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Asymmetric Synthesis of a Taxol C-Ring by Aldol Condensation and Radical Cyclization

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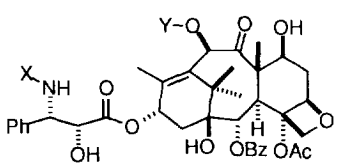
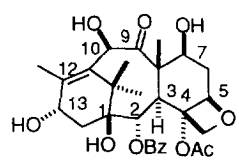
Abstract. In the context of a convergent approach to taxol, the asymmetric synthesis of a fully functionalized C-ring is described. Two asymmetric aldol reactions (Evans) are used to create the C5 and C7 stereocenters and the diastereoselective alkylation of a stereochemically and conformationally biased dioxanone to introduce, with the correct relative and absolute stereochemistry, the quaternary center at C8. Vinyl radical cyclization is used to close the C2,3 bond in good yield. This diastereoselective radical cyclization likely proceeds through a chair-like transition state with the maximum number of substituents equatorially disposed.

Since its isolation[1] taxol (**1**), with its complex, densely functionalized structure, potent antitumor activity achieved through a novel mechanism,[2,3] and severely limited natural abundance, has inspired legions of organic chemists to undertake the investigation of its semisynthesis from more available terpenoids, to correlate its activity with its structure, to probe its biosynthesis, and rise to the challenge of its synthesis. Indeed, very significant progress has been made in each of these domains. Thus, commercial production of taxol itself, and of its competitor taxotère (**2**),[4] is achieved by partial synthesis from the widespread 10-deacetylbaccatin III (**3**) and a multitude of syntheses of the side chain have been devised toward this end.[2,3] Much is now known about the relative importance of the various functional groups present in **1**, with those along the upper rim contibuting little, those along the lower edge being much more important, and the side chain absolutely crucial for tubulin binding and antitumor activity.[2,3,5] Significant advances have been made in elucidating the biosynthetic pathways for both the side chain[6] and the core skeleton,[7] and the possibility of production by microbial fermentation raised.[8] Enormous advances in the synthetic chemistry of taxol have been made.[9-14] Total syntheses have been achieved by the Holton,[15,16] Nicolaou,[17-20] Danishefsy,[21] and Wender[22] groups by widely differing routes. In this and the following paper we report our efforts toward a convergent synthesis of taxol.



1: X = PhCO; Y = Ac
2: X = t-BuOCO; Y = H



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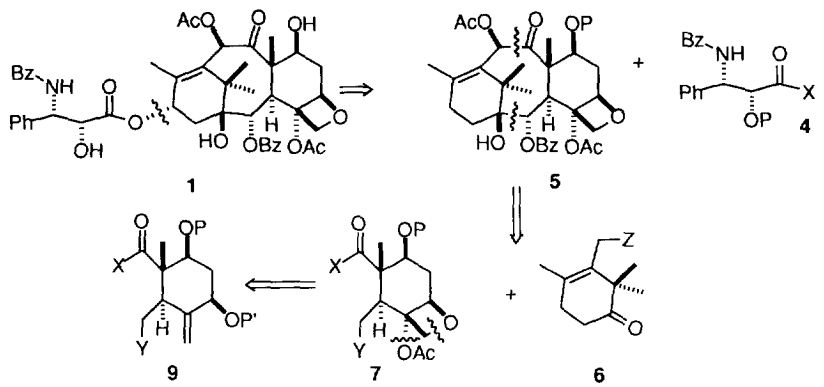
In contemplating a synthesis of taxol, and benefiting from the many approaches described in the literature, we sought to achieve maximum convergence as delineated by the disconnections in Scheme 1. The main advantage of such a scheme, aside from its convergent nature, being the minimization of adjustment of the peripheral functional groups at the level of the complete skeleton. This problem was only overcome in the linear Holton synthesis on the basis of a detailed knowledge and astute manipulation of the conformational

equilibria of the skeleton.[15,16] Thus, it was envisaged that a highly functionalized, optically pure C-ring (**9**) would, by means of chemistry developed by Clark[23] and employed by Danishefsky,[24] Paquette[25] and others,[26] be the precursor to the CD system **7** which in turn would be coupled with the achiral A ring **6** to give a 13-deoxybaccatin III derivative **5**. Following the precedent established by Kende,[27] and later Nicolaou in his total synthesis,[17-20] allylic oxidation of **5** with chromic anhydride would provide its 13-keto derivative whose highly selective reduction to a 13α-alcohol was predictable from the work of Potier.[28] A perceived advantage of this strategy, with the late introduction of the functionality at C13, is that it removes the need for protection and deprotection of one hydroxy group and, in a major simplification, renders the A-ring achiral. Here, we describe our successful asymmetric synthesis of the C-ring and, in the following paper,[29] the development of a strategy for the synthesis of the A-ring and fusion of the B and C-rings.

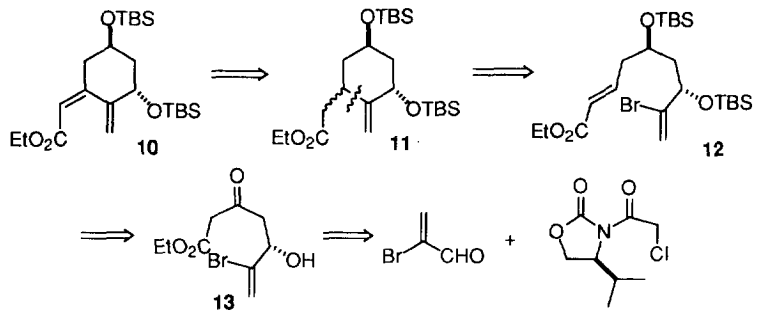


P and P' are generic protecting groups

Scheme 1

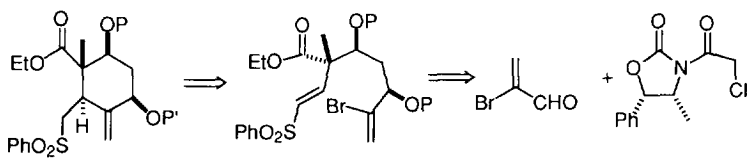
Widely differing approaches to the stereocontrolled synthesis of the taxol C-ring have been adopted by several groups. Nicolaou and coworkers, in their total synthesis, assembled the C-ring with full control of diastereoselectivity through clever use of the Diels Alder cycloaddition reaction.[17-20,30] However, the racemic nature of the product forced them to carry out a wasteful resolution at the level of the full ABC system. Subsequent work, in collaboration with Johnson, used an enzymic resolution of the C-ring itself and so potentially improves the sequence.[31] The Danishefsky, Watt, and Potier groups elected to synthesize the C ring, in enantiomerically pure form, from either the Wieland-Miescher ketone[21,32-34] or its lower homolog, the Hajos-Parrish ketone,[24,35] both of which are readily available in either antipodal modification. Jenkins and coworkers prepared a 7-deoxy C-ring system from D-glucose,[36] and syntheses of highly functionalized C-rings have been reported by several other groups.[26,37] Mukaiyama has described the fusion of a C-ring to a highly functionalized preformed B ring, and such a strategy, with the C-ring being appended to the AB skeleton,[38] was employed by Holton in his total synthesis, although with a different sequence of bond formations.[15,16]

Our interest in this convergent strategy was heightened when we recognized in **9** the gross structural features of the calcitriol A-ring (**10**) which we had previously synthesized by a radical cyclization of **12** to **11**, followed by dehydrogenation. In this synthesis the vinyl bromide **12** was accessed in a very few steps from the aldol **13** which itself was obtained by the Evans type asymmetric aldol condensation of α-bromoacrolein followed by a short homologation sequence (Scheme 2).[39,40]



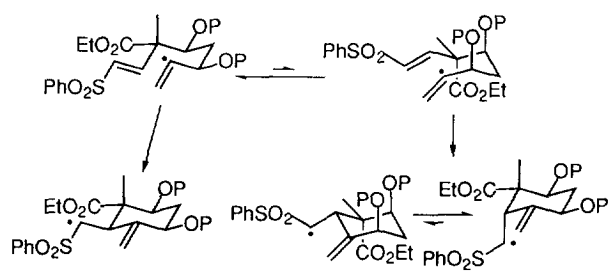
Scheme 2

Thus, it was anticipated that **9** would be available by radical cyclization of **14** (Scheme 3) and that this in turn could be accessed by a modification of the route used (Scheme 2) for the synthesis of **12**. The obvious differences between the two schemes are the need to form a *syn*- rather than *anti*-1,3-diol and the need to incorporate an additional quaternary center with control of stereochemistry in the latter.



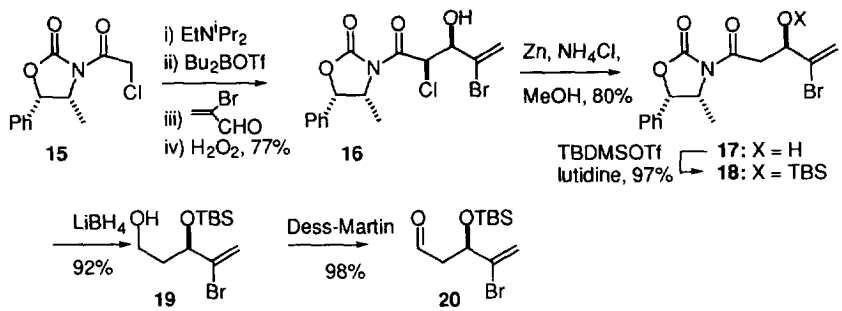
Scheme 3

Additionally, we reasoned that, although the cyclization of **12** to **11** gave an almost equimolar mixture of diastereomers, the rearrangement of **14** to **9** would occur very preferentially through one of two chair-like transition states and so be highly selective for the correct stereochemistry at C3[41] in **9** (Scheme 4). According to a study by Hanessian,[42] the diastereoselectivity in the 6-*exo*-trig cyclization of alkyl radicals onto activated alkenes is significantly better for *cis*- rather than *trans*-alkenes, which leads to the suggestion that selectivity would be further enhanced with a *cis*-vinyl sulfone as the radical trap. However, preliminary experiments demonstrated that *cis*-vinyl sulfones were converted to their *trans*-isomers in the presence of tributyltin hydride and AIBN more rapidly than bromine was abstracted from a vinyl bromide,[43] and we therefore chose to employ the *trans*-series as indicated in Scheme 4.



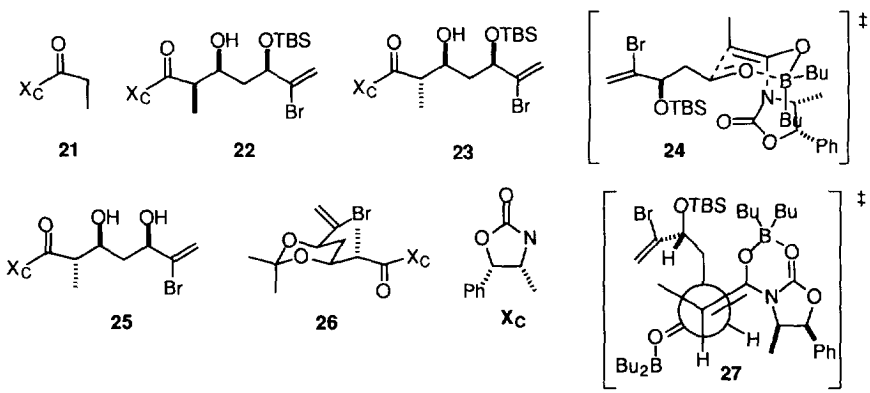
Scheme 4

Our synthesis began with the chloroacetyl oxazolidinone **15**,[44] whose *Z*-dibutyl enolborinate was condensed in the usual manner with α-bromoacrolein to give the *syn*-aldol **16** isolated, after chromatography on silica gel, as a single diastereomer in 77% yield. Treatment with zinc dust in methanol then removed the extraneous chlorine to give **17** in 80% yield, whose silylation with TBDMS triflate and lutidine provided **18** in 97% isolated yield. Reductive cleavage of the chiral auxiliary provided alcohol **19** in 92% yield and this was reoxidized with the Dess-Martin reagent to give 98% of the aldehyde **20** (Scheme 5).

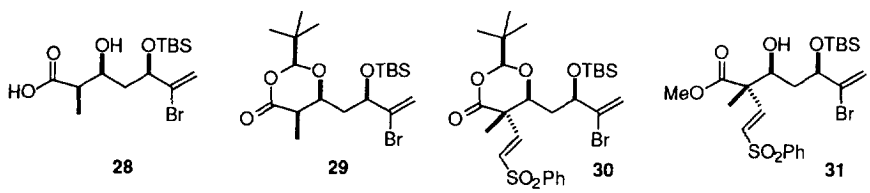


Scheme 5

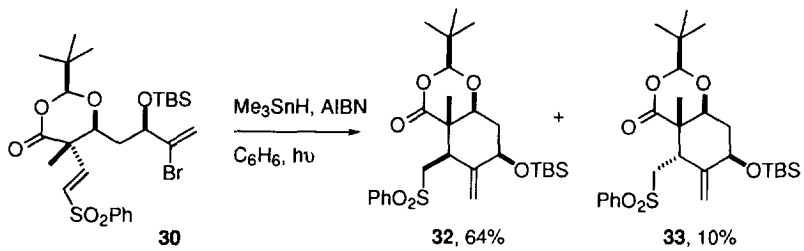
Condensation of aldehyde **20** with the enol borinate derved from propionyl oxazolidinone **21**[45] gave two aldols, **22** and **23**, in 75 and 12% yields, respectively. The stereochemistry of the major isomer was assigned on the grounds that it resulted from the standard Zimmerman-Traxler chair-like transition state **24**, as was confirmed subsequently following the radical cyclization step. Desilyation of the minor isomer gave diol **25** which was converted to the acetonide **26** in the usual manner. ^{1}H and ^{13}C-NMR spectral analysis of **26**, according to the Rychnovsky model,[46] revealed it to be in a chair conformation and, consequently, **25** to be a *syn*-diol. As both **22** and **23** are *syn*-diols, they result from the reaction of opposite faces of the enol borinate with the same face of the aldehyde and are correspondingly *syn* and *anti*-aldols, respectively. Assuming the *Z*-enolate of **21** is formed with the usual high selectivity, it is impossible to account for the formation of the minor, *anti*-aldol **23** in terms of any cyclic transition state[47] and, therefore, we suggest that it arises by a competing open transition state **27** much as suggested by Heathcock to rationalize similar observations.[48,49] We note that as both **22** and **23** differ only in configuration at C2 they could both, in principle, be carried forward in the synthesis. However, to date, we have not attempted to do so with **23**.



In order to prepare the quaternary center we turned to a system we had earlier expressly developed for the purpose[50] which, in turn, was based on chemistry advanced by the Seebach group.[51] Thus, reaction of **22** with lithium hydroxide and hydrogen peroxide in THF gave, after column chromatography, the corresponding acid **28** in 71% yield. This acid was treated at -78 °C in dichloromethane with pivalaldehyde, 2-trimethylsiloxypropane,[52] and a catalytic quantity of TMS triflate enabling isolation of the dioxanone **29** in 90% yield. This substance was a single diastereomer which exhibited a ^3J coupling of 4.1 Hz between the two ring protons consistent with the assigned stereochemistry and the all *syn* nature of **22**. Deprotonation of **29** with LiHMDS in THF at -78 °C followed by addition of *E*-2-bromovinyl phenyl sulfone and stirring for 9 h at that temperature led to the isolation of the adduct **30** in 47% yield. Unfortunately, we have not been able to optimize this step any further at the present time. Nevertheless, **30** was isolated as a single diastereomer within the limits of NMR detection and assigned the indicated stereochemistry in accordance with our model studies[50] and the predicted quenching of the enolate on the face opposite the side chain at the adjacent stereocenter. This assignment was confirmed, following cyclization, by n.O.e studies. All attempts at opening of the dioxane ring under acidic or basic conditions conducted with a view to obtaining ester **31** and related species resulted in the formation of complex reaction mixtures. This problem, as determined for the model series, is at least in part due to the tendency of **31** to undergo retroaldol fragmentation with the formation of a highly stabilized, extended enol(ate).[50]



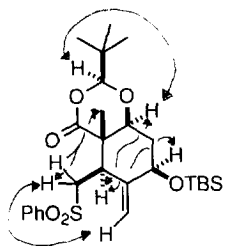
We were therefore constrained to conduct the radical cyclization reaction on the dioxanone **30**. This was achieved by photolysis with trimethyltin hydride[53] and AIBN in benzene at room temperature for 2 h. Purification by preparative TLC enabled the isolation of two products **32** and **33** in 64 and 10% yields respectively (Scheme 6).



Scheme 6

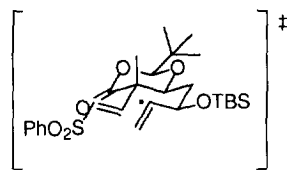
The stereochemistry of the major product was assigned with the aid of a NOESY study: Figure 1 shows the diagnostic enhancements for **32**. The ^{1}H-NMR spectrum of **32** is fully consistent with this structure and conformation, the only unusual feature being the abnormally downfield chemical shift (δ 5.04) for the 2-pro-*R* hydrogen. The minor isomer is correspondingly assigned the 3-epi stereochemistry **33**: its ^{1}H-NMR spectrum, most notably the coupling patterns within the H5,H6,H6',H7 spin system, closely

resembles that of **32**, and is suggestive of a strong structural and conformational homogeneity. The major differences between the two spectra are the resonances for H2 and H2' which in **33** have more typical chemical shifts for a sulfone substituted methylene group. This is consistent with their being in an axial position and no longer compressed between the exocyclic methylene and carbonyl groups as in **32**. The preferential formation of **32** is readily explained by cyclization through the chair-like transition state **34** (Fig 2). The somewhat unusual use of trimethyltin hydride, in place of the more typical tributyl or triphenyltin hydrides, was a result of the sensitivity of **32** to many of the purification protocols prescribed for the removal of organotin residues from reaction mixtures.[54] With this reagent, the volatile organotin byproducts are conveniently removed by exposure to high vacuum before purification on silica gel. The use of tris(trimethylsilyl)silane,[55] or indeed that of a catalytic quantity of stannane in conjunction with a reducing agent,[56-58] was avoided as was it felt that this might lead to the formation of formal endo-mode products through the homoallyl/cyclopropylmethyl rearrangement.



32

Fig 1. Diagnostic n.O.e.'s for **32**



34

Fig 2. Transition State for formation of **32**

In summary, we have prepared a highly functionalized taxol C-ring in enantiomerically pure fashion by straightforward use of stereocontrolled aldol reactions and a stereoselective radical cyclization.

Experimental Section

General. Melting points were recorded on a Thomas hotstage microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were run in $CDCl_3$ at 300 and 75 MHz, respectively. Chemical shifts are downfield from tetramethylsilane as internal standard. All solvents were dried and distilled by standard procedures. All reactions were run under a dry nitrogen or argon atmosphere. THF was distilled, under N_2, immediately prior to use from sodium benzophenone ketyl. Ether refers to diethyl ether. Specific rotations were recorded in $CHCl_3$ solution. Microanalyses were conducted by Midwest Microanalytical, Indianapolis, IN.

(+)-4(*R*)-Methyl-5(*S*)-phenyl-3-[4-bromo-2(*R*)-chloro-3(*R*)-hydroxy-4-pentenoyl]-2-oxazolidinone (16). A solution of dibutylboron triflate in dichloromethane (55 mL of 1M, 0.055 mol) was added dropwise to a solution of **15**[44] (12.68 g, 0.05 mol) in dichloromethane (130 mL) cooled to -75 °C, followed by addition of diisopropylethylamine (10.89 mL, 0.063 mol). The reaction mixture was allowed to warm to 0 °C over 0.5 h and then stirred at room temperature for 1.5 h before recooling to -75 °C, stirring for 0.5 h and addition of 2-bromoacrolein (20.24 g, 0.15 mol) at that temperature. The reaction mixture was stirred for 6 h at -75 °C and then allowed to come to room temperature overnight. Buffer solution (pH 7, 130 mL) was added at 0-5 °C, followed by MeOH (130 mL) and hydrogen peroxide (30%, 250 mL) and stirring continued for 1 h. The organic phase was then separated and the aqueous layer extracted with dichloromethane (2 x 150 mL). The combined organic phases were washed with brine (100 mL), dried

(Na_2SO_4), and the solvents removed under vacuum. The resulting oil was purified by silica gel chromatography (eluent: ether/pentane 1/2) to give **16** as an oil (15.02 g, 77%). $[\alpha]_D$ = +29° (c = 2.35); ^{1}H-NMR, δ: 0.92 (d, *J* = 6.6 Hz, 3 H), 3.68 (br.s, 1 H), 4.76-4.85 (m, 2 H), 5.75 (d, *J* = 7.3 Hz, 1 H), 5.76-5.79 (m, 1 H), 6.07 (d, *J* = 4.1 Hz, 1 H), 6.15-6.18 (m, 1 H), 7.27-7.32 (m, 2 H), 7.36-7.44 (m, 3 H); ^{13}C-NMR, δ: 13.8, 55.2, 57.0, 74.5, 79.4, 120.8, 125.6, 128.6, 128.8, 129.0, 132.5, 151.9, 167.4; IR, υ (cm^{-1}): 3542, 1787, 1710, 1369, 1353. Anal. Calcd. for $C_{15}H_{15}BrClNO_4$: C, 46.36, H, 3.89; N, 3.60. Found: C, 46.43; H, 3.94; N, 3.70.

(+)-4(*R*)-Methyl-5(*S*)-phenyl-3-[4-bromo-3(*R*)-hydroxy-4-pentenoyl]-2-oxazolidinone (17). Aldol **16** was dissolved in MeOH (400 mL) and treated with zinc powder (10.11 g, 0.155 mol) and ammonium chloride (8.27 g, 0.155 mol), and the resulting suspension vigorously stirred for 6 h at room temperature. Filtration, concentration, and chromatography on a short pad of silica gel (eluent: pentane/ether 3/1) provided colorless, crystalline **17** (11.00 g, 80%). M.p. 83-85° C (ether/pentane), $[\alpha]_D$ = +51° (c = 1.57); ^{1}H-NMR, δ: 0.91 (d, *J* = 6 Hz, 3 H), 3.33 (dd, *J* = 3.5 and 17.1 Hz, 1 H), 3.40 (d, *J* = 5.5 Hz, 1 H), 3.43 (dd, *J* = 8.8 and 17.1 Hz, 1 H), 4.65-4.73 (m, 1 H), 4.78 (quintet, *J* = 6.9 Hz, 1 H), 5.62 (d, *J* = 1.9 Hz, 1 H), 5.70 (d, *J* = 7.3 Hz, 1 H), 6.04 (dd, *J* = 1.0 and 1.9 Hz, 1 H), 7.27-7.33 (m, 2 H), 7.34-7.45 (m, 3 H); ^{13}C-NMR, δ: 14.5, 41.3, 54.8, 72.1, 79.3, 117.7, 125.6, 128.7, 128.9, 132.9, 134.0, 153.0, 171.1; IR, υ (cm^{-1}): 3586, 1786, 1701, 1371, 1349. Anal. Calcd. for $C_{15}H_{16}BrNO_4$: C, 50.87; H, 4.55; N, 3.95. Found: C, 50.89; H, 4.71; N, 3.84.

(+)-4(*R*)-Methyl-5(*S*)-phenyl-3-[4-bromo-3(*R*)-(^{t}butyldimethylsiloxy)-4-pentenoyl]-2-oxazolidinone (18). To a solution of **17** (1.00 g, 2.82 mmol) and 2,6-lutidine (0.043 mL, 3.7 mmol) in dichloromethane (10 mL), TBDMSOTf (0.78 mL, 3.4 mmol) was added at 0 - 5 °C. The reaction mixture was stirred at room temperature. for 4 h (monitored by TLC) before ethyl acetate (70 mL) was added, and the solution washed with saturated aqueous NH_4Cl (2 x 20 mL), brine (15 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The crystalline product (**18**) (1.28 g, 97%) was obtained after column chromotography on silica gel (eluent: hexane/ethyl acetate 3/1). M.p. 152-153 °C; $[\alpha]_D$ = +19.4° (c = 3.3); ^{1}H-NMR, δ: 0.096 (s, 6 H), 0.88 (s, 9 H), 0.90 (d, *J* = 7.8 Hz, 3 H), 3.24 (dd, *J* = 16.7 and 4.0 Hz, 1 H), 3.44 (dd, *J* = 16.7 and 8.0 Hz, 1 H), 4.76 (m, 1 H), 4.80 (dd, *J* = 3.4 and 8.2 Hz, 1 H), 5.57 (d, *J* = 1.7 Hz, 1 H), 5.63 (d, *J* = 7.4 Hz, 1 H), 5.99 (dd, *J* = 0.9 and 1.7 Hz, 1 H), 7.30-7.43 (m, 5 H); ^{13}C-NMR, δ: -5.2, -4.7, 14.7, 18.1, 25.9, 43.0, 54.7, 72.7, 79.0, 117.3, 125.8, 128.7, 128.8, 152.9, 169.7; IR, υ (cm^{-1}): 1782, 1706. Anal. Calcd. for $C_{21}H_{30}BrNO_4Si$: C, 53.84; H, 6.46. Found: C, 53.92; H, 6.57.

(+)-2-Bromo-3(*R*)-(^{t}butyldimethylsiloxy)-1-penten-5-ol (19). A solution of lithium borohydride (9.5 mL of a 2M solution in THF, 19 mmol) was added dropwise to a solution of **18** (1.78 g, 3.8 mmol) and dry MeOH (0.61 mL, 15 mmol) in THF (20 mL) cooled to -78 °C. The reaction mixture was warmed up to 0 °C and stirred for 3 h, before it was carefully poured into a mixture of ether (80 mL) and water (30 mL). The organic layer was separated and the aqueous layer extracted with ether (2 x 20 mL). The combined organic phase were washed with brime (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromotography (silica gel, eluent: hexane/ether 1/1) gave **19** as a colorless oil (1.03 g, 92%). $[\alpha]_D$ = +28.4° (c = 2.8); ^{1}H-NMR, δ: 0.09 (s, 3 H), 0.12 (s, 3 H), 0.92 (s, 9 H), 1.95 (q, *J* = 5.3 Hz, 2 H), 2.07 (br, 1 H), 3.71 (ddd, *J* = 5.3, 10.7, and 10.8 Hz, 1 H), 3.80 (ddd, *J* = 4.8, 10.7, and 10.9 Hz, 1 H), 4.42 (t, *J* = 5.3 Hz, 1 H), 5.59 (dd, *J* = 0.6 and 1.7 Hz, 1 H), 5.95 (dd, *J* = 1.2 and 1.7 Hz, 1 H); ^{13}C-NMR, δ: -5.3, -4.8, 18.1, 25.7, 37.4, 59.4, 75.3, 118.6, 135.8; IR, υ (cm^{-1}): 3349. Anal. Calcd. for $C_{11}H_{23}BrO_2Si$: C, 44.74; H, 7.85. Found: C, 44.79; H, 7.67.

4-Bromo-3(*R*)-(4-^{t}butyldimethylsiloxy)-4-pentenal (20). To a solution of compound (**19**) (1.0 g, 3.4 mmol) in dichloromethane (4 mL) was added freshly prepared Dess Martine periodinane[59,60] (1.58 g, 3.7 mmol) in dichloromethane (6 mL) at 0 °C over 2 min. The reaction mixture was then allowed to come to room temperature and was stirred for 2.5 h. Ether (80 mL) and 1.4 N sodium hydroxide solution (15 mL) were added to the suspension, the aqueous layer separated and the organic layer washed with sodium hydroxide solution (10 mL, 1.4 N), brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was twice taken up in toluene (2 mL) and reconcentrated to give aldehyde **20** (0.98 g, 99%) which was not purified further but used immediately in the next step. ^{1}H-NMR, δ: 0.08 (s, 6 H), 0.90 (s, 9 H), 2.62 (ddd, *J* = 1.9, 4.2, and 16.3 Hz, 1 H), 2.74 (ddd, *J* = 2.3, 7.1, and 16.3 Hz, 1 H), 4.61 (dd, *J* = 4.2, 7.0 Hz, 1 H), 5.52 (d, *J* = 1.7 Hz, 1 H), 5.92 (dd, *J* = 1.1 and 1.8 Hz, 1 H), 9.70 (t, *J* = 2.1 Hz, 1 H); ^{13}C-NMR, δ: -5.3, -4.8, 18.0, 25.6, 49.5, 72.1, 117.1, 135.2, 200.1; IR, υ (cm^{-1}): 1729.

(+)-4(*R*)-Methyl-5(*S*)-phenyl-3-[6-bromo-3(*S*)-hydroxy-5(*R*)-(^{t}butyldimethylsiloxy)-2(*R*)-methyl-6-heptenoyl]-2-oxazolidinone (22) and (+)-4(*R*)-Methyl-5(*S*)-phenyl-3-[6-bromo-3(*S*)-hydroxy-5(*R*)-(^{t}butyldimethylsiloxy)-2(*S*)-methyl-6-heptenoyl]-2-oxazolidinone (23). Diisopropylethylamine (0.81 mL, 4.66 mmol) was added to a solution of **21**[45] (0.99 g, 4.2 mmol) in dry toluene (6 mL) at -78 °C, followed by slow addition of a solution of dibutylboron triflate (4.1 mL of 1 M solution in dichloromethane, 4.1 mmol). The ensuing reaction mixture was stirred at -78 °C for 0.5 h and then allowed to come to 0 °C for 2.5 h, after which it was chilled to -78 °C and stirred 50 min before addition of aldehyde **20** (0.98 g, 3.4 mmol) in toluene (1.5 mL) via a cannula over 5 min. The resulting mixture was stirred for 30 min at -18 °C and then warmed to -42 °C and held there for 2.5 h before warming to 0 °C and addition of pH 7 phosphate buffer (4 mL) followed by MeOH (10 mL) and THF (6 mL). After 5 min, 30% aqueous hydrogen peroxide (30 mL) was added dropwise over 5 min and the reaction mixture stirred at 0 °C for 50 min before evaporation of the volatiles at room temperature. Ethyl acetate (60 mL) and water (20 mL) were added to the residue and the organic layer separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers washed with brine (20 mL), dried (Na_2SO_4), concentrated, and chromatographed (silica gel, eluent: ethyl acetate/hexane= 1/4) to provide 1.34 g (75%) of **22** and 0.21 g (12%) of its isomer (**23**). **22:** M.p. 123-124 °C; $[\alpha]_D$ = +16.1° (c = 2.1); ^{1}H-NMR, δ: 0.10 (s, 3 H), 0.12 (s, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.92 (s, 9 H), 1.27 (d, *J* = 7.1 Hz, 3 H), 1.80 - 1.95 (m, 2 H), 3.22 (br, 1 H), 3.78 (dq, *J* = 3.7 and 14.0 Hz, 1 H), 4.03 (dt, *J* = 3.5 and 8.9 Hz, 1 H), 4.39 (t, *J* = 6.5 Hz, 1 H), 4.79 (dq, *J* = 6.6 and 0.9 Hz, 1 H), 5.57 (d, *J* = 1.6 Hz, 1 H), 5.69 (d, *J* = 7.2 Hz, 1 H), 5.91 (d, *J* = 1.1 Hz, 1 H), 7.30-7.46 (m, 5 H); ^{13}C-NMR, δ: -5.06, -4.61, 11.0, 14.3, 18.1, 25.7, 39.9, 42.6, 54.8, 69.3, 75.4, 78.9, 117.6, 125.6, 129.7, 133.1, 137.2, 152.6, 176.6; IR, υ (cm^{-1}): 3530, 1784, 1689. Anal. Calcd. for $C_{24}H_{36}BrNO_5Si$: C, 54.74; H, 6.89. Found: C, 55.08; H, 7.08. **23:** M.p. 85-87 °C; $[\alpha]_D$ +31.5° (c = 3.5); ^{1}H-NMR, δ: 0.09 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 0.92 (d, *J* = 5.5 Hz, 3 H), 1.25 (d, *J* = 6.9 Hz, 3 H), 1.74 (ddd, *J* = 5.8, 10.0, and 14.1 Hz, 1 H), 1.98 (ddd, *J* = 2.7, 7.6, and 14.1 Hz, 1 H), 2.90 (d, *J* = 7.2 Hz, 1 H), 3.76 (ddt, *J* = 2.6, 7.1, and 9.8 Hz, 1 H), 3.94 (dq, *J* = 6.8 and 6.9 Hz, 1 H), 4.41 (dd, *J* = 5.9 and 7.4 Hz, 1 H), 4.78 (dq, *J* = 6.7 and 6.9 Hz, 1 H), 5.57 (d, *J* = 1.7 Hz, 1 H), 5.68 (d, *J* = 7.3 Hz, 1 H), 5.89 (d, *J* = 1.6 Hz, 1 H), 7.29-7.46 (m, 5 H); ^{13}C-NMR, δ:-5.1, -4.67, 14.4, 14.5, 18.1, 25.7, 41.1, 43.2, 55.0, 71.5, 74.8, 78.9, 117.8, 125.6, 128.7, 128.8, 133.0, 137.3, 153.0, 176.2; IR, υ (cm^{-1}): 3514, 1778, 1703. Anal. Calcd. for $C_{24}H_{36}BrNO_5Si$: C, 54.74; H, 6.89. Found: C, 54.63; H, 6.93.

(+)-4(*R*)-Methyl-5(*S*)-phenyl-3-[6-bromo-3(*S*),5(*R*)-dihydroxy-2(*S*)-methyl-6-heptenoyl]-2-oxazolidinone (25). Compound **23** (160.0 mg, 0.30 mmol) was dissolved in trifluoroacetic acid (1.8 mL), and the resulting mixture stirred at room temperature for 40 min before the trifluoroacetic acid was evaporated under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and then washed with sodium bicarbonate solution (2 x 10 mL) and brine (10 mL), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue purified by column chromatography (silica gel, eluent: hexane/ethyl acetate 3/2) to give **25** (82.2 mg. 66%). M.p. 61-62 °C; $[\alpha]_D$ = + 38.9° (c = 1.0); ^{1}H-NMR, δ: 0.93 (d, *J* = 6.6 Hz, 3 H), 1.28 (d, *J* = 6.6 Hz, 3 H), 1.73 (ddd, *J* = 8.6, 10.3, and 14.2 Hz, 1 H), 2.05 (ddd, *J* = 1.9, 4.2, 14.1 Hz, 1 H), 3.46 (d, *J* = 6.6 Hz, 1 H), 3.70 (d, *J* = 3.0 Hz, 1 H), 3.96 - 4.05 (m, 2 H), 4.43 (dt, *J* = 4.1 and 8.4 Hz, 1 H), 4.78 (quintet, *J* = 6.6 Hz, 1 H), 5.58 (d, *J* = 1.8 Hz, 1 H), 5.70 (d, *J* = 7.2 Hz, 1 H), 5.99 (dd, *J* = 0.9 and 1.8 Hz, 1 H), 7.30-7.47 (m, 5 H); ^{13}C-NMR, δ: 14.5(6), 14.6, 39.4, 43.5, 55.1, 73.7, 75.7, 79.0, 117.3, 125.6, 128.8, 128.9, 132.8, 135.7, 152.9, 176.2; IR, υ (cm^{-1}): 3443, 1761, 1667. Anal. Calcd. for $C_{18}H_{22}BrNO_5$: C, 52.44; H, 5.38. Found: C, 52.38; H, 5.42.

(+)-4(*R*)-Methyl-5(*S*)-phenyl-3-[6-bromo-3(*S*),5(*R*)-(isopropylidenedioxy)-2(*S*)-methyl-6-heptenoyl]-2-oxazolidinone (26). Diol **25** (18.0 mg, 0.04 mmol) and pyridinium p-toluenesulfonate (4.5 mg, 0.02 mmol) were dissolved in dry dichloromethane (0.5 mL), followed by dropwise addition of 2-methoxypropene (0.47 mmol, 34.0 mg) at room temperature. The reaction mixture was stirred for 3 h at room temperature, then the solvent was removed under reduced pressure and **26** (8.4 mg, 44%) isolated as an oil by preparative TLC on silica gel (eluent, hexane/ethyl acetate 3/1). $[\alpha]_D$ = +104.5° (c = 0.8); ^{1}H-NMR, δ: 0.86 (d, *J* = 6.6 Hz, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 1.35 (s, 3 H), 1.40 (s, 3 H), 1.41 (q, *J* = 11.5 Hz, 1 H), 1.99 (dt, *J* = 2.5 and 12.7 Hz, 1 H), 4.05 (dq, *J* = 2.0 and 6.8 Hz, 1 H), 4.18 (dt, *J* = 2.4 and 11.5 Hz, 1 H), 4.37 (dd, *J* = 2.4 and 9.2 Hz, 1 H), 4.82 (dq, *J* = 0.9 and 6.6 Hz, 1 H), 5.58 (dd, *J* = 1.2 and 1.7 Hz, 1 H), 5.66 (d, *J* = 7.5 Hz, 1 H), 5.99 (dd, *J* = 1.3 and 1.7 Hz, 1 H), 7.30-7.45 (m, 5 H); ^{13}C-NMR, δ: 12.5, 14.4, 19.6, 29.7, 33.0, 42.8, 54.6, 71.7, 72.9, 78.5, 99.2, 116.6, 125.7, 128.7, 128.7, 132.8, 133.5, 152.7, 175.5; 1783, 1689. Anal. Calcd. for $C_{21}H_{26}BrNO_5$: C, 54.55; H, 5.95. Found: C, 54.65; H, 5.89.

(+)-6-Bromo-5(*R*)-(^{t}butyldimethylsiloxy)-3(*S*)-hydroxy-2(*R*)-methyl-6-heptenoic Acid (28). To a solution of **22** (0.72 g, 1.4 mmol) in THF (30 mL) at 0 °C was added a solution of lithium hydroxide monhydrate (0.115 g, 2.7 mmol), and hydrogen peroxide (1.240 g of 30% in water, 10.9 mmol) in water (7.5 mL). The reaction mixture was stirred for 5 h at room temperature then carefully quenched with a saturated solution of sodium bisulfite at 0 °C and diluted with water (30 mL). The water layer was washed with dichloromethane (2 x 20 mL), then carefully acidified to pH 3 with hydrochloric acid (3 N), and extracted with ethyl acetate (3 x 30 mL). The extracts were dried (Na_2SO_4) and concentrated in vacuo to give a residue of crude acid (251 mg). The initial dichloromethane washings were concentrated under reduced pressure and the residue taken up in tetrahydrofuran (30 mL) and resubjected to the hydrolysis protocol to give a further 191 mg of crude acid. Column chromatography (silica gel, eluent: ethyl actetate/hexane 1/1) of the combined crude product gave **28** (0.355 g, 71%). $[\alpha]_D$ = + 10.3° (c = 0.9); ^{1}H-NMR, δ: 0.04 (s, 3 H), 0.07 (s, 3 H), 0.85 (s, 9 H), 1.15 (d, *J* = 7.2 Hz, 3 H), 1.75 (d, *J* = 6.6 Hz, 1 H), 1.77 (dd, *J* = 2.7 and 11.2 Hz, 1 H), 2.56 (dq, *J* = 4.2 and 7.2 Hz, 1 H), 3.98 (dt, *J* = 4.9 and 6.9 Hz, 1 H), 4.31 (t, *J* = 6.5 Hz, 1 H), 5.51 (d, *J* = 1.8 Hz, 1 H), 5.84 (d, *J* = 1.1 Hz, 1 H); ^{13}C-NMR, δ: -5.1, -4.5, 11.0, 18.0, 25.7, 29.3, 44.3, 70.2, 76.3, 117.5, 136.6, 179.3; IR, υ (cm^{-1}): 3438, 1704. FAB HRMS. Calcd. for $C_{14}H_{28}BrO_4Si$: 367.0940. Found: 367.0942 (MH^+).

(+)-2(*S*)-^{t}Butyl-4(*S*)-[3-bromo-2(*R*)-(^{t}butyldimethylsiloxy)-3-buten-1-yl]-5(*R*)-methyl-1,3-dioxan-6-one (29). To a solution of **(28)** (27.0 mg, 0.07 mmol) and 4Å molecular sieves (20 mg) in dry

dichloromethane (1mL) cooled to -78 °C was added pivalaldehyde (12.7 mg, 0.15 mmol) and isopropoxytrimethylsilane (38.4 mg, 0.30 mmol) followed by TMSOTf (6.57 mg, 0.03 mmol). The resulting mixture was stirred at -78 °C for 0.5 h and then warmed to -15 °C and held there for 8.0 h before pyridine (5 μL) was added and then the volatiles evaporated *in vacuo*. Column chromotography (silica gel, eluent: ethyl acetate/hexane 1/4) of the residue gave **29** (29.0 mg, 90%). $[\alpha]_D$ = +6.9° (c = 0.8); ^{1}H-NMR, δ: 0.08 (s, 6 H), 0.90 (s, 9 H), 0.98 (s, 9 H), 1.26 (d, *J* = 7.3 Hz, 3 H), 1.75 (ddd, *J* = 3.1, 8.0, and 14.2 Hz, 1 H), 1.94 (ddd, *J* = 4.2, 9.7, and 14.1 Hz, 1 H), 2.64 (dq, *J* = 4.1 and 7.3 Hz, 1 H), 3.95 (ddd, *J* = 3.2, 4.1, and 7.3 Hz, 1 H), 4.33 (dd, *J* = 4.2 and 8.0 Hz, 1 H), 4.85 (s, 1 H), 5.57 (d, *J* = 1.5 Hz, 1 H), 5.84 (dd, *J* = 0.8 and 1.5 Hz, 1 H); ^{13}C-NMR, δ: -5.2, -4.8, 12.0, 18.1, 23.8, 25.7, 35.3, 37.2, 39.3, 72.4, 73.3, 108.0, 117.4, 136.5, 172.4; IR, υ (cm^{-1}): 1749. Anal. Calcd. for $C_{19}H_{35}BrO_4Si$: C, 52.40; H, 8.10. Found: C, 52.60; H, 8.00.

(-)-2(*S*)-^{t}Butyl-4(*S*)-[3-bromo-2(*R*)-(^{t}butyldimethylsiloxy)-3-buten-1-yl]-5(*S*)-methyl-5(*S*)-[2(*E*)-phenylsulfonylethenyl]-1,3-dioxan-6-one (30). To a solution of hexamethyldisilazane (96.6 mg, 0.60 mmol) in dry THF (0.8 mL) cooled to 0 °C was added dropwise a solution of butyllithium (0.276 mL of a 2 M solution in pentane, 0.55 mmol). After stirring for 15 min and cooling to -78 °C, a solution of **29** (200.0 mg, 0.46 mmol) in dry THF (1.0 mL) was added dropwise by cannula over 5 min. The reaction mixture was then stirred for 40 min at this temperature before a solution of 2(*E*)-bromovinyl phenyl sulfone[50] (171.0 mg, 0.69 mmol) in dry THF (0.8 mL) was added by cannula. The reaction mixture was stirred at -78 °C for 9 h and then warmed to room temperature over 1 h before it was quenched with pH 7 phosphate buffer (10 mL). The organic layer was separated and the water layer extracted with ether (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo. The oily residue was purified by column chromatography (silica gel, eluent: ether/hexane 1/3) to give **30** (130.4 mg, 47%) as a colorless oil. $[\alpha]_D$ = -19.7° (c=2.5); ^{1}H-NMR, δ: 0.09 (s, 3 H), 0.10 (s, 3 H), 0.92 (s, 9 H), 0.98 (s, 9 H), 1.41 (s, 3 H), 1.64 (dd, *J* = 8.3, 14.3 Hz, 1 H), 1.97 (ddd, *J* = 3.7, 7.1, and 14.3 Hz, 1 H), 3.90 (d, *J* = 10.1 Hz, 1 H), 4.32 (dd, *J* = 3.1 and 8.2 Hz, 1 H), 4.85 (s, 1 H), 5.56 (d, *J* = 1.3 Hz, 1 H), 5.86 (s, 1 H), 6.61 (d, *J* = 15.4 Hz, 1 H), 6.89 (d, *J* = 15.4 Hz, 1 H), 7.52-7.90 (m, 5 H); ^{13}C-NMR, δ: -5.0, 18.0, 18.2, 23.7, 25.8, 35.1, 35.5, 48.8, 73.2, 75.5, 109.2, 117.6, 127.9, 129.4, 133.6, 136.2, 139.7, 142.7, 170.1; IR, υ (cm^{-1}): 1738, 1626. FAB HRMS. Calcd. for $C_{27}H_{42}BrO_6SSi$: 601.16542. Found: 601.16548 (MH^+).

(+)-4(*S*)-^{t}Butyl-8(*R*)-(^{t}butyldimethylsiloxy)-1(*S*)-methyl-9-methylidene-3,5-dioxa-10(*R*)-(phenylsulfonylmethyl)bicyclo[4.4.0]-2-decanone (32) and (-)-4(*S*)-^{t}Butyl-8(*R*)-(^{t}butyldimethylsiloxy)-1(*S*)-methyl-9-methylidene-3,5-dioxa-10(*S*)-(phenylsulfonylmethyl)bicyclo[4.4.0]-2-decanone (33). Vinyl bromide (**30**) (25.0 mg, 0.042 mmol), trimethyltin hydride[53] (8.9 mg, 0.05 mmol) and AIBN (4.0 mg, 0.02 mmol) were dissolved in benzene (0.8 mL) in quartz tube and irradiated with a 125W medium pressure Hg lamp for 2 h at room temperature. The volatiles were then removed under reduced pressure, and the residue purified by preparative TLC on silica gel (eluent: ether/hexane 1/3) to give **32** (14.0 mg, 64%) and **33** (2.2 mg, 10%). **32**: $[\alpha]_D$ = +0.8° (c = 0.3); ^{1}H-NMR, δ: 0.11 (s, 6 H), 0.93 (s, 9 H), 0.97 (s, 9 H), 1.04 (s, 3 H), 1.66 (q, *J* = 11.8 Hz, 1 H), 2.14 (dt, *J* = 4.0 and 11.9 Hz, 1 H), 3.01 (br.d, *J* = 10.0 Hz, 1 H), 3.56 (dd, *J* = 10.3 and 14.5 Hz, 1 H), 3.82 (dd, *J* = 4.2 and 12.3 Hz, 1 H), 4.01 (dd, *J* = 4.8 and 11.4 Hz, 1 H), 5.00 (s, 1 H), 5.04 (dd, *J* = 1.2 and 14.6 Hz, 1 H), 5.17 (s, 1 H), 5.60 (t, *J* = 1.67 Hz, 1 H), 7.53-7.63 (m, 3 H), 7.94-7.97 (m, 2 H); ^{13}C-NMR, δ: -5.0, -4.9, 13.4, 25.8, 26.0, 29.7, 35.3, 36.6, 38.6, 46.1, 70.0, 76.3, 77.2, 110.0, 111.8, 127.9, 129.2, 133.5, 142.0, 143.9, 173.4; IR, υ (cm^{-1}): 1716. FAB HRMS. Calcd. for $C_{27}H_{43}O_6SSi$: 523.25496. Found: 523.25617 (MH^+). **33**: $[\alpha]_D$ = -

4.1° (c = 1.1); ^{1}H-NMR, δ: 0.14 (2 s, partially resolved, 6 H), 0.94 (s, 9 H), 0.96 (s, 9 H), 1.23 (s, 3 H), 1.72 (q, *J* = 11.9 Hz, 1 H), 2.16 (dt, *J* = 5.3, 11.2 Hz, 1 H), 3.19 (d, *J* = 5.8 Hz, 1 H), 3.21 (s, 1 H), 3.42 (dd, *J* = 5.6 and 10.4 Hz, 1 H), 3.86 (dd, *J* = 4.3 and 12.4 Hz, 1 H), 4.36 (dd, *J* = 5.7 and 11.3 Hz, 1 H), 4.96 (s, 1 H), 5.10 (t, *J* = 1.7 Hz, 1 H), 5.47 (t, *J* = 1.9 Hz, 1 H), 7.54-7.66 (m, 3 H), 7.85 - 7.95 (m, 2 H); ^{13}C-NMR, δ: -5.2, -4.9, 19.2, 23.9, 25.8, 35.4, 36.2, 43.2, 47.0, 55.0, 67.0, 73.1, 77.2, 110.3, 116.0, 128.1, 129.2, 133.8, 139.4, 142.2, 172.7; IR, υ (cm^{-1}): 1739. FAB HRMS. Calcd. for $C_{27}H_{43}O_6SSi$: 523.25496(5). Found: 523.25495(8).

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