C-6 is essentially linear, stretching out through a carbon–carbon double bond. In the case of the latter, however, the substituents are two –SEt groups, which spread out and thus are obviously much bulkier than their counterpart in **54**. Hence, the larger steric crowding created by the branched dithioacetal in **57** appeared to be the culprit.

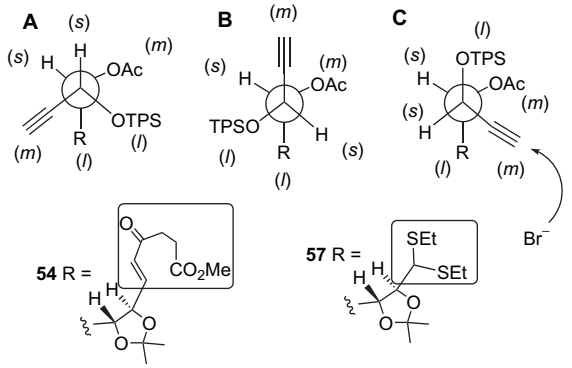
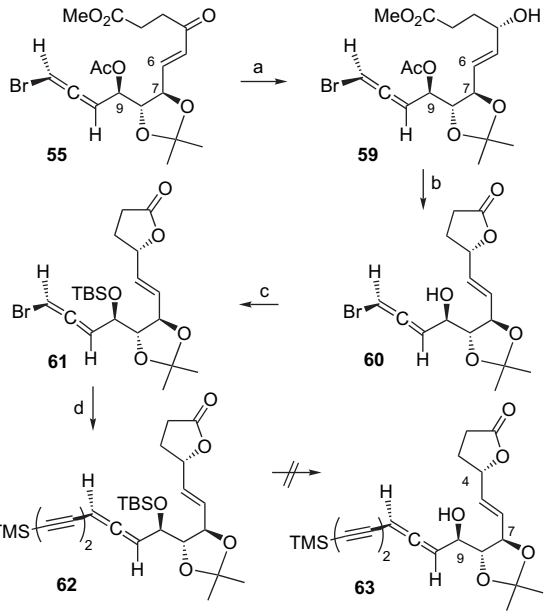


Figure 2. Newman projections of the conformers of **54** and **57**. The relative size of the substituents on each of the two central carbons of the Newman projections is shown by (*s*), (*m*), and (*l*) (standing for small, medium, and large, respectively).

As removal of the acetyl group could be rather difficult at later stages once the labile diyne moiety was installed, we preferred to execute this deprotection task before the coupling reaction during the elaboration of the lactone moiety. In the event, the ketone carbonyl group in **55** was reduced under the CBS conditions. As (*R*)-2-methyl-CBS-oxazaborolidine was used here as the chiral additive, the configuration of **59** at the C-4 is expected to be opposite to that in **44** (Scheme 19).

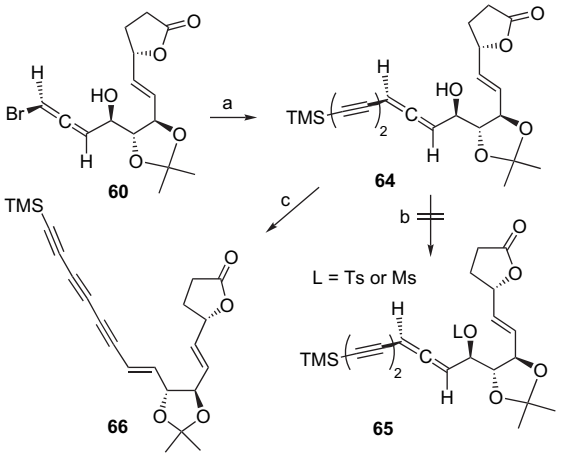


Scheme 19. (a) (*R*)-2-Methyl-CBS-oxazaborolidine/BH_3·SMe_2/THF/0 °C/10 min, 83%; (b) 0.2 M NaOMe/0 °C/25 min, then PPTS (cat)/toluene/60 °C, 75%; (c) TBSOTf/2,6-lutidine/CH_2Cl_2/0 °C, 80%; (d) TMSC≡C–C≡CH/Pd(Ph_3P)$_2Cl_2$/CuI/*i*-Pr_2NEt/EtOAc/−20 °C to rt, 77%.

The resultant **59** was further converted into **60** by sequential treatment with NaOMe and PPTS. The hydroxyl group was then protected as a TBS ether before concatenation with TMSC≡C–C≡CH under the same conditions as in the synthesis of **52**. Although the coupling product was still an inseparable mixture of the allene isomers as in the previous cases, one of them predominated with the optical rotation of the same direction as of cepacin A indicating a different allene configuration from that in **52**.

Up to this point it seemed that we were only a few steps away from the target structure. We only needed to convert the TBS protected hydroxyl group into a good leaving group and remove the acetonide protecting group to free the diol before eventually making the epoxy ring at a final step. However, things turned out much more complicated than we expected. All efforts[37] to remove the TBS group failed. This made it impossible to proceed to make a good leaving group at C-9. To get around this problem, we next attempted the coupling reaction with alcohol **60**.

With a free hydroxyl group at the C-9, the coupling could also occur, though the yield was somewhat lower (Scheme 20). However, the subsequent activation of the hydroxyl group ran into problem again. No matter what sulfonation reagent (MsCl, *p*-TsCl or *p*-Ts_2O) was used, in the absence of DMAP no reaction took place. Addition of DMAP did lead to a rather fast reaction. The starting **64** disappeared very quickly. The product, however, was not the expected **65** but the triyne–ene **66**. It seemed that **65** was highly unstable and extremely labile to the undesired elimination.



Scheme 20. (a) TMSC≡C–C≡CH/$Pd(Ph_3P)_2Cl_2$/CuI/*i*-Pr_2NEt/EtOAc/−20 °C to rt, 54%; (b) MsCl/Py, or MsCl/Et_3N, or *p*-TsCl/Py or *p*-TsCl/Et_3N, or *p*-Ts_2O/Py; (c) *p*-TsCl/Py/DMAP (cat) or *p*-Ts_2O/Et_3N/DMAP (cat), 75%.

3. Conclusions

The unassuming size of cepacin A belies its complexity as a target for chemical synthesis. Many unexpected yet interesting problems turned up along our way to arrive at the final target structure. We managed to solve some of them, including the bromoallenation through tuning the size of neighboring groups and the coupling with diyne by changing the solvent. The eventual construction of the epoxy ring in the presence of the labile diyne–allene motif is still to be done. The control over the allene configuration is also to be improved.

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature using the following instruments: Varian Mercury 300 or a Bruker Avance 300 instrument (operating at 300 MHz for proton), Bruker Avance 400 (400 MHz for ^1H), or Varian Inova-600 (600 MHz for ^1H). The FTIR spectra were scanned with a Perkin Elmer 983 or a Nicolet Avatar 360 FT-IR spectrometer. The EIMS, EIHRMS, ESIMS, and ESIHRMS were recorded on an HP5989A, a Finnigan MAT 8430, a PE Mariner API-TOF (or an Agilent Technologies LC/MSD SL), and a Bruker APEXIII 7.0 Tesla FT-MS spectrometer, respectively. Elemental analyses were performed on an Elementar VarioEL III instrument. Optical rotations were measured on a Perkin–Elmer 341 or an Agilent Technologies P-1030 polarimeter. Dry THF, Et_2O, toluene, and petroleum ether (PE) and *n*-hexane were distilled over Na/Ph_2CO under argon. Dry CH_2Cl_2, EtOAc, Et_3N, Et_2NH, *i*-Pr_2NEt, and $HNTMS_2$ were distilled over CaH_2 under argon and kept over 4 Å molecular sieves. Dry DMSO, DMF, and pyridine were stirred with CaH_2 under N_2 for 24 h and distilled under reduced pressure. Dry MeOH was refluxed/distilled over Mg turnings under argon. Dry acetone was distilled over P_2O_5 under argon.

4.1.1. Synthesis of ketone-ester 12. HgO (red, 800 mg, 3.69 mmol) and $HgCl_2$ (800 mg, 2.95 mmol) were added to a solution of **11** (500 mg, 1.49 mmol) in MeCN/H_2O (10:1 v/v, 11 mL) stirred at ambient temperature. One hour later the mixture was filtered through Celite (washing with CH_2Cl_2). The filtrate and washings were washed with aq 20% KI and satd $NaHCO_3$ in turn and dried over anhydrous $MgSO_4$. Removal of the solvent left a colorless oil (the intermediate aldehyde, 308 mg, 1.34 mmol, 90% yield). Part of this aldehyde (93 mg, 0.40 mmol) and the Wittig reagent **9** (190 mg, 0.50 mmol) were dissolved in toluene (10 mL) and heated to reflux with stirring overnight. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (3:7 Et_2O/PE) to give **12** as a yellowish oil (109 mg, 0.32 mmol, 80% from **11**): FTIR (film) 3000, 1740, 1700, 1370, 1220, 1160, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, J=15.9, 4.4 Hz, 1H), 6.47 (dd, J=15.9, 1.3 Hz, 1H), 4.56 (ddd, J=6.1, 4.4, 1.7 Hz, 1H), 4.18–4.08 (m, 2H), 4.00–3.92 (m, 1H), 3.73–3.64 (m, 4H), 2.92 (t, J=6.9 Hz, 2H), 2.65 (t, J=6.6 Hz, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H); EIMS m/z (%) 342 (M^+, 2.3), 327 (16.2), 43 (100), 101 (89.6), 55 (69.6), 115 (56.7), 169 (39.4), 59 (36.5), 94 (33.5), 41 (25.9); EIHRMS calcd for $C_{16}H_{23}O_7$ ($[M-CH_3]^+$) 327.1444, found 327.1420.

4.1.2. Synthesis of lactone 14. $NaBH_4$ (127 mg, 3.34 mmol) was added in portions to a solution of **12** (541 mg, 1.58 mmol) and $CeCl_3\cdot 7H_2O$ (1.280 g, 3.44 mmol) in anhydrous MeOH (7.5 mL) stirred at 0 °C. After completion of the addition, the mixture was stirred for another 5 min before the reaction was quenched by addition of H_2O. The mixture was then diluted with EtOAc, washed with aq satd $NaHCO_3$, and dried over anhydrous $MgSO_4$. The residue left by removal of the solvent was chromatographed on silica gel (3:1 EtOAc/PE) to afford **13** as a colorless oil (434 mg, 1.26 mmol, 80% yield): FTIR (film) 3485, 2936, 1776, 1734, 1371, 1167, 1065, 976, 919, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98–5.88 (m, 2H), 4.38 (t, J=7.7 Hz, 1H), 4.28–4.18 (m, 1H), 4.16–4.08 (m, 2H), 3.98–3.90 (m, 1H), 3.73–3.64 (m, 4H), 2.47 (td, J=7.1,

2.4 Hz, 2H), 2.00–2.09 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H); EIMS *m/z* (%) 329 (M^+-CH_3, 5.1), 43 (100), 101 (70.6), 59 (48.4), 115 (47.4), 85 (28.2), 167 (25.9), 41 (25.9).

A solution of **13** (943 mg, 2.74 mmol) and *p*-TsOH (60 mg, 0.32 mmol) in dry acetone (40 mL) was heated to reflux with stirring under argon for 10 h. After cooling to ambient temperature, the acid in the mixture was neutralized with powdered Na_2CO_3 and traces of H_2O. The solids were filtered off. The filtrate was concentrated on a rotary evaporator and the residue was chromatographed on silica gel (4:1 CH_2Cl_2/EtOAc) to afford **14** as a yellowish oil (600 mg, 1.92 mmol, 70%): FTIR (film) 3413, 2947, 2894, 1723, 1670, 1192, 1048, 964, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90–5.75 (m, 2H), 5.10–4.90 (m, 1H), 4.45–4.38 (m, 1H), 4.18–4.05 (m, 2H), 3.68 (q, J=6.0 Hz, 1H), 3.70–3.60 (m, 1H), 2.60–2.50 (m, 2H), 2.49–2.34 (m, 1H), 2.10–1.95 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H); EIMS *m/z* (%) 297 (M^+-CH_3, 2.5), 43 (100), 99 (45.4), 101 (39.1), 55 (33.5), 87 (31.4), 59 (27.8), 41 (20.0), 113 (13.9); EIHRMS calcd for $C_{15}H_{21}O_6$ ($[M^+-CH_3]$) 297.1338, found 297.1352.

4.1.3. Removal of terminal acetonide in 13 (15). A solution of **13** (37 mg, 0.11 mmol) and *p*-TsOH (5 mg, 0.03 mmol) in anhydrous MeOH (5 mL) was stirred at ambient temperature overnight. The reaction mixture was diluted with EtOAc, washed with satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (9:1 EtOAc/MeOH) gave **15** as a yellowish oil (19 mg, 0.07 mmol, 64% yield): FTIR (film) 3427 (br), 2987, 1770, 1182, 977 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95–5.88 (m, 2H), 5.05–4.95 (m, 1H), 4.48 (dd, J=8.0, 5.0 Hz, 1H), 3.90–3.81 (m, 1H), 3.80–3.68 (m, 3H), 2.57 (dt, J=3.5, 1.3 Hz, 2H), 2.50–2.40 (m, 1H), 2.08–1.96 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H); EIMS *m/z* (%) 257 (M^+-CH_3, 4.9), 43 (100), 59 (56.7), 55 (48.6), 41 (38.9), 85 (29.7), 137 (29.2), 79 (26.5), 81 (25.9); EIHRMS calcd for $C_{12}H_{17}O_7$ ($[M^+-CH_3]$) 257.1025, found 257.1039.

4.1.4. Removal of terminal acetonide in 14 (15). Alternatively, **15** could also be obtained from **14**. A mixture of **14** (560 mg, 1.79 mmol), $CeCl_3\cdot 7H_2O$ (1.38 g, 3.70 mmol), and oxalic acid (17 mg, 0.19 mmol) in MeCN (9 mL) was stirred at ambient temperature until TLC showed disappearance of **14**. The acid was neutralized with powdered Na_2CO_3 and the solvent was removed on a rotary evaporator. The residue was dissolved in EtOAc, washed with satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (100:6 EtOAc/MeOH) gave **15** as a colorless oil (193 mg, 0.71 mmol, 40%).

4.1.5. Protection of 15 with TBSCl (16). A solution of **15** (10 mg, 0.037 mmol), imidazole (20 mg, 0.15 mmol), DMAP (4.5 mg, 0.037 mmol), and TBSCl (50 mg, 0.33 mmol) in anhydrous DMF (0.2 mL) was stirred at ambient temperature under argon until TLC showed complete disappearance of the starting **15**. The reaction mixture was diluted with EtOAc, washed in turn with 0.5 N HCl and satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (1:2 EtOAc/PE) gave **16** as a colorless oil (10 mg, 0.02 mmol, 54% yield): FTIR (film) 2930, 1785, 1255, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92–5.86 (m, 2H), 4.96 (br, 1H), 4.55(d, J=7.4 Hz, 1H), 3.97–3.88 (m, 2H), 3.60–3.50 (m, 2H), 2.55 (td, J=6.6, 3.6 Hz, 2H), 2.48–2.37 (m, 1H), 2.08–1.95 (m, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H); ESIMS *m/z* 523.3 ($[M+Na]^+$). Anal. Calcd for $C_{25}H_{48}O_6Si_2$: C, 59.96; H, 9.66. Found C, 59.82; H, 9.64.

4.1.6. Protection of the primary hydroxyl group in 15 with PivCl (18). Pivaloyl chloride (70 μL, 0.45 mmol) was added to a solution of **15** (118 mg, 0.43 mmol) and dry Et_3N (0.2 mL) in dry CH_2Cl_2 (4 mL) stirred in an ice-water bath. The mixture was then stirred at ambient temperature overnight before being diluted with EtOAc, washed in turn with 0.5 N HCl and satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (1:12 EtOAc/PE) gave **16** as a colorless oil (85 mg, 0.25 mmol, 58% yield): FTIR (film) 3483 (br), 2983, 1777, 1729, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (t, J=3.5 Hz, 2H), 5.04–4.95 (m, 1H), 4.51 (dd, J=7.7, 4.9 Hz, 1H), 4.26 (dd, J=11.8, 3.3 Hz, 1H), 4.15 (dd, J=11.8, 6.8 Hz, 1H), 4.04–3.94 (m, 1H), 3.68–3.59 (m, 1H), 2.56 (td, J=6.6, 1.7 Hz, 2H), 2.50–2.40 (m, 1H), 2.10–1.95 (m, 1H), 1.43 (s, 3H), 1.27 (s, 3H), 1.24 (s, 9H); ESIMS *m/z* 379.1 ($[M+Na]^+$); ESIHRMS calcd for $C_{18}H_{28}O_7Na$: 379.1727, found 379.1721.

4.1.7. TBS protection of 18 (19). To a solution of **18** (80 mg, 0.23 mmol) in dry DMF (0.4 mL) stirred at ambient temperature under argon were added in turn imidazole (70 mg, 0.51 mmol), TBSCl (75 mg, 0.50 mmol), and a catalytic amount of DMAP. The mixture was stirred at ambient temperature overnight before being diluted with EtOAc, washed with 0.5 N HCl and satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (1:3 EtOAc/PE) gave **19** as a colorless oil (852 mg, 0.11 mmol, 52% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 5.98–5.82 (m, 2H), 5.06–4.92 (m, 1H), 4.52–4.42 (m, 1H), 4.10–3.90 (m, 2H), 3.88–3.70 (m, 1H), 2.10–1.95 (m, 1H), 1.44 (s, 1.5H), 1.43 (s, 1.5H), 1.29 (s, 1.5H), 1.26 (s, 1.5H), 1.23 (s, 4.5H), 1.22 (s, 4.5H), 0.92 (s, 4.5H), 0.90 (s, 4.5H), 0.13 (s, 1.5H), 0.11 (s, 1.5H), 0.06 (s, 1.5H), 0.05 (s, 1.5H). (IR and MS were the same as that for **24a/24b**, the enantiopure samples.)

4.1.8. Conversion of 11 into 20. A solution of **11** (1.121 g, 3.34 mmol), $CeCl_3\cdot 7H_2O$ (2.437 g, 6.54 mmol), and oxalic acid (22 mg, 0.24 mmol) in MeCN (20 mL) was stirred at ambient temperature until TLC showed complete disappearance of **11**. With cooling (ice-water bath), the excess acid was neutralized with Na_2CO_3. The solids were filtered off. The filtrate was diluted with EtOAc, washed with satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (2:3 EtOAc/PE) gave the intermediate diol as a colorless oil (811 mg, 2.74 mmol, 82% yield).

Alternatively, the hydrolysis could also be performed as follows. A solution of **11** (10.505 g, 31.30 mmol) in 80% HOAc (80 mL) was stirred at 60 °C for 2 h. After cooling to ambient temperature, the HOAc was removed on a rotary evaporator. The residue was diluted with EtOAc, washed in

turn with satd aq $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (2:3 EtOAc/PE) gave the intermediate diol as a colorless oil (6.948 g, 23.47 mmol, 75% yield): FTIR (film) 3403 (br), 2929, 1454, 1240, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (dd, J=6.8, 4.2 Hz, 1H), 4.12 (t, J=6.9 Hz, 1H), 4.02 (d, J=4.1 Hz, 1H), 3.90–3.70 (m, 3H), 2.80–2.60 (m, 5H), 2.01 (t, J=6.5 Hz, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 1.15 (t, J=7.4 Hz, 6H).

Pivaloyl chloride (1.7 mL, 13.70 mmol) was added dropwise to a solution of the above mentioned diol (3.880 g, 12.83 mmol) and dry Et_3N (6 mL) in CH_2Cl_2 (25 mL) stirred in an ice-water bath. After completion of the addition, the bath was removed and the mixture was stirred at ambient temperature (overnight) until TLC showed completion of the reaction. The mixture was diluted with EtOAc, washed with 0.5 N HCl and satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (1:12 EtOAc/PE) gave the intermediate diol as a yellowish oil (3.605 g, 9.90 mmol, 77% yield): $[\alpha]_D^{25}$ +61.1 (c 1.0, $CHCl_3$). FTIR (film) 3485 (br), 2973, 1731, 1481, 1241, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (dd, J=11.8, 2.4 Hz, 1H), 4.36 (dd, J=3.3 Hz, 1H), 4.19 (dd, J=11.8, 6.1 Hz, 1H), 4.10 (dd, J=8.2, 6.9 Hz, 1H), 4.03 (d, J=3.6 Hz, 1H), 3.91–3.86 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 1.28 (t, J=7.4 Hz, 3H), 1.27 (t, J=7.4 Hz, 3H), 1.24 (s, 9H); EIMS m/z (%) 319 (M^+-Et, 1.2), 303 (4.0), 262 (29.8), 261 (39.1), 217 (22.3), 187 (43.7), 159 (28.4), 143 (36.9), 135 (100), 85 (36.1), 57 (81.5). Anal. Calcd for $C_{17}H_{32}O_5S_2$: C, 53.65; H, 8.48. Found C, 53.38; H, 8.35.

4.1.9. TBS protection of 20 (21). A solution of **20** (83.605 g, 9.90 mmol), imidazole (2.841 g, 20.71 mmol), and TBSCl (2.203 g, 14.69 mmol) in dry DMF (4 mL) was stirred at ambient temperature under argon overnight. The mixture was extracted with petroleum ether (10 mL) thrice. The combined petroleum ether layers were diluted with Et_2O, washed in turn with 0.5 N HCl and satd aq $NaHCO_3$ before being dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (1:24 EtOAc/PE) gave **21** as a colorless oil (4.660 g, 9.53 mmol, 95% yield): $[\alpha]_D^{26}$ +52.02 (c 0.50, $CHCl_3$). FTIR (film) 2920, 2686, 1445, 1424, 1250, 1139, 1069, 991, 872 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32–4.25 (m, 3H), 4.10 (dd, J=11.8, 3.6 Hz, 1H), 3.98–3.90 (m, 2H), 2.86–2.67 (m, 4H,), 1.46 (s, 3H), 1.38 (s, 3H), 1.31–1.20 (m, 15H), 0.85 (s, 9H), 0.15(s, 3H), 0.14 (s, 3H); EIMS m/z (%) 419 ($M^+-SC_2H_5-CH_3$, 3.9), 375 (13.8), 335 (3.6), 57 (100), 73 (45.6), 199 (40.8), 159 (32.5), 75 (29.5); ESIMS 517.30 ([M+Na]$^+$); HRMS calcd for $C_{23}H_{46}O_5S_2SiNa$ (M^+-CH_3) 517.2448; found, 517.2464.

4.1.10. Conversion of 21 to 22. A mixture of **21** (565 mg, 1.14 mmol), yellow HgO (653 mg, 3.0 mmol), $HgCl_2$ (626 mg, 2.3 mmol) in MeCN (10 mL) and H_2O (1 mL) was stirred at ambient temperature for 1 h. The solids were filtered off through Celite (washing with 150 mL of CH_2Cl_2). The filtrate and washings were combined, washed with 20% aq KI and satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Rotary evaporation left the intermediate aldehyde as a colorless oil, which was dissolved in dry toluene (15 mL) and treated with Wittig reagent **9** (470 mg, 1.21 mmol) at reflux temperature until TLC showed disappearance of the starting aldehyde (ca. 10 h). Toluene was removed by rotary evaporation. The residue was diluted with Et_2O and cooled in a refrigerator overnight. The supernatant ethereal solution was poured out and concentrated on a rotary evaporator to leave a residue, which was chromatographed on silica gel (1:9 EtOAc/PE) to give **22** as a yellowish oil (533 mg, 1.07 mmol, 94% from **21**): $[\alpha]_D^{25}$ +6.62 (c 1.80, $CHCl_3$). FTIR (film) 2919, 1686, 1650, 1298, 1141, 1021, 969 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (dd, J=15.7, 4.4 Hz, 1H), 6.45 (dd, J=15.9, 1.4 Hz, 1H), 4.61 (dt, J=7.4, 1.3 Hz, 1H), 4.06 (dd, J=11.8, 5.0 Hz, 1H), 4.08–4.00 (m, 1H), 3.86 (dd, J=7.42, 5.5 Hz, 1H), 3.68 (s, 3H), 2.91 (t, J=6.6 Hz, 2H), 2.64 (t, J=6.9 Hz, 2H), 1.45 (s, 3H), 1.39 (s, 3H), 1.21 (s, 9H), 0.91 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 178.2, 173.1, 143.7, 129.1, 110.0, 80.5, 77.0, 65.2, 51.8, 35.3, 27.7, 27.2, 27.0, 26.5, 25.7, 18.0, −4.47, −4.53; EIMS m/z (%) 485 (M^+-CH_3, 1.7), 443 (2.0), 57 (100), 159 (39.7), 73 (26.4), 115 (22.8), 41 (18.5), 283 (18.1), 94 (18.0), 259 (17.0); EIHRMS calcd for $C_{24}H_{41}O_8Si$ ([$M-CH_3$]$^+$) 485.2571; found 485.2531.

4.1.11. Reduction of 22 with $NaBH_4$ (23a and 23b). $NaBH_4$ (118 mg, 3.11 mmol) was added in portions to a solution of **22** (705 mg, 1.41 mmol) in MeOH (4 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred for 5 min before addition of water to quench the reaction. The solvent was removed by rotary evaporation and the residue was diluted with EtOAc, washed in turn with 0.5 N HCl and satd aq $NaHCO_3$ before being dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (3:7 EtOAc/PE) gave a mixture of **23a** and **23b** as a colorless oil (501 mg, 1.0 mmol, 71% yield), which could be further separated into pure **23a** and **23b** by a second chromatography on silica gel eluting with 8:1 CH_2Cl_2/EtOAc.

Data for **23a** (the more polar component): $[\alpha]_D^{25}$ +20.2 (c 1.05, $CHCl_3$). FTIR (film) 3431, 2917, 1686, 1427, 1144, 1020, 989, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dd, J=15.4, 5.2 Hz, 1H), 5.73 (dd, J=15.4, 6.6 Hz, 1H), 4.48 (t, J=7.5 Hz, 1H), 4.24–4.16 (m, 1H), 4.12–4.04 (m, 2H), 3.94 (d, J=7.9 Hz, 1H), 3.80 (dd, J=7.7, 3.5 Hz, 1H), 3.67 (s, 3H), 2.46 (t, J=7.4 Hz, 2H), 2.08–2.00 (m, 1H), 1.98–1.78 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.20 (s, 9H), 0.89 (s, 9H), 0.11 (s, 6H); EIMS m/z (%) 57 (100), 73 (33.3), 259 (31.9), 159 (29.4), 85 (22.5), 43 (15.4), 55 (14.7), 75 (14.2); ESIMS m/z 525.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{25}H_{46}O_8SiNa$ ([M+Na]$^+$), 525.2877; found 525.2854.

Data for **23b** (the less polar component): $[\alpha]_D^{25}$ +5.9 (c 2.25, $CHCl_3$). FTIR (film) 3431, 2919, 1686, 1427, 1404, 1020, 988, 961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dd, J=15.3, 6.3 Hz, 1H), 5.63 (dd, J=15.4, 7.1 Hz, 1H), 4.45 (t, J=7.7 Hz, 1H), 4.24–4.10 (m, 3H), 3.83 (d, J=6.6 Hz, 1H), 3.80 (dd, J=8.3, 3.0 Hz, 1H), 3.68 (s, 3H), 2.45 (t, J=7.4 Hz, 2H), 1.98–1.80 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.21 (s, 9H), 0.89 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 174.2, 137.1, 129.3, 108.9, 80.5, 76.4, 71.2, 69.0, 64.8, 51.7, 38.8, 31.4, 30.0, 27.2,

27.0, 26.9, 25.8, 18.0, −4.4, −4.8; ESIMS *m/z* 525.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{25}H_{46}O_8SiNa$ 525.2863 ([M+Na]$^+$); found 525.2854.

4.1.12. Lactonization of 23 (24a and 24b). A solution of **23a** or **23b** (63 mg, 0.13 mmol) and PPTS (8 mg) in benzene (10 mL) was heated to reflux for 2 h. After cooling to ambient temperature, a small amount of powdered Na_2CO_3 and traces of water were added. The mixture was stirred for a while before the solvent was removed on a rotary evaporator. The residue was diluted with EtOAc, washed with satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Removal of the solvent left **24a** or **24b** as a yellowish oil (100% yield), which was rather pure as shown by ^{1}H NMR.

Data for **24a** (derived from **23a**): $[\alpha]_D^{25}$ +32.36 (*c* 0.80, $CHCl_3$). FTIR (film) 2958, 1783, 1732, 1462, 1162, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dd, *J*=15.7, 4.7 Hz, 1H), 5.87 (dd, *J*=15.7, 5.0 Hz, 1H), 4.95 (q, *J*=7.1 Hz, 1H), 4.49 (dd, *J*=7.7, 4.7 Hz, 1H), 4.10–4.00 (m, 3H), 3.85 (dd, *J*=7.7, 3.6 Hz, 1H), 2.55 (dt, *J*=6.3, 2.5 Hz, 2H), 2.41 (sextet, *J*=7.9 Hz, 1H), 2.08–1.98 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.22 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz) δ 178.2, 176.7, 131.3, 130.3, 109.3, 80.7, 79.4, 76.8, 70.1, 65.2, 38.8, 28.4, 28.3, 27.2, 27.0, 26.7, 25.7, 18.0, −4.5, −4.7; ESIMS *m/z* 493.4 ([M+Na]$^+$); ESIHRMS calcd for $C_{24}H_{42}O_7SiNa$ ([M+Na]$^+$), 493.2592; found, 493.2573.

Data for **24b** (derived from **23b**): $[\alpha]_D^{25}$ −3.1 (*c* 1.75, $CHCl_3$). FTIR (film) 2919, 1732, 1682, 1446, 1299, 1019, 998 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (dd, *J*=15.6, 5.2 Hz, 1H), 5.87 (dd, *J*=15.6, 5.4 Hz, 1H), 4.98 (dd, *J*=14.1, 4.9 Hz, 1H), 4.49 (dd, *J*=7.7, 5.5 Hz, 1H), 4.10–4.00 (m, 3H), 3.84 (dd, *J*=7.7, 4.0 Hz, 1H), 2.56–2.50 (m, 2H), 2.42 (sextet, *J*=6.4 Hz, 1H), 2.04–1.98 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.21 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz) δ 178.1, 176.5, 131.3, 130.6, 81.0, 79.3, 77.0, 70.3, 65.4, 38.8, 28.4, 28.2, 27.2, 27.0, 26.8, 25.8, 18.0, −4.48, −4.46; EIMS *m/z* (%) 455 (M^+-CH_3, 1.5), 413 (3.3), 57 (100), 41 (27.5), 73 (23.9), 159 (23.7), 43 (21.3), 85 (20.8), 259 (19.8), 75 (18.6); HRMS calcd for $C_{23}H_{39}O_7Si$ ([M−CH_3]$^+$) 455.2465; found 455.2444.

4.1.13. Reduction of 24 with DIBAL-H (25a and 25b). DIBAL-H (0.8 mL, 1.0 M, in toluene) was added to a solution of **24a** or **24b** (100 mg, 0.22 mmol) in dry CH_2Cl_2 (5 mL) stirred in a dry ice–acetone bath under argon. After completion of the addition, the stirring was continued at the same temperature for 30 min before quenching the reaction with MeOH (added dropwise). The reaction mixture was diluted with EtOAc, washed in turn with satd aq potassium sodium tartrate and satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Removal of the solvent left **25a** or **25b** as a colorless oil (80 mg, 0.21 mmol, 95% yield).

Data for **25a** (derived from **24a**): FTIR (film) 3423 (br), 2930, 1253, 1054 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00–5.65 (m, 2H), 5.58 (br, 1H), 5.50 (br, 1H), 4.68 (q, *J*=6.6 Hz, 1H), 4.55–4.38 (m, 2H), 3.97–3.80 (m, 2H), 3.64 (br, 2H), 2.15–1.90 (m, 4H), 1.42 (s, 3H), 1.40 (s, 3H), 0.91 (s, 9H), 0.11 (s, 7H); ESIMS *m/z* 411.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{19}H_{36}O_6SiNa$ ([M+Na]$^+$) 411.2173; found 411.2179.

Data for **25b** (derived from **24b**): FTIR (film) 3423 (br), 2953, 1379, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96–5.70 (m, 2H), 5.56 (br, 1H), 5.47 (br, 1H), 4.65 (q, *J*=6.6 Hz, 1H), 4.50–4.30 (m, 2H), 3.90–3.75 (m, 2H), 3.61 (br, 2H), 2.22–1.90 (m, 4H), 1.39 (s, 3H), 1.26 (s, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ESIMS *m/z* 411.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{19}H_{36}O_6SiNa$ ([M+Na]$^+$) 411.2173; found 411.2180.

4.1.14. Oxidation of 25 and addition of TMSC≡CLi to 26 (27b). (Method A) PCC oxidation. A mixture of **25** (640 mg, 1.65 mmol), PCC (2.113 g, 10.01 mmol), and NaOAc (1.012 g, 10.21 mmol) in dry CH_2Cl_2 (10 mL) was stirred at ambient temperature for 6 h. After dilution with Et_2O, the reaction mixture was washed with satd aq $NaHCO_3$ and dried over anhydrous $MgSO_4$. Removal of the solvent and column chromatography on silica gel (1:3 EtOAc/PE) gave **26** as a colorless oil (320 mg, 0.89 mmol, 50% yield).

(Method B) IBX oxidation. A solution of **25** (792 mg, 2.04 mmol) and IBX (3.009 g, 10.75 mmol) in DMSO (25 mL) was stirred at ambient temperature for 2 h. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent and column chromatography on silica gel (1:3 EtOAc/PE) gave **26** as a colorless oil (614 mg, 1.60 mmol, 78% yield).

(Method C) Dess–Martin oxidation. A solution of **25** (218 mg, 0.56 mmol) and Dess–Martin periodinane (784 mg, 1.85 mmol) in dry CH_2Cl_2 (8 mL) and dry pyridine (1 mL) was stirred at 0 °C until TLC showed disappearance of the starting alcohol. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent and column chromatography on silica gel (1:3 EtOAc/PE) gave **26** as a colorless oil (90 mg, 0.23 mmol, 41% yield).

Data for **26a** (derived from **25a**): FTIR (film) 3501 (br), 2857, 1778, 1737, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 5.88 (dd, *J*=15.6, 5.2 Hz, 1H), 5.72 (dd, *J*=16.2, 6.6 Hz, 1H), 4.93 (q, *J*=6.6 Hz, 1H), 4.53 (t, *J*=7.2 Hz, 1H), 4.26 (dd, *J*=4.3, 1.1 Hz, 1H), 3.99 (dd, *J*=8.2, 3.6 Hz, 1H), 2.53 (td, *J*=6.7, 1.7 Hz, 2H), 2.40 (sextet, *J*=5.5 Hz, 1H), 2.03–1.90 (m, 1H), 1.42 (s, 6H), 0.89 (s, 9H), 0.08 (s, 7H); EIMS *m/z* (%) 369 (M^+-CH_3, 4.1), 327 (5.4), 153 (100), 73 (91.1), 85 (67.5), 75 (57.6), 117 (38.3).

Data for **26b** (derived from **25b**): FTIR (film) 3500 (br), 2857, 1778, 1738, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.6 (d, *J*=1.4 Hz, 1H), 6.31 (dd, *J*=17.9, 3.6 Hz, 1H), 5.88–5.75 (m, 1H), 5.67–5.56 (m, 1H), 4.52 (br q, *J*=7.7 Hz, 1H), 4.25–4.23 (m, 1H), 3.97–3.94 (m, 1H), 2.22–1.90 (m, 2H), 1.80–1.65 (m, 2H), 1.42 (s, 6H), 0.89 (s, 9H), 0.08 (s, 6H).

n-BuLi (0.14 mL, 1.6 M in hexane, 0.22 mmol) was added to a solution of TMSC≡CH (32 μL, 0.21 mmol) in dry THF (2 mL) stirred in a dry ice–acetone bath under argon. After completion of the addition the stirring was continued for 15 min before a solution of **26b** (138 mg, 0.36 mmol)

in dry THF (2 mL) was introduced via a syringe. The mixture was stirred at the same temperature for 3 h, then at ambient temperature overnight. Satd aq NH_4Cl was added to quench the reaction. The mixture was diluted with EtOAc, washed with satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Removal of the solvent and column chromatography on silica gel (1:1 EtOAc/PE) gave **27b** as a colorless oil (70 mg, 0.145 mmol, 40% yield): FTIR (film) 3460, 2928, 2174, 1778, 1462, 1251, 1165, 973 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.05–5.85 (m, 2H), 5.04–4.96 (m, 1H), 4.60–4.52 (m, 2H), 4.06 (br, 1H), 3.85 (td, J=7.4, 1.1 Hz, 1H), 3.72–3.66 (m, 1H), 2.60–2.50 (m, 2H), 2.49–2.38 (m, 1H), 2.10–1.97 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 0.92 (s, 9H), 0.18 (s, 9H), 0.12 (s, 6H). ESIMS 505.2 ([M+Na$^+$]), 500.3 ([M+NH_4^+]); ESIHRMS calcd for $C_{24}H_{42}O_6Si_2Na$ ([M+Na$^+$]) 505.24326; found 505.2412.

4.1.15. TES protection of 20 (28). A solution of **20** (3.605 g, 9.90 mmol), imidazole (2.841 g, 20.71 mmol), and TESCl (2.203 g, 14.69 mmol) in dry DMF (4 mL) was stirred at ambient temperature under argon overnight. The mixture was extracted with petroleum ether (10 mL) thrice. The combined petroleum ether layers were diluted with Et_2O (100 mL), washed in turn with 0.5 N HCl and satd aq $NaHCO_3$ before being dried over anhydrous $MgSO_4$. Rotary evaporation and column chromatography on silica gel (1:24 EtOAc/PE) gave **21** as a colorless oil (4.660 g, 9.53 mmol, 95% yield): $[\alpha]_D^{25}$ +61.8 (c 1.0, $CHCl_3$). FTIR (film) 2971, 1737, 1480, 1458, 1282, 1159, 878 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32–4.25 (m, 3H), 4.10 (dd, J=11.8, 3.6 Hz, 1H), 3.99 (m, 1H), 3.95 (d, J=3.1 Hz, 1H), 2.82–2.70 (m, 4H), 1.46 (s, 3H), 1.36 (s, 3H), 1.28 (t, J=7.4 Hz, 3H), 1.26 (t, J=7.4 Hz, 3H), 1.23 (s, 9H), 0.97 (t, J=7.8 Hz, 9H), 0.66 (q, J=7.9 Hz, 6H); EIMS m/z (%) 330 (M^+−HCOCH $(SEt)_2$, 3.2), 329 (3.9), 301 (2.1), 271 (24.1), 243 (9.9), 199 (10.4), 169 (10.8), 135 (51.7), 85 (29.3), 57 (100). Anal. Calcd for $C_{23}H_{46}O_5S_2Si$: C, 55.83; H, 9.37. Found C, 55.97; H, 9.09.

4.1.16. Removal of Piv protecting group in 28 (29). DIBAL-H (50 mL, 1.0 M in cyclohexane) was added to a solution of **28** (10.216 g, 20.63 mmol) in dry CH_2Cl_2 (100 mL) stirred in a dry ice–acetone bath under argon. After completion of the addition, the stirring was continued at the same temperature for 30 min before quenching the reaction with MeOH (added dropwise). Satd aq potassium sodium tartrate (100 mL) was added. After stirring for 30 min, the mixture was extracted with Et_2O (100 mL×3). The combined ethereal layers were washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent and chromatography on silica gel (1:8 EtOAc/PE) afforded **29** as a colorless oil (7.660 g, 18.68 mmol, 91% yield): $[\alpha]_D^{20}$ +55.7 (c 1.0, $CHCl_3$). FTIR (film) 3490 (br), 2957, 1456, 1239, 1085, 976, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29 (dd, J=7.3, 3.2 Hz, 1H), 4.20 (t, J=7.0 Hz, 1H), 3.98 (d, J=3.1 Hz, 1H, H-3), 3.83 (dt, J=6.6, 4.5 Hz, 1H), 3.71 (dd, J=6.1, 4.2 Hz, 2H), 2.83–2.65 (m, 4H), 2.17 (t, J=6.4 Hz, 1H, OH), 1.46 (s, 3H), 1.38 (s, 3H), 1.27 (t, J=7.4 Hz, 3H), 1.26 (t, J=7.4 Hz, 6H), 0.99 (t, J=7.8 Hz, 9H), 0.67 (q, J=7.5 Hz, 6H); EIMS m/z (%) 411 (M^+, 1.8), 291 (86.7), 217 (73.5), 145 (69.8), 135 (62.6), 117 (86.4), 87 (87.8), 75 (62.3), 115 (100). Anal. Calcd for $C_{18}H_{38}O_4S_2Si$: C, 52.64; H, 9.33. Found: C, 52.69; H, 9.19.

4.1.17. Oxidation of 29 and addition of TMSC≡CH to 30 (31a and 31b). SO_3·Py (550 mg, from Acros, 48–53%) in dry DMSO (4 mL) was added to a solution of **29** (490 mg, 1.20 mmol) in dry CH_2Cl_2 (4 mL) stirred in an ice-water bath under argon. When TLC showed completion of the oxidation (ca. 15 min), the bath was removed. The reaction mixture was diluted with Et_2O (150 mL), washed with satd aq $NaHCO_3$ (25 mL×2), and dried over anhydrous $MgSO_4$. Removal of the solvent and chromatography on silica gel (1:10 EtOAc/PE) afforded aldehyde **30** as a colorless oil (401 mg, 0.98 mmol, 82% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, J=1.4 Hz, 1H), 4.38 (dd, J=7.4, 4.9 Hz, 1H), 4.32 (dd, J=7.4, 4.0 Hz, 1H), 4.27 (dd, J=3.8, 1.4 Hz, 1H), 3.88 (d, J=4.9 Hz, 1H), 2.80–2.60 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 1.272 (t, J=7.4 Hz, 3H), 1.267 (t, J=7.4 Hz, 3H), 0.99 (t, J=7.8 Hz, 9H), 0.67 (q, J=8.0 Hz, 6H).

n-BuLi (2.8 mL, 1.6 M in hexane, 4.5 mmol) was added to a solution of TMSC≡CH (0.65 mL, 4.6 mmol) in dry THF (50 mL) stirred in a dry ice–acetone bath under argon. After completion of the addition the stirring was continued at −78 °C for 15 min before a solution of **30** (1.340 g, 3.28 mmol) in dry THF (5 mL) was introduced via a syringe. The mixture was stirred at the same temperature for 3 h. Satd aq NH_4Cl was added to quench the reaction. The mixture was diluted with Et_2O (200 mL), washed with satd aq $NaHCO_3$, and dried over anhydrous $MgSO_4$. Removal of the solvent and column chromatography on silica gel (1:20 Et_2O/PE) gave **31a** (791 mg, 1.56 mmol) and **31b** (547 mg, 1.08 mmol) as colorless oils (81% total yield).

Data for **31a** (the more polar component): $[\alpha]_D^{20}$ +25.0 (c 0.82, $CHCl_3$). FTIR (film) 3468 (br), 2958, 2174, 1456, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (dd, J=4.6, 3.6 Hz, 1H), 4.43 (dd, J=7.4, 2.4 Hz, 1H), 4.33 (dd, J=7.4, 6.1 Hz, 1H), 4.10 (d, J=2.4 Hz, 1H), 3.95 (dd, J=3.8, 5.9 Hz, 1H), 2.85–2.68 (m, 4H), 2.33 (d, J=4.3 Hz, 1H, OH), 1.47 (s, 3H), 1.39 (s, 3H), 1.28 (t, J=7.6 Hz, 3H), 1.27 (t, J=7.4 Hz, 3H), 0.98 (t, J=8.0 Hz, 9H), 0.70 (q, J=8.0 Hz, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.8, 102.9, 92.3, 83.4, 79.4, 76.1, 65.7, 53.5, 27.4, 27.1, 14.6, 14.4, 6.9, 5.2, −0.2; EIMS m/z (%) 445 (2.5), 415 (3.1), 313 (23.9), 254 (23.7), 181 (96.9), 149 (49.9), 135 (40.6), 115 (68.3), 87 (100); ESIMS m/z 524.2 ([M+NH_4]$^+$). Anal. Calcd for $C_{23}H_{46}O_4S_2Si_2$: C, 54.50; H, 9.15. Found C, 54.61; H, 9.10.

Data for **31b** (the less polar component): $[\alpha]_D^{20}$ +15.5 (c 1.03, $CHCl_3$). FTIR (film) 3471 (br), 2958, 2174, 1250, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, J=2.7 Hz, 1H), 4.44 (dd, J=7.3, 2.3 Hz, 1H, H-2), 4.24 (dd, J=8.8, 7.0 Hz, 1H), 4.12 (d, J=2.7 Hz, 1H), 3.66 (dt, J=8.9, 3.4 Hz, 1H), 2.82–2.68 (m, 4H), 2.55 (d, J=3.7 Hz, 1H, OH), 1.48 (s, 3H), 1.39 (s, 3H), 1.29 (t, J=7.4 Hz, 3H), 1.28 (t, J=7.4 Hz, 3H), 0.99 (t, J=7.6 Hz, 9H), 0.69 (br q, $J\approx$8 Hz, 6H), 0.18 (s, 9H); EIMS: m/z (%) 415 (19.9), 339 (19.0), 295 (44.3), 241 (47.3), 181 (97.2), 87 (100); ESIMS m/z 524.3 ([M+NH_4]$^+$). Anal. Calcd for $C_{23}H_{46}O_4S_2Si_2$: C, 54.50; H, 9.15. Found C, 54.70; H, 9.18.

4.1.18. Acetylation of 31a (32). Ac_2O (2 mL) and DMAP (100 mg, 0.81 mmol) were added to a solution of **31a**

(991 mg, 1.955 mmol) in dry Et_3N (3.3 mL) and dry CH_2Cl_2 (7 mL) stirred at ambient temperature overnight. The solvent was removed on a rotary evaporator and chromatography on silica gel (1:11 Et_2O/PE) afforded acetate **32** as a colorless oil (876 mg, 1.596 mmol, 82% yield): $[\alpha]_D^{25}$ −14.7 (*c* 0.70, $CHCl_3$). FTIR (film) 2958, 2182, 1754, 1249, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (d, *J*=2.0 Hz, 1H), 4.34 (dd, *J*=6.8, 2.2 Hz, 1H), 4.27 (t, *J*=7.2 Hz, 1H), 4.00 (d, *J*=2.0 Hz, 1H, H-1), 3.88 (dd, *J*=7.9, 2.4 Hz, 1H), 2.82–2.62 (m, 4H), 2.13 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H), 1.15–1.11 (m, 6H), 1.00 (t, *J*=7.3 Hz, 9H), 0.69 (q, *J*=7.2 Hz, 6H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 110.1, 98.8, 92.7, 84.5, 78.4, 75.6, 67.0, 54.0, 27.3, 27.0, 25.4, 24.5, 14.5, 14.3, 6.8, 5.0, −0.4; ESIMS *m/z* 566.2 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{25}H_{48}O_5S_2Si_2Na$ ([M+Na]$^+$) 571.2384; found 571.2374. Anal. Calcd for $C_{25}H_{48}O_5S_2Si_2$: C, 54.70; H, 8.81. Found C, 55.18; H, 8.97.

4.1.19. Conversion of 32 into 33. NBS (114 mg, 0.64 mmol) was added to a solution of **32** (47 mg, 0.085 mmol) in 5:1 (v/v) MeCN/H_2O (3 mL). After stirring for 7 min, aq Na_2SO_3 was added, followed by 1:1 (v/v) *n*-hexane/CH_2Cl_2. The phases were separated. The organic layer was washed with satd aq $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was dissolved in toluene (3 mL) and treated with **9** (58 mg, 0.15 mmol) at 70–80 °C (bath) until TLC showed completion of the reaction. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (1:5 EtOAc/PE) to give **33** as a colorless oil (26 mg, 0.047 mmol, 55% from **32**).

Alternatively, solid I_2 (1.330 g, 5.2 mmol) was added in portions to a mixture of **32** (869 mg, 1.59 mmol) and powdered $NaHCO_3$ (890 mg, 10.59 mmol) in 5:1 (v/v) acetone/water (15 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred for 15 min before the reaction was quenched with satd aq $Na_2S_2O_3$. The mixture was diluted with Et_2O (200 mL), washed in turn with satd aq $Na_2S_2O_3$, satd aq $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left the intermediate aldehyde as a yellowish oil (558 mg, 1.26 mmol), which was dissolved in toluene (8 mL) and treated with Wittig reagent **9** (500 mg, 1.28 mmol) at 70–80 °C (bath) until TLC showed completion of the reaction. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (1:5 EtOAc/PE) to give **33** as a colorless oil (581 mg, 1.05 mmol, 83% from **32**): $[\alpha]_D^{25}$ −31.0 (*c* 1.0, $CHCl_3$). FTIR (film) 2956, 2182, 1746, 1220, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dd, *J*=16.0, 4.2 Hz, 1H), 6.45 (dd, *J*=15.6, 1.8 Hz, 1H), 5.55 (d, *J*=2.2 Hz, 1H), 4.70–4.60 (m, 1H), 4.05–3.97 (m, 2H), 3.68 (s, 3H), 2.91 (t, *J*=6.8 Hz, 2H), 2.64 (t, *J*=6.7 Hz, 2H), 2.11 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 0.99 (t, *J*=7.7 Hz, 9H), 0.68 (q, *J*=7.9 Hz, 6H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 173.0, 169.0, 144.0, 128.8, 110.4, 98.7, 93.0, 80.1, 77.0, 76.6, 74.4, 66.3, 51.6, 35.1, 27.5, 26.7, 26.4, 20.9, 6.7, 4.8, −0.5; ESIMS *m/z* 572.3 ([M+NH_4]$^+$). Anal. Calcd for $C_{27}H_{46}O_8Si_2$: C, 58.45; H, 8.36. Found: C, 58.35; H, 8.37.

4.1.20. CBS reduction of 33 (34). A solution of ketone **33** (300 mg, 0.54 mmol) in dry THF (4 mL) was added via a syringe over 1.5 h (using a syringe pump) to a solution of (*S*)-2-methyl-CBS-oxazaborolidine (0.20 mL, 1.0 M in toluene, 0.20 mmol) and $BH_3 \cdot SMe_2$ (0.3 mL, 2.0 M in THF, 0.60 mmol) in dry THF (3 mL) stirred in an ice-water bath under argon. After completion of the addition, the stirring was continued at the same temperature for 1 h (when TLC showed completion of the reduction). MeOH was added to quench the reaction. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (1:1 Et_2O/PE) to give **34** as a colorless oil (186 mg, 0.33 mmol, 61% yield, 6:1 mixture of the two epimers as shown by ^1H NMR), which was used in the next step. By repeated chromatography a small pure sample of the major isomer (expected to be the one with the configuration drawn in the structure for **34**) was obtained, from which the following physical and spectroscopic data were collected: $[\alpha]_D^{25}$ −32.3 (*c* 0.65, $CHCl_3$). FTIR (film) 3487 (br), 2955, 2181, 1743, 1224.3, 743.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dd, *J*=15.3, 5.0 Hz, 1H), 5.78 (dd, *J*=15.8, 5.7 Hz, 1H), 5.47 (d, *J*=4.4 Hz, 1H), 4.48 (t, *J*=6.1 Hz, 1H), 4.21 (br q, *J*=4.5 Hz, 1H), 4.00 (dd, *J*=5.4, 4.1 Hz, 1H), 3.88 (dd, *J*=7.2, 5.7 Hz, 1H), 3.68 (s, 3H), 2.48 (t, *J*=7.4 Hz, 2H), 2.12 (s, 3H), 1.93 (d, *J*=4.6 Hz, 1H, OH), 1.92–1.76 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 0.99 (t, *J*=8.12 Hz, 9H), 0.68 (q, *J*=7.7 Hz, 6H), 0.18 (s, 9H); ESIMS *m/z* 579.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{27}H_{48}O_8Si_2Na$ ([M+Na]$^+$) 579.2780; found 579.2779.

4.1.21. Lactonization of 34 (35). A solution of **34** (208 mg, 0.37 mmol) and PPTS (10 mg, 0.04 mmol) in dry toluene (5 mL) was stirred at 40–50 °C (bath) until TLC showed completion of the reaction. The reaction mixture was diluted with Et_2O (100 mL), washed in turn with satd aq $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and chromatography on silica gel (1:1 Et_2O/PE) gave the lactone **35** as a colorless oil (115 mg, 0.22 mmol, 59% yield). Data for the major isomer: $[\alpha]_D^{25}$ −48.2 (*c* 1.65, $CHCl_3$). FTIR (film) 2957, 2181, 1782, 1752, 1223, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00–5.85 (m, 2H), 5.50 (d, *J*=2.9 Hz, 1H), 5.02–4.95 (m, 1H), 4.52 (dd, *J*=6.7, 4.1 Hz, 1H), 4.02–3.90 (m, 2H), 2.57 (td, *J*=6.2, 1.6 Hz, 2H), 2.48–2.38 (m, 1H), 2.12 (s, 3H), 2.10–2.00 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 0.99 (t, *J*=7.5 Hz, 9H), 0.68 (q, *J*=7.7 Hz, 6H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 169.2, 131.7, 129.3, 109.4, 99.1, 92.7, 80.6, 79.6, 74.3, 66.4, 28.4, 26.9, 20.9, 6.8, 4.9, −0.4. ESIMS *m/z* 547.2 ([M+Na]$^+$); ESIHRMS calcd for $C_{26}H_{44}O_7Si_2Na$ ([M+Na]$^+$) 547.2518; found 547.2525.

4.1.22. Removal of silyl protecting groups in 31b (36). Powdered K_2CO_3 (714 mg, 5.17 mmol) was added to a solution of **31b** (2.328 g, 4.60 mmol) in 2:1 (v/v) MeOH/THF (30 mL) stirred in an ice-water bath. The stirring was continued at the same temperature for 30 min. The reaction mixture was diluted with EtOAc (200 mL), washed with brine (30 mL×2), and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:2 EtOAc/PE) afforded diol **36** as a colorless oil (1.397 g, 4.36 mmol, 95% yield).

Alternatively, a solution of **31b** (1.420 g, 2.81 mmol) and *n*-Bu_4NF (6 mL, 1.0 M in THF, 6.0 mmol) in THF (10 mL) was stirred at ambient temperature for 5 min. Satd aq NH_4Cl was added, followed by EtOAc. The phases were

separated and the organic layer was washed, dried, and chromatographed as described above to give diol **36** as a colorless oil (808 mg, 2.52 mmol, 90% yield).

Data for **36**: $[\alpha]_D^{20}$ +69.5 (*c* 1.66, $CHCl_3$). FTIR (film) 3427 (br), 2984, 2929, 2116, 1454, 1243, 1077, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (ddd, *J*=6.3, 4.0, 2.2 Hz, 1H, H-5), 4.43 (dd, *J*=6.7, 4.0 Hz, 1H, H-2), 4.21 (dd, *J*=8.6, 6.8 Hz, 1H, H-3), 4.07 (d, *J*=4.2 Hz, 1H, H-1), 3.77 (ddd, *J*=8.9, 4.5, 1.3 Hz, 1H, H-4), 2.80–2.70 (m, 4H, SCH_2), 2.66 (d, *J*=5.8 Hz, 1H, O*H*), 2.58 (d, *J*=1.8 Hz, 1H, H-7), 1.49 (s, 3H), 1.41 (s, 3H), 1.289 (t, *J*=7.3 Hz, 3H), 1.281 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.6, 83.5, 80.9, 78.9, 75.6, 75.0, 64.7, 53.2, 27.3, 27.1, 25.4, 25.0, 14.4, 14.3; EIMS *m/z* (%) 320 (M^+, 3.4), 302 (1.5, M^+-H_2O), 241 (18.4), 201 (7.9), 167 (10.7), 135 (91.9), 127 (41.5), 59(100); EIHRMS calcd for $C_{14}H_{24}O_4S_2$ 320.11160; found 320.11439. Anal. Calcd for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55. Found C, 52.00; H, 8.03.

4.1.23. Conversion of diol 36 into acetonide 37. A solution of **36** (121 mg, 0.38 mmol) and PPTS (23 mg, 0.12 mmol) in 2,2-dimethoxypropane (3 mL) was stirred at ambient temperature overnight. The mixture was diluted with EtOAc (60 mL), washed with satd aq $NaHCO_3$ (10 mL×2), and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and chromatography on silica gel (1:20 EtOAc/PE) gave diacetonide **37** (configuration assigned on the basis of 2D NMR, marked here using the cepacin A atom numbering system) as a colorless oil (130 mg, 0.36 mmol, 95% yield): $[\alpha]_D^{20}$ +105.9 (*c* 1.0, $CHCl_3$). FTIR (film) 3274, 2986, 2115, 1455, 1227, 1066, 856 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (dd, *J*=5.6, 2.0 Hz, 1H, H-10), 4.50 (dd, *J*=8.8, 7.6 Hz, 1H, H-8), 4.39 (dd, *J*=7.6, 2.4 Hz, 1H, H-7), 4.07 (d, *J*=2.1 Hz, 1H, H-6), 4.02 (dd, *J*=8.8, 5.6 Hz, 1H, H-9), 2.79–2.69 (m, 4H, SCH_2), 2.62 (d, *J*=1.9 Hz, 1H, H–C≡C), 1.53 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.293 (t, *J*=7.4 Hz, 3H), 1.286 (t, *J*=7.4 Hz, 3H); EIMS *m/z* (%) 360 (M^+, 7.6), 345 (2.5), 299 (4.0), 287 (3.9), 241 (26.5), 167 (92.2), 135 (89.4), 81 (64.4), 43 (100). Anal. Calcd for $C_{17}H_{28}O_4S_2$: C, 56.63; H, 7.83. Found C, 56.49; H, 8.03.

4.1.24. Conversion of 31a into 38. Solid I_2 (5.737 g, 22.58 mmol) was added in portions to a mixture of **31a** (3.834 g, 7.58 mmol) and powdered $NaHCO_3$ (4.580 g, 54.52 mmol) in 5:1 (v/v) acetone/water (70 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred for 20 min before the reaction was quenched with satd aq $Na_2S_2O_3$. The mixture was diluted with Et_2O (300 mL), washed in turn with satd aq $Na_2S_2O_3$, satd aq $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left the intermediate aldehyde as a yellowish oil (558 mg, 1.26 mmol), which was dissolved in toluene (50 mL) and treated with Wittig reagent **9** (3.115 g, 8.19 mmol) at 70–80 °C (bath) until TLC showed completion of the reaction. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (1:5 EtOAc/PE) to give **38** (cis/trans=1:4) as a colorless oil (2.822 g, 5.51 mmol, 73% from **31a**).

Data for the trans-isomer (major isomer): $[\alpha]_D^{20}$ +14.7 (*c* 0.86, $CHCl_3$). FTIR (film) 3470 (br), 2956, 2170, 1742, 1250, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (dd, *J*=15.8, 4.5 Hz, 1H), 6.50 (dd, *J*=15.9, 1.7 Hz, 1H), 4.88 (ddd, *J*=7.6, 4.5, 1.7 Hz, 1H), 3.99 (d, *J*=7.7 Hz, 1H), 3.75 (d, *J*=9.5 Hz, 1H), 3.68 (s, 3H), 3.67 (d, *J*=10 Hz, 1H), 2.94 (s, 1H, OH), 2.92 (t, *J*=6.6 Hz, 2H), 2.64 (t, *J*=7.1 Hz, 2H), 1.49 (s, 3H), 1.42 (s, 3H), 0.97 (t, *J*=8.0 Hz, 9H), 0.64 (q, *J*=8.0 Hz, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 173.1, 144.6, 128.7, 109.3, 102.8, 93.4, 80.5, 76.1, 74.7, 51.6, 34.7, 27.7, 26.7, 26.3, 6.7, 6.6, 5.0, 4.6, −0.4; ESIMS *m/z* 530.2 ($[M+NH_4]^+$); EIMS *m/z* (%) 497 (M^+-CH_3, 0.8), 425 (1.5), 407 (3.6), 309 (8.4), 241 (100), 183 (48.3), 115 (87.1); EIHRMS calcd for $C_{24}H_{41}O_7Si_2$ (M^+-CH_3) 497.2391; found 497.2399.

4.1.25. Tosylation of 38 and desilylation of 39 (40). *p*-TsCl (252 mg, 1.31 mmol) was added to a solution of **38** (444 mg, 0.87 mmol) and DMAP (325 mg, 2.66 mmol) in dry CH_2Cl_2 (1 mL) and Et_3N (1 mL) stirred in an ice-water bath. The bath was removed and the mixture was stirred at ambient temperature overnight. The reaction mixture was then diluted with EtOAc (80 mL), washed with satd aq NH_4Cl, and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:4 EtOAc/PE) afforded tosylate **39** as a yellowish oil (424 mg, 0.64 mmol, 74% yield), which gave the following data: ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.3 Hz, 2H), 6.89 (dd, *J*=15.9, 4.4 Hz, 1H), 6.42 (dd, *J*=16.0, 1.5 Hz, 1H), 5.24 (d, *J*=2.7 Hz, 1H), 4.63–4.59 (m, 1H), 4.03 (dd, *J*=7.1, 2.8 Hz, 1H), 3.84, (t, *J*=7.0 Hz, 1H), 3.68 (s, 3H), 2.92 (t, *J*=6.8 Hz, 2H), 2.63 (t, *J*=6.5 Hz, 2H), 2.45 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 0.96 (t, *J*=7.8 Hz, 9H), 0.67 (q, *J*=7.9 Hz, 6H), 0.02 (s, 9H).

The tosylate **39** (641 mg, 0.96 mmol) was dissolved in 2:1 (v/v) MeOH/THF (21 mL). With cooling (ice-water bath) and stirring, powdered K_2CO_3 (131 mg, 0.95 mmol) was added. The mixture was stirred at the same temperature for 25 min before being diluted with EtOAc (100 mL), washed with brine (30 mL×2), and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:3 EtOAc/PE) delivered **40** as a colorless oil (523 mg, 0.88 mmol, 92% yield): $[\alpha]_D^{20}$ −21.5 (*c* 0.90, $CHCl_3$). FTIR (film) 3272, 2955, 2120, 1740, 1682, 1371, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.5 Hz, 2H), 7.35 (d, *J*=8.5 Hz, 2H), 6.87 (dd, *J*=15.9, 4.1 Hz, 1H), 6.41 (dd, *J*=16.1, 1.9 Hz, 1H), 5.28 (t, *J*=2.3 Hz, 1H), 4.59 (ddd, *J*=8.5, 4.0, 1.5 Hz, 1H), 4.01 (dd, *J*=7.8, 2.1 Hz, 1H), 3.85 (dd, *J*=7.6, 7.0 Hz, 1H), 3.69 (s, 3H), 2.92 (t, *J*=6.6 Hz, 2H), 2.64 (t, *J*=6.5 Hz, 2H), 2.46 (s, 3H), 2.42 (d, *J*=2.0 Hz, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 0.95 (t, *J*=7.9 Hz, 9H), 0.58 (br q, *J*=7.8 Hz, 6H); EIMS *m/z* (%) 579 (M^+-CH_3, 3.0), 507 (2.0), 335 (18.0), 257 (100), 183 (23.6), 154 (19.5), 115 (68.3), 94 (20.5). Anal. Calcd for $C_{29}H_{42}O_9SSi$: C, 58.56; H, 7.12. Found C, 58.18; H, 7.22.

4.1.26. Conversion of tosylate 40 into bromoallene 41. A solution of tosylate **40** (521 mg, 0.88 mmol) in dry THF (5 mL, another 2 mL to assist the transfer) was added via a syringe to a dry flask containing $CuBr\cdot SMe_2$ (629 mg, 3.06 mmol, recrystallized) and LiBr (250 mg, 2.87 mmol, dried) stirred at ambient temperature under argon. The mixture was heated to reflux under argon for 10 h. After being

cooled to ambient temperature, the reaction mixture was diluted with EtOAc (100 mL), washed with satd aq NH_4Cl (30 mL×2), and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:4 EtOAc/PE) gave bromoallene **41** as a colorless oil (271 mg, 0.54 mmol, 61% yield) along with unreacted **40** (141 mg, 0.23 mmol).

Data for **41**: $[\alpha]_D^{27}$ −53.9 (*c* 1.59, $CHCl_3$). FTIR (film) 2955, 2877, 1961, 1740, 1682, 1214, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (dd, *J*=15.9, 4.8 Hz, 1H), 6.45 (dd, *J*=15.8, 1.4 Hz, 1H), 6.11 (dd, *J*=6.0, 1.7 Hz, 1H), 5.36 (dd, *J*=6.9, 5.5 Hz, 1H), 4.62 (ddd, *J*=7.8, 4.6, 1.4 Hz, 1H), 4.42 (ddd, *J*=8.6, 5.8, 1.5 Hz, 1H), 3.79 (dd, *J*=7.7, 5.2 Hz, 1H), 3.70 (s, 3H), 2.93 (t, *J*=6.6 Hz, 2H), 2.65 (t, *J*=6.7 Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 0.99 (t, *J*=7.9 Hz, 9H), 0.68 (q, *J*=7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.85, 197.46, 172.98, 143.34, 129.04, 110.21, 100.77, 83.39, 77.02, 74.22, 70.78, 51.61, 35.10, 27.58, 26.80, 26.69, 6.64, 4.74; EIMS *m/z* (%) 487 (M^+-CH_3, 0.8), 437 (3.0), 435 (3.0), 335 (4.5), 263 (16.7), 261 (16.6), 182 (39.4), 183 (54.4), 184 (7.5), 153 (32.9), 115 (100), 87 (41.6); EIHRMS calcd for $C_{21}H_{32}O_6BrSi$ (M^+-CH_3) 487.1151; found 487.1186.

4.1.27. Removal of the TES group in 41 (42). *n*-Bu_4NF (1.4 mL, 1.0 M in THF) was added to a solution of **41** (672 mg, 1.33 mmol) in THF (10 mL) stirred in an ice-water bath. After stirring for 6 min, satd aq NH_4Cl (2 mL) was introduced, followed by EtOAc (100 mL). The phases were separated, the organic layer was washed with satd aq NH_4Cl (2 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:2 EtOAc/PE) afforded **42** as a colorless oil (500 mg, 1.29 mmol, 97% yield): $[\alpha]_D^{26}$ +11.82 (*c* 1.15, $CHCl_3$). FTIR (film) 3466, 2988, 1960, 1737, 1679, 1636, 1373, 1215, 1060, 858, 658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (dd, *J*=15.9, 5.2 Hz, 1H), 6.48 (dd, *J*=15.9, 1.5 Hz, 1H), 6.22 (dd, *J*=5.9, 2.7 Hz, 1H), 5.50 (t, *J*=5.7 Hz, 1H), 4.65 (ddd, *J*=7.7, 5.0, 1.5 Hz, 1H), 4.55–4.50 (m, 1H), 3.85 (dd, *J*=8.0, 5.1 Hz, 1H), 3.69 (s, 3H), 2.92 (t, *J*=6.6 Hz, 2H), 2.65 (t, *J*=6.7 Hz, 2H), 2.36 (d, *J*=4.2 Hz, 1H), 1.48 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 197.8, 173.2, 143.0, 129.4, 110.4, 100.1, 82.7, 76.9, 75.5, 68.5, 51.7, 35.3, 27.6, 26.8, 26.7; EIMS *m/z* (%) 373 (M^+-15, 1.9), 375 (1.9), 241 (21.2), 183 (86.9), 167 (25.9), 115 (76.1), 94 (55.1), 81 (77.3); HRMS calcd for $C_{15}H_{18}O_6Br$ ($M-CH_3$) 373.0487; found 373.0316.

4.1.28. Synthesis of epoxide 46 from alcohol 42. Step 1 (tosylation of **42**). DMAP (33 mg, 0.27 mmol) and *p*-TsCl (121 mg, 0.63 mmol) were added to a solution of **42** (167 mg, 0.43 mmol) in dry CH_2Cl_2 (8 mL) and Et_3N (2 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature overnight before being diluted with EtOAc (60 mL), washed with satd aq NH_4Cl (2 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:2 EtOAc/PE) afforded tosylate **43** as a colorless oil (168 mg, 0.31 mmol, 72% from **42**), from which the following data were acquired: $[\alpha]_D^{26}$ −43.2 (*c* 0.91, $CHCl_3$). FTIR (film) 2989, 1967, 1737, 1681, 1648, 1598, 1438, 1371, 1190, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J*=8.3 Hz, 2H), 7.37 (dd, *J*=8.3 Hz, 2H), 6.76 (dd, *J*=15.9, 5.5 Hz, 2H), 6.43 (dd, *J*=15.9, 1.5 Hz, 1H), 6.02 (dd, *J*=5.9, 1.8 Hz, 1H), 5.29 (dd, *J*=6.5, 5.9 Hz, 1H), 5.17 (ddd, *J*=7.2, 5.6, 1.6 Hz, 1H), 4.57 (ddd, *J*=7.5, 5.6, 1.4 Hz, 1H), 3.92 (dd, *J*=7.5, 5.6 Hz, 1H), 3.69 (s, 3H), 2.91 (t, *J*=6.6 Hz, 2H), 2.64 (t, *J*=6.6 Hz, 2H), 2.46 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H).

Step 2 (CBS reduction). The above obtained tosylate **43** (70 mg, 0.13 mmol) was dissolved in dry THF (2 mL) and added via a syringe over 5 min to a solution of (*S*)-2-methyl-CBS-oxazaborolidine (0.20 mL, 1.0 M in toluene, 0.20 mmol) and $BH_3\cdot SMe_2$ (0.08 mL, 2.0 M in THF) in dry THF (2 mL) stirred in an ice-water bath under argon. After completion of the addition, the stirring was continued at the same temperature for 10 min. MeOH was added to quench the reaction. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (2:3 EtOAc/PE) to give the intermediate alcohol as a colorless oil (56 mg, 0.10 mmol, 77% from **43**) along with unreduced ketone **43** (13 mg, 0.023 mmol). The following data were acquired from the intermediate alcohol: $[\alpha]_D^{26}$ −31.6 (*c* 0.96, $CHCl_3$). FTIR (film) 3501 (br), 2987, 1966, 1736, 1372, 1245, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.5 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 5.94 (dd, *J*=5.7, 1.6 Hz, 1H), 5.93 (dd, *J*=15.2, 6.1 Hz, 1H), 5.71 (dd, *J*=15.4, 7.7 Hz, 1H), 5.26 (dd, *J*=6.8, 5.6 Hz, 1H), 5.13 (ddd, *J*=8.4, 5.8, 1.8 Hz, 1H), 4.40 (t, *J*=7.9 Hz, 1H), 4.23 (m, 1H), 3.86 (dd, *J*=7.9, 5.8 Hz, 1H), 3.69 (s, 3H), 2.50–2.40 (m, 2H), 2.46 (s, 3H), 2.21 (d, *J*=3.9 Hz, 1H), 2.00–1.80 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.80, 174.25, 145.10, 138.09, 137.86, 133.7, 129.9, 127.9, 127.1, 127.0, 110.1, 95.5, 81.0, 80.9, 78.6, 78.2, 76.7, 75.2, 70.6, 70.5, 51.6, 31.6, 29.8, 27.0, 26.6, 21.6.

Step 3 (lactonization). The above obtained intermediate alcohol (144 mg, 026 mmol) was dissolved in toluene (6 mL) and treated with PPTS (14 mg, 0.05 mmol) at 40–50 °C (bath) until TLC showed completion of the reaction. The reaction mixture was diluted with EtOAc (50 mL), washed in turn with satd aq $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (1:1 EtOAc/PE) gave lactone **44** as a colorless oil (111 mg, 0.22 mmol, 85% from the intermediate alcohol), from which the following data were measured: $[\alpha]_D^{30}$ −39.4 (*c* 1.42, $CHCl_3$). FTIR (film) 2987, 1966, 1776, 1597, 1456, 1370, 1215, 1095, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.4 Hz, 2H), 7.37 (d, *J*=7.7 Hz, 2H), 5.98 (dd, *J*=5.7, 1.7 Hz, 1H), 5.97 (dd, *J*=16.5, 5.6 Hz, 1H), 5.80 (dd, *J*=16.5, 6.5 Hz, 1H), 5.25 (t, *J*=6.1 Hz, 1H), 5.12 (ddd, *J*=1.4, 5.4, 8.2 Hz, 1H), 5.00 (br q, *J*=6.0 Hz, 1H), 4.45 (t, *J*=7.3 Hz, 1H), 3.87 (dd, *J*=7.7, 5.7 Hz, 1H), 2.60–2.37 (m, 2H), 2.46 (s, 3H), 2.10–2.00 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H).

Step 4 (hydrolysis of acetonide). The above obtained lactone **44** (111 mg, 0.22 mmol) was dissolved in dry CH_2Cl_2 (5 mL), to which $BF_3\cdot Et_2O$ (5 μL, 0.05 mmol) and $HS(CH_2)_3SH$ (50 μL, 0.49 mmol) were added. The mixture was stirred at ambient temperature until TLC showed completion of the reaction. The mixture was diluted with EtOAc (50 mL), washed with brine (10 mL×2), and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (3:1 EtOAc/PE) gave diol **45** as

a colorless oil (72 mg, 0.15 mmol, 69% from **44**), from which the following data were obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.1 Hz, 2H), 5.98–5.81 (m, 3H), 5.37 (dd, J=6.7, 5.9 Hz, 1H), 5.01–4.97 (m, 2H), 4.45 (br s, 1H), 3.72–3.63 (m, 1H), 2.80–2.72 (m, 1H), 2.63–2.38 (m, 3H), 2.47 (s, 3H), 2.10–1.95 (m, 2H).

Step 5 (epoxidation). Powdered K_2CO_3 (18 mg, 0.13 mmol) was added to a solution of diol **45** (72 mg, 0.15 mmol) in 50:1 (v/v) Et_2O/H_2O (5 mL) stirred at ambient temperature until TLC showed completion of the reaction. The mixture was diluted with EtOAc (50 mL), washed with brine (10 mL×2), and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (3:1 EtOAc/PE) gave epoxide **46** (with the NMR signals assigned on the basis of 2D NMR) as a colorless oil (30 mg, 0.10 mmol, 77% from **45**): $[\alpha]_D^{20}$ −123.5 (c 0.6, $CHCl_3$). FTIR (film) 3438 (br), 3050, 2990, 1957, 1770, 1458, 975, 897, 657 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, J=5.7 Hz, 1H, H-12), 6.00–5.89 (m, 2H, H-5 and H-6), 5.16 (dd, J=7.9, 5.6 Hz, 1H, H-10), 5.03 (m, 1H, H-4), 4.26 (m, 1H, H-7), 3.55 (dd, J=8.1, 2.0 Hz, 1H, H-9), 3.07 (m, 1H, H-8), 2.62–2.54 (m, 2H, H-2), 2.48 (m, 1H, H-3), 2.10 (d, J=6.9 Hz, 1H, OH), 2.05 (m, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7 (C-11), 176.8 (C-1), 131.0 (C-5/6), 130.0 (C-6/5), 98.1 (C-10), 79.5 (C-4), 74.9 (C-12), 69.7 (C-7), 61.6 (C-8), 52.0 (C-9), 28.4 (C-2), 28.2 (C-3); EIMS m/z (%) 161 (5.1, C-12 to C-8 fragment), 159 (4.5, C-12 to C-8 fragment), 142 (5.7), 141 (6.9, C-7 to C-1 fragment), 123 (10.3), 113 (8.7), 95 (30.3), 81 (100); ESIMS m/z 323.1 ([M+Na]$^+$); ESIHRMS calcd for $C_{12}H_{13}O_4BrNa$ ([M+Na]$^+$) 322.9878; found 322.9889.

4.1.29. Coupling of 41 with TMSC≡CH. $PdCl_2(PPh_3)_2$ (3.06 mg, 4.35 μmol), CuI (2.72 mg, 14.22 μmol), and i-Pr_2NH (0.26 mL) were quickly added to a solution of **41** (29 mg, 57 μmol) and TMSC≡CH (11 mg, 90 μmol) in dry de-aired EtOAc (2 mL) at −20 °C under argon with precaution against strong light. The mixture was stirred while the temperature was allowed to rise to 0 °C over 30 min. The stirring was then continued at ambient temperature until TLC showed completion of the reaction (ca. 20 min). Satd aq NH_4Cl was added, followed by Et_2O. The phases were separated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (1:4 Et_2O/PE) gave **51** as a yellowish oil (24 mg, 44 μmol, 77%): $[\alpha]_D^{25}$ +50.0 (c 0.04, $CHCl_3$). FTIR (film) 2956, 2158, 1953, 1742, 1250, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dd, J=15.2, 11.5, 4.6 Hz, 1H), 6.42 (d, J=15.8 Hz, 1H), 5.54–5.48 (m, 1.3H), 5.40 (t, J=7.7 Hz, 0.4H), 4.60–4.56 (m, 1H), 4.34–4.28 (m, 1H), 3.80–3.76 (m, 1H), 3.69 (s, 3H), 2.91 (t, J=6.7 Hz, 2H), 2.64 (t, J=6.7 Hz, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1.00–0.95 (m, 9H), 0.71–0.62 (m, 6H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 197.8, 173.3, 143.7, 129.5, 110.6, 97.4, 96.3, 95.0, 84.1, 78.7, 71.4, 52.0, 35.4, 27.9, 27.1, 27.1, 27.0, 7.0, 5.0, −0.002; ESIMS m/z 543.2 ([M+Na]$^+$); ESIHRMS calcd for $C_{27}H_{44}O_6Si_2Na$ ([M+Na]$^+$) 543.2569; found 543.2559.

4.1.30. Coupling of 41 with TMSC≡C–C≡CH. The procedure was the same as that employed in the synthesis of **51** given above, except that the TMSC≡CH was replaced by TMSC≡C–C≡CH. Yield: 59%. Data for **52** (a yellowish-light brown oil): $[\alpha]_D^{25}$ +45.0 (c 0.02, $CHCl_3$). FTIR (film) 2956, 2201, 2104, 1950, 1743, 1251, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (ddd, J=15.5, 10.0, 4.8 Hz, 1H), 6.43 (dd, J=15.8, 5.2 Hz, 1H), 5.54 (d, J=4.8 Hz, 1H), 4.61–4.56 (m, 1H), 4.36–4.33 (m, 1H), 3.80–3.75 (m, 1H), 3.69 (s, 3H), 2.92 (t, J=6.6 Hz, 2H), 2.64 (t, J=6.6 Hz, 2H), 1.45 (s, 3H), 1.41 (s, 3H), 0.97 (t, J=6.7 Hz, 9H), 0.64 (q, J=8.0 Hz, 6H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 198.0, 173.6, 143.8, 129.8, 110.9, 96.0, 90.9, 88.2, 84.2, 77.7, 76.5, 71.5, 69.5, 52.2, 35.6, 28.2, 27.4, 27.3, 27.26, 7.2, 5.3, −0.001; ESIMS m/z 567.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{29}H_{44}O_6Si_2Na$ ([M+Na]$^+$) 567.2569; found 567.2577.

4.1.31. Oxidation of 31a into ketone 31c. Method A. A mixture of MnO_2 (181 mg, 2.0 mmol) and **31a** (62 mg, 0.12 mmol) in dry CH_2Cl_2 (4 mL) was heated to reflux with stirring until TLC showed disappearance of the starting material. The solids were filtered off (washing with CH_2Cl_2). The filtrate/washings were evaporated to dryness and the residue was chromatographed on silica gel (1:15 EtOAc/PE) to give ketone **31c** as a yellowish oil (35 mg, 0.07 mmol, 58% yield).

Method B. A solution of **31a** (2.300 g, 4.54 mmol) and Dess–Martin periodinane (1.900 g, 4.48 mmol) in dry CH_2Cl_2 (50 mL) was stirred at ambient temperature for 20 min. The reaction mixture was worked up as usual and chromatographed on silica gel (1:15 EtOAc/PE) to give ketone **31c** as a colorless oil (1.650 g, 3.27 mmol, 72% yield): $[\alpha]_D^{20}$ +19.7 (c 1.10, $CHCl_3$). FTIR (film) 2960, 2152, 1685, 1252 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51–4.45 (m, 2H), 4.42–4.38 (m, 1H), 3.82–3.79 (m, 1H), 2.82–2.64 (m, 4H), 1.46 (s, 3H), 1.40 (s, 3H), 1.28 (t, J=7.5 Hz, 6H), 0.99 (t, J=7.9 Hz, 9H), 0.66 (q, J=7.8 Hz, 6H), 0.27 (s, 9H); ESIMS m/z 527.2 ([M+Na]$^+$). Anal. Calcd for $C_{23}H_{44}O_4S_2Si_2$: C, 54.71; H, 8.78. Found C, 55.08; H, 9.17.

4.1.32. DIBAL-H reduction of 31c into 31b. DIBAL-H (3.5 mL, 1.0 M, 3.50 mmol) was added to a solution of **31c** (1.600 g, 3.17 mmol) in dry CH_2Cl_2 (530 mL) stirred at −78 °C. The stirring was then continued at the same temperature for 40 min. Excess DIBAL-H was destroyed by addition of MeOH. The mixture was diluted with EtOAc (200 mL), washed in turn with satd aq potassium sodium tartrate and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography on silica gel (1:20 Et_2O/PE) gave **31b** as a colorless oil (1.250 g, 2.48 mmol, 80% yield).

4.1.33. Conversion of 31b into 38′. The procedure, yield and the cis/trans ratio were the same as that reported for converting **31a** into **38**, except that the **31a** was replaced by **31b**.

Data for the trans-isomer (major isomer): $[\alpha]_D^{20}$ −7.3 (c 0.97, $CHCl_3$). FTIR (film) 3497 (br), 2956, 2174, 1743, 1372, 1251, 845 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (dd, J=16.0, 4.4 Hz, 1H), 6.49 (dd, J=16.1, 1.6 Hz, 1H), 4.72 (ddd, J=5.9, 4.2, 1.9 Hz, 1H), 4.64 (d, J=3.5 Hz, 1H), 3.78 (dd, J=7.4, 3.6 Hz, 1H), 3.75–3.67 (m, 1H), 3.68 (s, 3H), 2.94 (t, J=6.8 Hz, 2H), 2.67 (t, J=6.7 Hz, 2H), 1.45

(s, 3H), 1.41 (s, 3H), 1.01 (t, J=7.7 Hz, 9H), 0.699 (t, J=7.6 Hz, 3H), 0.691 (q, J=7.7 Hz, 3H), 0.16 (s, 9H); ESIMS m/z 535.3 ([M+Na]$^+$). Anal. Calcd for $C_{25}H_{44}O_7Si_2$: C, 58.56; H, 8.65. Found C, 58.27; H, 8.74.

4.1.34. Tosylation of 38′ and desilylation of 39′ (40′). The tosylation procedure and yield were the same as that reported above for converting **38** into **39**, except that **38** was replaced by **38′**. The following data were acquired from the intermediate **39′**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 7.09 (dd, J=16.0, 3.8 Hz, 1H), 6.43 (dd, J=15.9, 1.9 Hz, 1H), 4.83–4.79 (m, 3H), 4.30 (dd, J=7.4, 3.5 Hz, 1H), 3.68 (s, 3H), 2.90 (t, J=6.7 Hz, 2H), 2.62 (t, J=6.5 Hz, 2H), 2.44 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H), 0.93 (t, J=8.0 Hz, 9H), 0.605 (q, J=7.5 Hz, 3H), 0.597 (q, J=8.2 Hz, 3H), 0.15 (s, 9H). ESIMS m/z 689.35 ([M+Na]$^+$).

The desilylation of **39′** to give **40′** was performed using the same procedure for converting **39** into **40** with the same yield.

Data for **40′**: FTIR (film) 3273, 2955, 2117, 1741, 1177 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.6 Hz, 2H), 7.06 (dd, J=16.3, 2.8 Hz, 1H), 6.44 (dd, J=16.1, 1.8 Hz, 1H), 4.86–4.80 (m, 3H), 4.30–4.24 (m, 1H), 3.69 (s, 3H), 2.92 (dt, J=7.0, 3.1 Hz, 2H), 2.64 (t, J=6.8 Hz, 2H), 2.53 (d, J=1.7 Hz, 1H), 2.45 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H), 0.94 (t, J=8.4 Hz, 9H), 0.58 (br q, J=7.8 Hz, 6H); EIMS m/z (%) 579 (M$^+$−CH_3, 3.0), 507 (2.0), 335 (18.0), 257 (100), 183 (23.6), 154 (19.5), 115 (68.3), 94 (20.5); ESIMS m/z 617.20 ([M+Na]$^+$). Anal. Calcd for $C_{29}H_{42}O_9SSi$: C, 58.56; H, 7.12. Found C, 58.21; H, 7.02.

4.1.35. Desilylation of 38′ (53). A solution of **38′** (848 mg, 1.66 mmol) and n-Bu_4NF (3.5 mL, 1.0 M in THF, 3.5 mmol) in THF (8 mL) was stirred at 0 °C for 10 min. Satd aq NH_4Cl was added, followed by EtOAc. The phases were separated and the organic layer was washed with brine, dried over Na_2SO_4, and chromatographed on silica gel (2:3 EtOAc/PE) to give diol **53** as a colorless oil (460 mg, 1.41 mmol, 85% yield): $[\alpha]_D^{20}$ −4.6 (c 1.4, $CHCl_3$). FTIR (film) 3458 (br), 2988, 2115, 1736, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (dd, J=15.6, 4.5 Hz, 1H), 6.48 (dd, J=15.6, 1.4 Hz, 1H), 4.71 (td, J=6.4, 1.4 Hz, 1H), 4.63 (br s, 1H), 3.92–3.85 (m, 2H), 3.38 (br d, J=4.8 Hz, 1H), 3.13 (br d, J=3.8 Hz, 1H), 2.94 (t, J=6.2 Hz, 2H), 2.64 (t, J=6.5 Hz, 2H), 2.58 (d, J=2.5 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H); ESIMS m/z 349.1 ([M+Na]$^+$); ESIHRMS calcd for $C_{16}H_{22}O_7Na$ ([M+Na]$^+$) 349.1258; found 349.1271.

4.1.36. Conversion of 53 into 54. A solution of **53** (384 mg, 1.18 mmol), DMAP (287 mg, 2.35 mmol), and TPSCl (400 mg, 1.32 mmol) in dry CH_2Cl_2 (14 mL) was stirred at 40 °C overnight. When TLC showed completion of the reaction, the heating bath was removed. Another portion of DMAP (200 mg, 1.63 mmol) and Ac_2O (150 mg, 1.47 mmol) were introduced. The mixture was stirred at ambient temperature until TLC showed completion of the reaction. Usual workup and chromatography (1:4 EtOAc/PE) afforded **54** as a colorless oil (476 mg, 0.75 mmol, 64% from **53**): $[\alpha]_D^{20}$ −6.7 (c 1.40, $CHCl_3$). FTIR (film) 3275, 2961, 2127, 1743, 1217, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (s, 2H), 6.71 (dd, J=15.8, 5.6 Hz, 1H), 6.38 (dd, J=15.8, 1.1 Hz, 1H), 5.46–5.39 (m, 2H), 4.62 (td, J=6.0, 1.0 Hz, 1H), 4.09 (heptet, J=6.7 Hz, 2H), 4.00 (t, J=7.5 Hz, 1H), 3.69 (s, 3H), 2.94–2.88 (m, 3H), 2.63 (t, J=6.4 Hz, 2H), 2.40 (d, J=2.3 Hz, 1H), 2.07 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.29–1.24 (m, 18H); EIMS m/z (%) 619 (M$^+$−15, 5.5), 311 (2.9), 283 (21.6), 267 (47.4), 154 (68.2), 43 (100). Anal. Calcd for $C_{33}H_{46}O_{10}S$: C, 62.44; H, 7.30. Found C, 62.34; H, 7.48.

4.1.37. Conversion of 57 into 54. The above mentioned **54** could also be prepared from **57** (derived from **36**, vide infra) following the same procedure employed for conversion of **31a** into **38** except that **31a** was replaced by **57**. The yield over the two steps from **57** (deprotection of the thioacetal in **57** and the following Wittig reaction with **9**) was 82%.

4.1.38. Conversion of 54 into bromoallene 55. A solution of tosylate **54** (2.600 g, 4.10 mmol) in dry THF (15 mL, another 10 mL to assist the transfer) was added via a syringe to a dry flask containing $CuBr\cdot SMe_2$ (629 mg, 3.06 mmol, recrystallized) and LiBr (250 mg, 2.87 mmol, dried) stirred at ambient temperature under argon. The mixture was heated to reflux under argon for 3 h. After being cooled to ambient temperature, the reaction mixture was diluted with EtOAc (400 mL), washed with satd aq NH_4Cl (50 mL×2), and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:3 EtOAc/PE) gave bromoallene **55** as a colorless oil (1.520 g, 3.53 mmol, 86% yield): $[\alpha]_D^{20}$ −63.6 (c 0.75, $CHCl_3$). FTIR (film) 2989, 1964, 1743, 1682, 1228, 856 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, J=15.9, 5.7 Hz, 1H), 6.45 (dd, J=15.8, 1.5 Hz, 1H), 6.18 (dd, J=5.2, 1.6 Hz, 1H), 5.54 (td, J=5.4, 2.1 Hz, 1H), 5.48 (t, J=5.6 Hz, 1H), 4.54 (td, J=5.6, 1.3 Hz, 1H), 3.99 (dd, J=8.0, 5.5 Hz, 1H), 3.97 (s, 3H), 2.93 (t, J=6.8 Hz, 2H), 2.67 (t, J=6.4 Hz, 2H), 2.13 (s, 3H), 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 197.4, 173.1, 169.4, 141.7, 130.12, 110.9, 96.4, 80.8, 77.3, 75.4, 69.3, 51.8, 35.5, 27.6, 26.9, 26.8, 26.73; ESIMS m/z 448.1 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{18}H_{23}O_7BrNa$ ([M+Na]$^+$) 453.0519; found 453.0509. Anal. Calcd for $C_{18}H_{23}O_7Br$: C, 50.13; H, 5.38. Found C, 50.49; H 5.45.

4.1.39. Conversion of 36 into 57. A solution of **36** (118 mg, 0.37 mmol), DMAP (66 mg, 0.54 mmol), and TPSCl (134 mg, 0.44 mmol) in dry CH_2Cl_2 (6 mL) was stirred at 40 °C for 6.5 h. Usual aqueous workup and chromatography (1:8 EtOAc/PE) gave **56** as a colorless oil (185 mg, 0.3 1 mmol, 85% from **36**), from which the following data were obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 2H), 5.41 (t, J=2.4 Hz, 1H), 4.40 (dd, J=5.9, 3.7 Hz, 1H), 4.20–4.08 (m, 3H), 4.08 (dd, J=5.1, 1.8 Hz, 1H), 4.00 (d, J=3.8 Hz, 1H), 2.91 (heptet, J=6.6 Hz, 1H), 2.80–2.64 (m, 4H), 2.55 (d, J=5.4 Hz, 1H), 2.48 (d, J=2.1 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.33–1.25 (m, 24H).

The above prepared alcohol **56** (68 mg, 0.12 mmol) was dissolved in dry CH_2Cl_2 (3 mL), to which DMAP (33 mg, 0.27 mmol) and Ac_2O (30 mg, 0.29 mmol) were introduced in turn. The mixture was stirred at ambient temperature until TLC showed completion of the reaction. Usual aqueous

workup and chromatography (1:10 EtOAc/PE) gave **57** as a colorless oil (60 mg, 0.095 mmol, 79% from **56**).

The above two-step transformation could be better fulfilled in a one-pot way. A solution of **36** (1.700 g, 5.31 mmol), DMAP (1.400 g, 11.47 mmol), and TPSCl (2.700 g, 8.94 mmol, added in portions) in dry CH_2Cl_2 (50 mL) was stirred at 50 °C (bath temperature) for 2.5 h. After the mixture was cooled to ambient temperature, DMAP (0.400 g, 3.27 mmol) and Ac_2O (762 mg, 7.47 mmol) were added. The mixture was stirred at ambient temperature for 4 h. Usual aqueous workup and chromatography (1:10 EtOAc/PE) delivered **57** as a colorless oil (3.131 g, 4.98 mmol, 94% over the two steps from **36** via **56**): $[\alpha]_D^{20}$ +22.7 (*c* 1.22, $CHCl_3$). FTIR (film) 3275, 2963, 2127, 1755, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (s, 2H), 5.48 (t, *J*=3.3 Hz, 1H), 5.39 (dd, *J*=6.3, 2.8 Hz, 1H), 4.44–4.37 (m, 2H), 4.10 (heptet, *J*=6.7 Hz, 2H), 3.83 (d, *J*=2.8 Hz, 1H), 2.91 (heptet, *J*=6.5 Hz, 1H), 2.80–2.60 (m, 4H), 2.45 (d, *J*=2.3 Hz, 1H), 2.08 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.29–1.23 (m, 24H); EIMS *m/z* (%) 509 (31.4), 435 (12.45), 267 (21.6), 135 (41.1), 43 (100). Anal. Calcd for $C_{31}H_{48}O_7S_3$: C, 59.20; H, 7.69. Found C, 59.54; H, 7.44.

4.1.40. CBS reduction of 55 (59). A solution of ketone **55** (864 mg, 0.20 mmol) in dry THF (10 mL) was added via a syringe (driven by a syringe pump) over 10 min to a solution of (*R*)-2-methyl-CBS-oxazaborolidine (2.3 mL, 1.0 M in toluene, 2.3 mmol) and $BH_3 \cdot SMe_2$ (1.1 mL, 2.0 M in THF) in dry THF (5 mL) stirred in an ice-water bath under argon. After completion of the addition, the stirring was continued at the same temperature for 1 min. MeOH was added to quench the reaction. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (2:3 EtOAc/PE) to give the alcohol **59** as a colorless oil (721 mg, 1.70 mmol, 83% yield). The de value of this reduction was ca. 86% by HPLC analysis.

Data for **59**: $[\alpha]_D^{20}$ −50.1 (*c* 1.05, $CHCl_3$). FTIR (film) 3482 (br), 1964, 1739, 1229, 876 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (td, *J*=5.4, 1.1 Hz, 1H), 5.89 (dd, *J*=15.5, 5.9 Hz, 1H), 5.75 (ddd, *J*=15.4, 6.9, 1.2 Hz, 1H), 5.55–5.39 (m, 2H), 4.37 (t, *J*=7.7 Hz, 1H), 4.24 (br s, 1H), 3.92 (dd, *J*=8.1, 4.7 Hz, 1H), 3.70 (s, 3H), 2.48 (td, *J*=7.3, 1.9 Hz, 2H), 2.12 (s, 3H), 2.13–2.05 (m, 1H), 1.99–1.77 (m, 2H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 174.1, 169.5, 137.6, 127.1, 109.8, 96.2, 80.8, 78.1, 74.9, 70.4, 69.1, 51.6, 31.6, 29.8, 26.9, 26.6, 20.7; MALDI-MS *m/z* 455.1 ([M+Na]$^+$); MALDI-HRMS calcd for $C_{18}H_{25}BrO_7Na$ ([M+Na]$^+$) 455.0675; found 455.0686. Anal. Calcd for $C_{18}H_{25}BrO_7$: C, 49.90; H, 5.82. Found C, 50.05; H, 5.91.

4.1.41. Synthesis of 60 from 59. A solution of **59** (721 mg, 1.70 mmol) in 0.2 M methanolic MeONa (15 mL) was stirred at 0 °C for 25 min. Satd aq NH_4Cl was then added to quench the reaction. The reaction mixture was diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was dissolved in toluene (20 mL) and treated with PPTS (30 mg, 0.11 mmol) at 50–60 °C with stirring for 3 h. The mixture was diluted with EtOAc, washed in turn with satd aq $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (2:3 EtOAc/PE) gave **60** as a colorless oil (458 mg, 1.28 mmol, 75% from **59**): $[\alpha]_D^{20}$ +16.8 (*c* 1.20, $CHCl_3$). FTIR (film) 3446 (br), 2987, 1960, 1771, 1181, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, *J*=5.7, 1.9 Hz, 1H), 5.95 (dd, *J*=15.5, 5.6 Hz, 1H), 5.87 (dd, *J*=15.6, 5.8 Hz, 1H), 5.47 (t, *J*=5.5 Hz, 1H), 5.00 (q, *J*=6.9 Hz, 1H), 4.51–4.42 (m, 2H), 3.81 (dd, *J*=7.9, 4.7 Hz, 1H), 2.80 (br s, 1H), 2.60–2.54 (m, 2H), 2.50–2.38 (m, 1H), 2.07–1.98 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 147.0, 131.1, 130.7, 109.9, 100.1, 82.9, 79.5, 77.0, 75.4, 68.2, 28.4, 28.3, 27.0, 26.9; MALDI-MS *m/z* 381.1 ([M+Na]$^+$); MALDI-HRMS calcd for $C_{15}H_{19}BrO_5$ ([M+Na]$^+$) 381.0299; found 381.0291. Anal. Calcd for $C_{15}H_{19}BrO_5$: C, 50.15; H, 5.33. Found C, 49.77; H, 5.44.

4.1.42. TBS protection of 60 and subsequent coupling leading to 62. 2,6-Lutidine (0.34 mL, 2.92 mmol) and TBSOTf (0.30 mL, 1.31 mmol) were added to a solution of **60** (217 mg, 0.60 mmol) in dry CH_2Cl_2 (8 mL) stirred at −78 °C under argon. The bath temperature was then allowed to rise naturally to 0 °C. When TLC showed completion of the reaction, the mixture was diluted with Et_2O, washed with brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:2 Et_2O/PE) afforded **61** as a colorless oil (228 mg, 0.48 mmol, 80% yield), from which the following data were obtained: ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (dd, *J*=5.6, 1.9 Hz, 1H), 5.90 (t, *J*=4.6 Hz, 2H), 5.34 (dd, *J*=6.3, 5.7 Hz, 1H), 4.53 (dd, *J*=7.8, 5.0 Hz, 1H), 4.49–4.40 (m, 1H), 3.79–3.73 (m, 1H), 2.60–2.52 (m, 2H), 2.48–2.36 (m, 1H), 2.10–2.00 (m, 1H), 1.430 (s, 3H), 1.417 (s, 3H), 0.93 (s, 9H), 0.129 (s, 3H), 0.112 (s, 3H).

The above prepared **61** (228 mg, 0.48 mmol) was then transformed to **62** (192 mg, 0.37 mmol, 77% yield) using the same procedure employed above for converting **41** to **51** (with **41** and TMSC≡CH replaced by **60** and TMSC≡C–C≡CH, respectively).

Data for **62** (an essentially colorless oil, chromatography, eluting with 1:3 Et_2O/PE): $[\alpha]_D^{25}$ +25.86 (*c* 0.47, $CHCl_3$). FTIR (film) 2958, 2200, 2100, 1949, 1783, 1251, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (ddd, *J*=6.4, 2.0, 0.7 Hz, 1H), 5.92 (dd, *J*=3.0, 1.8 Hz, 2H), 5.86 (dd, *J*=1.5, 0.5 Hz, 1H), 5.55 (ddd, *J*=8.0, 6.6, 1.8 Hz, 1H), 5.03–4.94 (m, 1H), 4.55–4.48 (m, 1H), 4.42–4.35 (m, 1H), 3.80–3.74 (m, 1H), 2.60–2.50 (m, 2H), 2.48–2.35 (m, 1H), 2.08–1.95 (m, 1H), 1.44–1.42 (three singlets, 6H), 0.92 (s, 9H), 0.22 (s, 4.5H), 0.20 (s, 4.5H), 0.17 (s, 3H), 0.14 (s, 3H); ESIMS *m/z* 537.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{28}H_{42}O_5Si_2Na$, 537.2463; found, 537.2486.

4.1.43. Synthesis of 64 from 60. The procedure was the same as that employed for converting **41** to **51** (with **41** and TMSC≡CH replaced by **60** and TMSC≡C–C≡CH, respectively). Yield (chromatography using 1:2 EtOAc/PE): 54%.

Data for **64** (an essentially colorless oil, chromatography, eluting with 1:3 Et_2O/PE): $[\alpha]_D^{20}$ −31.0 (*c* 0.40, $CHCl_3$). FTIR (film) 3448 (br), 2986, 2201, 2102, 1948, 1775, 1251, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (d,

J=15.8, 5.0 Hz, 1H, part of AB system), 5.87 (d, J=16.0, 6.2 Hz, 1H, part of AB system), 5.67–5.63 (m, 1H, H-12), 5.59 (td, J=6.7, 1.1 Hz, 1H, H-10), 5.01 (br q, J=7.1 Hz, 1H, H-4), 4.51 (dd, J=8.2, 7.2 Hz, 1H, H-7), 4.46–4.43 (m, 1H, H-9), 3.81 (dd, J=8.0, 4.1 Hz, 1H, H-8), 2.61–2.52 (m, 2H), 2.50–2.38 (m, 1H), 2.34 (d, J=4.1 Hz, 1H, OH-H), 1.46 (s, 3H), 1.45 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 215.8 (C-11), 180.0 (C-1), 133.0, 132.8, 111.1 (C-18), 96.6 (C-10), 90.7 (C-15), 89.1 (C-16), 84.7 (C-8), 82.1 (C-4), 79.5 (C-12), 78.0 (C-7), 76.4 (C-13), 70.7 (C-14), 70.5 (C-9), 29.7, 29.6, 27.6, 27.5, −0.1 (with the NMR signals assigned on the basis of DEPT and 2D spectra); ESIMS m/z 423.2 ([M+Na]$^+$); ESIHRMS calcd for $C_{22}H_{28}O_5SiNa$ ([M+Na]$^+$) 423.1598; found 423.1586.

4.1.44. Treatment of 64 with *p*-TsCl leading to 66. DMAP (5 mg, 0.04 mmol) and *p*-TsCl (33 mg, 0.173 mmol) were added to a solution of **64** (70 mg, 0.18 mmol) in dry Et_3N (0.1 mL) and CH_2Cl_2 (4 mL) stirred at 0 °C. After completion of the addition, the mixture was stirred at the same temperature for 2 h before the bath was removed. The stirring was continued at ambient temperature until TLC showed disappearance of the starting material. The mixture was diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (1:3 EtOAc/PE) afforded **66** as a colorless oil (51 mg, 0.14 mmol, 75% yield): $[\alpha]_D^{20}$ +78.8 (c 0.90, $CHCl_3$). FTIR (film) 2930, 2182, 2169, 2073, 1778, 1372 cm^{-1}; UV (EtOH) λ_{max}=341, 318, 298, 281, 252, 239, 220, 213, 198 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, J=15.8, 5.7 Hz, 1H), 5.95–5.76 (m, 3H), 4.99 (q, J=5.9 Hz, 1H, H-4), 4.18–4.09 (m, 2H, H-7, 8), 2.60–2.53 (m, 2H), 2.49–2.40 (m, 1H), 2.07–1.97 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 143.4, 132.2, 128.5, 111.1, 110.2, 89.4, 87.9, 80.8, 80.7, 78.9, 75.8, 74.4, 67.1, 61.2, 28.4, 28.1, 26.9, 26.7, 0.6; ESIMS m/z 400.2 ([M+NH$_4$]$^+$); ESIHRMS calcd for $C_{22}H_{26}O_4SiNa$ ([M+Na]$^+$) 405.1493; found 405.1496.

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