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Synthesis and Asymmetric Alkylation of Glucose-Derived Bicyclic Oxazinones: An Evaluation of their Use as "Chiral Glycines".

Mikaela N. Keynes, Marion A. Earle, Manjula Sudharshan and Philip G. Hultin*

Department of Chemistry, University of Manitoba, Winnipeg MB, Canada R3T 2N2

Abstract: We have prepared structurally novel bicyclic oxazinones based on *D*-glucopyranose. The lithium enolates of these compounds undergo highly diastereoselective alkylation reactions with reactive alkyl halides, in modest yields. Use of the phosphazene P4 base enhances the yields of these processes, suggesting that metal enolate aggregation is at least partly responsible for the depressed yields. The stereochemistry of the products has been unequivocally ascertained by nOe measurements and *ab initio* calculations. Copyright © 1996 Elsevier Science Ltd

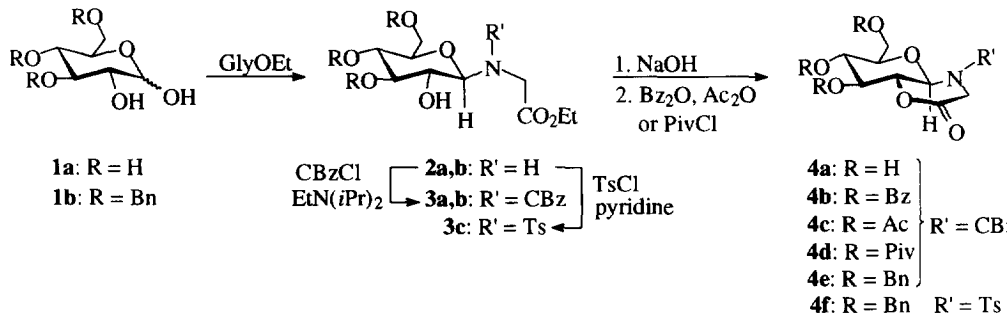
Carbohydrate chiral auxiliaries have been surprisingly under-utilized in organic synthesis.[1] This is perhaps because reactions involving conformationally mobile ligands attached at either the anomeric position or at other hydroxyl groups do not consistently achieve satisfactory levels of diastereoselectivity. The most selective uses of carbohydrate auxiliaries are those in which this flexibility has been restrained, most often by coordination of a metal ion.[1] While considering this issue in the design of carbohydrate-based chiral templates, we noted the potential of bicyclic oxazinones such as **4**. These oxazinones connect a glycine fragment to *D*-glucopyranose by both an *N*-glycosidic bond and a lactone linkage to the C-2 OH of the sugar.[2] The decalin-like structure should be sufficiently rigid to undergo highly diastereoselective and predictable alkylation reactions at the glycine C_α. Oxazinones of this type might thus serve as "chiral glycines" in the asymmetric synthesis of α-amino acids.

The asymmetric synthesis of α-amino acids is a topic of considerable current importance,[3] and the "chiral glycine" approach is among the most versatile methods available at present. Excellent "chiral glycines" have been developed, notably by Schöllkopf, Seebach, and Williams, among others.[3] Nevertheless, we noted the high cost per mole of these compounds, and also the fact that liberation of the amino acid product frequently destroys an expensive chiral auxiliary. A "chiral glycine" based on inexpensive *D*-glucose and incorporating an easily cleaved *N*-glycosidic linkage might address both of these issues. This paper describes our straightforward synthesis of oxazinones **4**, which represent (to our knowledge) a previously unknown type of carbohydrate derivative.[4] We also present our investigation of some very diastereoselective alkylation reactions of these compounds, which allow an assessment of their potential as chiral templates.

RESULTS AND DISCUSSION

The synthesis of these glucose-derived oxazinones is depicted in Scheme 1. We readily prepared large amounts of crystalline *N*-β-*D*-glucosylglycine ethyl ester (**2a**) by the published procedure.[5] Treatment with

CBz-Cl and *N,N*-diisopropylethylamine blocked the amine, to afford **3a** (60-70%); the more nucleophilic bases pyridine or triethylamine promoted rapid cleavage of the *N*-glycosidic bond of **2a**. We observed that **2a** was very sensitive to hydrolysis even at neutral pH, but that the *N*-glycosidic linkage of carbamate-protected **3a** was stable in aqueous solutions at pH 2-12. Thus, aqueous NaOH cleanly hydrolyzed the ester function, to afford the corresponding carboxylic acid. Oxazinone **4a** slowly formed on heating this acid with 1.22 M HCl in acetic acid, in the presence of 4Å molecular sieves, but the reaction did not go to completion. A better method was treatment of the carboxylate salt obtained from hydrolysis of **3a** with an acyl halide or anhydride in pyridine.[4,6] The cyclization process was faster than acylation of the glucose hydroxyls, since we observed triol oxazinone **4a** as an intermediate by TLC. Thus, use of an excess of benzoic anhydride gave **4b** (60%), and acetic anhydride treatment provided **4c** (60%). While neither acetate nor benzoate esters would be sufficiently stable during formation of an enolate, the pivalate appeared to be suitable.[7] Treatment of the carboxylate with pivaloyl chloride afforded crystalline **4d** (83%).



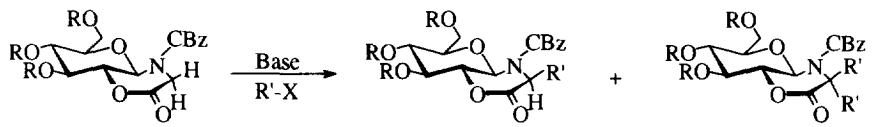
Scheme 1

The benzyl ether-protected oxazinone **4e** could not be prepared by benzylation of **4a**. However, condensation of 3,4,6-tri-*O*-benzyl-*D*-glucopyranose[8] with glycine ethyl ester in refluxing chloroform gave **2b** (79%). Recrystallization at this point removed a minor byproduct, apparently resulting from acid-catalyzed Amadori rearrangement[9] during the condensation. *N*-glycoside **2b** was more resistant to hydrolysis than was **2a**, and likewise nucleophilic amine bases did not significantly degrade it. Nevertheless, protection of **2b** with CBz-Cl was successful only in the presence of *N,N*-diisopropylethylamine as base, giving **3b** (98%).[10] We have also prepared the *N*-tosyl derivative **3c**, by treatment of **2b** with carefully purified TsCl in pyridine (59%). Use of unpurified TsCl led to substantial amounts of the Amadori byproduct. The esters **3b** and **3c** were hydrolyzed and the intermediate salts were cyclized using either acetic or benzoic anhydride, to give benzyl-blocked templates **4e** (80% recrystallized yield) and **4f** (44%). We have performed the sequences leading to **4d-f** successfully on multi-gram scales.

We next performed alkylations using the reactive electrophiles methyl iodide or allyl bromide, in order to ascertain the potential of **4d-f** in asymmetric synthesis (Scheme 2). We examined the formation of the enolates of oxazinones **4d,e** in THF solution using lithium, sodium, or potassium hexamethyldisilazide (Li-, Na-, or KHMDS) as well as LDA. It was clear that the best results were obtained using LiHMDS, and this base was used for the remainder of our study. We noted that LDA destroyed **4e** at -75 °C within 10 minutes. Seebach and Williams have also reported that oxazolidinone and oxazinone templates display a similar intolerance towards LDA.[11] In the absence of HMPA, the lithium enolate of pivalate-blocked **4d** was essentially inert to the

electrophiles at temperatures at or below -65 °C. In contrast, addition of HMPA to the reaction at -65 °C led to rapid product formation.[12] Other coordinating solvents or additives such as DME, TMEDA, 12-crown-4, or 15-crown-5 had no effect.

In the absence of HMPA, the lithium enolate of benzyl-blocked oxazinone **4e** was sluggishly reactive towards methyl iodide or allyl bromide, but addition of HMPA promoted rapid reaction. Reactions with **4e** were accompanied however, by significant decomposition of the enolate even at low temperatures. This was a particular problem when HMPA was present in the reaction mixture *prior* to the addition of the electrophile. Use of DME as solvent had no effect, while the crown ethers were only modestly effective additives to promote alkylation. TMEDA alone did not enhance the reactivity of the enolate of **4e**. Curiously, while methylation of **4e** using TMEDA/HMPA gave results essentially identical to those obtained with HMPA alone, allylation in the presence of TMEDA/HMPA required rapid warming to ≥ -20 °C in order to obtain products. Allylations of **4e** containing both TMEDA and HMPA, which were quenched at -65 °C afforded only recovered **4e**!



4d: R = Piv
4e: R = Bn

5a,b: R' = CH_3
7a,b: R' = CH_2CHCH_2
9: R = Piv, R' = CH_3CH_2

6a,b: R' = CH_3
8a,b: R' = CH_2CHCH_2
10: R = Piv, R' = CH_3CH_2

Oxazinone	R'-X	Conditions	Combined Yield	Product(s)	Mono:Di Ratio	Monoalkyl d.e.
4d	CH_3I	B	57%	**5a**	1.0 : 0.0	>98%
	CH_2CHCH_2Br	B	48%	**7a + 8a**	1.0 : 1.1	>98%
		F	69%	**7a + 8a**	1.0 : 3.2	>98%
	CH_3CH_2Br	F	70%	**9 + 10**	2.2 : 1.0	>98%
4e	CH_3I	A	23%	**5b**	1.0 : 0.0	n.d.
		B	56%	**5b**	1.0 : 0.0	92%
		C	51%	**5b**	1.0 : 0.0	98%
	CH_2CHCH_2Br	A	25%	**7b**	1.0 : 0.0	n.d.
		B	51%	**7b + 8b**	1.0 : 1.0	>98%
		D	43%	**7b + 8b**	1.9 : 1.0	>98%
		E	52%	**7b + 8b**	1.7 : 1.0	76%
		F	70%	**7b + 8b**	1.3 : 1.0	>98%

A: LiHMDS, THF, < -65° B: LiHMDS, THF/HMPA, < -65°
C: LiHMDS, THF/TMEDA/HMPA, < -65°
D: LiHMDS, THF/TMEDA/HMPA, -65° → r.t. rapidly
E: LiHMDS, THF/TMEDA /HMPA, -65° → -20° slowly
F: P4 base, THF, -95° → r.t.

Scheme 2

The methylation reactions provided essentially only the monomethylated products **5a,b**, as well as some recovered starting oxazinone. Traces of dimethylated products **6a,b** could be obtained from reactions involving

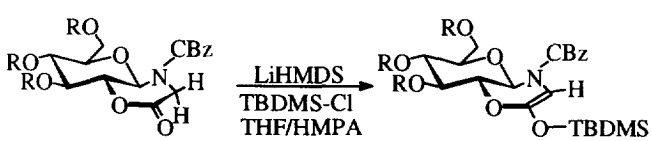
large excesses of methyl iodide and long reaction times. Allylation always provided mixtures of monoallylated **7a,b**, diallylated **8a,b** and unreacted **4d,e**. The yields obtained after chromatography were modest at best, as shown in Scheme 2. The lithium enolate of **4d** was not reactive towards ethyl bromide at -65 °C, despite addition of HMPA. Warming to 0 °C decomposed the enolate before any ethylated product formed.

Despite the modest chemical yields, ^{1}H nmr spectra of both crude and purified monoalkylated products showed that the alkylations conducted and quenched at < -65 °C were highly diastereoselective. We could detect the presence of a small amount of ***epi*-5a,b** in some spectra of methylated products **5a** and **5b** as a second methyl doublet at *ca.* δ 1.83. In the allylations of either **4d** or **4e** conducted at low temperature, we could detect no signals due to a minor diastereomer. TLC likewise did not show any minor monoallylated product. However, when the allylation reaction of **4e** was allowed to warm *slowly* to -20 °C before quenching, a new minor product was evident by TLC. This was isolated and identified as ***epi*-7b**, by its ^{1}H nmr spectrum. We found no sign of ***epi*-7b** in reactions that were warmed *quickly* before quenching. It was thus evident that some *slow* equilibration of the initially formed **7b** occurred as the temperature rose.

The lack of enolate reactivity in the absence of HMPA and the tendency for decomposition, suggested that internal coordination and/or aggregation of the lithium enolate might be the problem. Kunz has noted that acyclic carbohydrate ester enolates may be especially unstable towards ketene formation when lithium strongly interacts with the leaving group oxygen.[13] The phosphazene "Pn" bases are non-aggregating, and comparable in strength to LiHMDS.[14] In particular, the *t*-butyl P4 base has been used in stereoselective alkylations of esters and dioxanones.[14b,c] We therefore also studied alkylation reactions of **4d** and **4e** using the P4 base (Scheme 2).

The P4 base is not suitable for methylations,[14b] but it promoted allylation of **4d** in 69% yield (**7a**:**8a** 1.0:3.2), and allylation of **4e** in 70% yield (**7b**:**8b** 1.3:1.0). The P4-induced reactions also afforded only a single monoalkylated diastereomer; no ***epi*-7** was detectable in any example, despite the fact that these reactions were allowed to warm to room temperature. The P4 base also successfully induced ethylation of **4d** to give monoethyl **9** (48%) as a single diastereomer, as well as diethyl **10** (22%), in contrast to the failure of LiHMDS. There was no need for the addition of HMPA in any reaction using P4. These results seem to confirm our premise that aggregation and/or tight coordination of the counter-ion by the carbohydrate auxiliary are responsible for the disappointing product yields we have obtained.

N-Tosylated oxazinone **4f** was surprisingly fragile under the condition of enolate formation, and always decomposed before any alkylated products could be observed, even when deprotonated by P4 base. We were surprised to obtain traces of *N*-allyl toluenesulfonamide from attempted allylation of **4f** promoted by P4, indicating the possibility of an α-elimination pathway for decomposition.



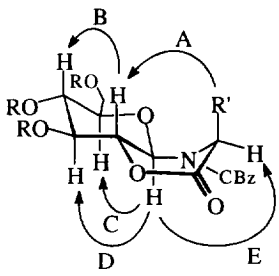
4d: R = Piv
4e: R = Bn

11a: R = Piv (63%)
11b: R = Bn (78%)

Scheme 3

We have successfully trapped the lithium enolates of **4d** and **4e** as their TBDMS enol ethers **11a,b** (Scheme 3), showing that they can indeed be cleanly formed. No reaction occurred in the absence of HMPA, but **11a,b** were formed quantitatively on addition of this cosolvent. ^{1}H nmr of the crude products indicated complete conversion, and only impurities originating from excess silylating reagent were observed. The isolated yields after rapid flash

chromatography reflect the sensitivity of the silyl enol ether function to silica gel. Silyl chlorides are "fast" electrophiles, and the high trapping yields obtained in these experiments indicate that decomposition must be much slower than *O*-silylation but competitive with *C*-alkylation under the reaction conditions.



	A	B	C	D	E
4d	17%	-	15%	14%	*a*
4e	*a*	-	*b*	11%	2%
5a	18%	11%	17%	16%	~0%
5b	14%	-	13%	11%	0%
7a	20%	13%	-	-	-
7b	15%	4.5%	-	-	-
9	19%	11%	15%	14%	0%

a resonances overlap
b H-6 signal partly obscured by H_2O in solvent

Figure 1: Observed nOe data.

We determined the stereochemistry of the monoalkylated products **5a,b**, **7a,b** and **9** by ^{1}H nmr. The ^3J couplings among the glucose hydrogens confirmed that this ring maintained the expected chair conformation in **4** and in all the products. This provided us with a set of stable reference points from which to determine the configuration of the new stereocentre by nuclear Overhauser effect (nOe) analysis. The relevant nOe observations are summarized in Figure 1. The strong nOe between the substituent R′ (R′ = H, CH_3 or CH_2CHCH_2) and H-2 of the glucosyl ring, plus the lack of any significant nOe between the anomeric hydrogen and either R′ or its adjacent methine proton, clearly indicated that the new centre had the *S* configuration in **5**, **7** and **9**. It also showed that the oxazinone rings of **4d,e** as well as of **5a,b**, **7a,b**, and **9** adopted boat conformations, with the R′ group occupying an axial "flagpole" position.

To aid our analysis of these nOe data, we have calculated optimized geometries for **4e** and for its carbamate-substituted pyrano[3,2-b]oxazin-2-one skeleton **12**. Semi-empirical AM1 calculations on **4e** converged to a boat conformation from a number of starting geometries. Similar *ab initio* calculations on **12** at the 6-31G* level confirmed that the boat was indeed preferred (Figure 2), and provided interproton distances consistent with the observed nOes (Figure 1). Curiously, the chair conformation was not a local minimum for these com-

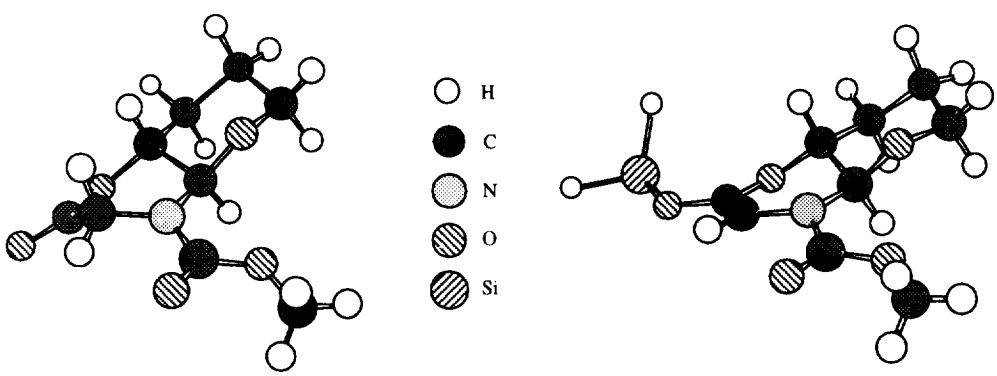


Figure 2: 6-31G* optimized conformations of **12** (left) and **13**.

pounds according to either AM1 or 6-31G* calculations, although STO-3G did identify a stable chair conformer. The preference for the boat geometry appears to be a consequence of keeping the ester portion of the structure as close to a planar *E* conformation as possible (torsions in the 6-31G* boat of 165-167° vs. 136-137° in the STO-3G chair), while minimizing unfavorable steric interactions between the carbamate and the glucosyl ring oxygen.

These conformational preferences also illuminate the origin of the high diastereoselectivity of these reactions. While Seebach found that pyramidalization of a carbamate nitrogen strongly influences the steric environment of several acylated imidazolidinones, oxazolidinones and oxazinones,[15] this does not appear to be the case with **4**. The STO-3G basis set pyramidalized the carbamate (which explains why STO-3G predicts a stable chair conformer), but the 6-31G* calculations predict essentially no nitrogen distortion. Negligible pyramidalization is calculated for the simplified silyl enol ether **13**, related to **11** (Figure 2), which we have taken as a model for the enolate. Presumably this slight distortion reduces $A^{1,3}$ strain between the carbamate and the vinylic hydrogen, which would increase if the carbamate were planar. However, the carbamate is not positioned to hinder approach to the reactive centre, assuming **13** to be a good model for the enolate geometry. Such steric interference would require quite extreme pyramidalization at nitrogen. In fact, there seem to be no steric barriers hindering approach to either enolate face.

We believe that stereoelectronic influences rationalize the observed diastereoselectivity best. The preference for axial approach to and alkylation of 6-membered cyclic enolates is well known.[16] The flexibility of most 6-membered ring systems often masks this effect, but our decalin-like system is conformationally locked, and the axial positions are unambiguous. There are thus only two alkylation pathways that can afford axially substituted products: reaction at the enolate *re*-face *via* a chair-like transition state, or at the enolate *si*-face *via* a boat-like transition state. If the chair conformer is unstable, as indicated by our calculations, the chair-like transition state would probably encounter similar destabilizing interactions and thus be energetically penalized relative to the boat-like transition geometry. Alkylation from the *si*-face of the enolate *via* this boat-like transition state forms the observed monoalkylated products **5**, **7** and **9**. We also conclude that any second alkylation occurs rapidly, since the formation of dialkylated products is not accompanied by epimerization of the monoalkylated material.

This study was initiated by two ideas: that the novel bicyclic oxazinones **4** could be synthesized easily and relatively cheaply, and that they would provide a consistently high level of diastereoselectivity in alkylation reactions. Our results clearly confirm these premises. On the other hand, while good alkylation yields can be obtained using the P4 base, the evident instability of the lithium enolates of **4** and their tendency to dialkylate mean that these *enolates* are unlikely to compete effectively with existing "chiral glycines" in the asymmetric synthesis of α-amino acids. Nevertheless, the readily-made silyl enol ethers **11**, and the possibility of preparing electrophilic α-bromocarbonyl derivatives,[17] may permit efficient uses of these templates. We are now examining these reactions, as well as conditions for separating the amino acid products from the carbohydrate. We will report the results of these experiments in due course.

EXPERIMENTAL

Reagents and solvents requiring purification and/or drying were treated according to literature methods before use.[18] Solutions of lithium hexamethyldisilazide (LiHMDS) in THF or hexanes were prepared periodically from redistilled hexamethyldisilazane and a solution of *n*-butyllithium in hexanes (Aldrich). Base

solutions were assayed by titration.[19] The P4 base was obtained from Fluka as a 1.0 M solution in hexanes, and was used as such. Reactions requiring dry conditions were performed under a positive pressure of dry nitrogen or argon, in glassware dried overnight at 140-180°C. Alkylation reactions were quenched with 1 M sodium phosphate pH 7.0 buffer. "Drying" refers to the use of anhydrous $MgSO_4$. Flash chromatography was performed on silica gel 60, eluting with the solvent mixtures indicated. Nuclear magnetic resonance spectra were acquired on Bruker AM 300 or AMX 500 instruments, at a temperature of 300 K unless otherwise indicated. Proton chemical shifts (reported to the nearest 0.01 ppm) were measured using the residual ^1H signal(s) of the deuterated solvent as an internal reference, while ^{13}C chemical shifts (to the nearest 0.1 ppm) were referenced to the solvent ^{13}C signal. Signal assignments were confirmed by COSY, HSQC, and/or homonuclear decoupling experiments. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph Ontario, Canada.

_N_-(β-_D_-glucopyranosyl)-_N_-(benzyloxycarbonyl)glycine ethyl ester (3a).

A solution of _N_-(β-_D_-glucopyranosyl)glycine ethyl ester[5] (**2a**, 5.00 g, 18.9 mmol) in dry DMF (25 mL) was dried over 4Å molecular sieves for 40 min. The solution was transferred to a fresh flask *via* a syringe, the sieves were rinsed with DMF (5 mL), and the rinsings were added to the reaction vessel. _N,N_-Diisopropylethylamine (3.60 mL, 20.7 mmol) was added, followed by benzyl chloroformate (4.0 mL, 28.0 mmol). After 1.5 h, the solution was concentrated under vacuum, the residue was evaporated twice with small portions of toluene, and dried under high vacuum. Chromatography (hexanes: EtOAc 3:1 → 0:1) gave **3a** (5.36 g, 71%).

$[\alpha]_D^{25}$ = +22.4° (c 1.24, EtOH).

^1H nmr (DMSO-d_6, 383 K) δ 1.18 (t, 3H, J = 7.1, CH_3), 3.14-3.36 (m, 4H, H-2, H-3, H-4, H-5), 3.51 (ddd, 1H, J = 11.6, J = 4.8, J = 5.6, H-6), 3.69 (ddd, 1H, J = 11.6, J = 2.5, J = 5.1, H-6'), 3.82 (dd, 1H, J = 5.1, J = 5.6, O*H*), 3.94 (d, 1H, J = 17.5, C*H*C=O), 4.07 (d, 1H, J = 17.5, C*H*C=O), 4.12 (q, 2H, J=7.1, CH_2CH_3), 4.29 (d, 1H, J = 4.1, O*H*), 4.45 (d, 1H, J = 4.8, O*H*), 4.49 (d, 1H, J = 3.4, O*H*), 5.07 (d, 1H, J = 8.9, H-1), 5.14 (s, 2H, CH_{2CBz}), 7.35 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr (DMSO-d_6, 383 K) δ 13.2 (CH_3), 43.4 (CH_2C=O), 60.0, 60.9 (CH_2), 66.3 (CH_{2CBz}), 69.7, 69.9, 76.4, 78.4 (C-2, C-3, C-4, C-5), 84.8 (C-1), 126.6, 127.0, 127.6 (C_{Ar}), 135.8 (4° C_{Ar}), 154.6 (C=O_{CBz}), 169.6 (C=O_{ester}) ppm.

Anal. calc'd. for $C_{18}H_{25}O_9N$: C, 54.13; H, 6.31; N, 3.51; found: C, 54.06; H, 6.49; N, 3.50.

(4a_R_, 6_R_, 7_R_, 8_S_, 8a_R_)-4-(benzyloxycarbonyl)-6-(benzoyloxy)methyl-7,8-bis(benzoyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (4b).

Ester **3a** (4.73 g, 11.8 mmol), in a minimum amount of 95% EtOH, was treated with 0.3 M aqueous NaOH (47.0 mL, 14.1 mmol). After 3 h, the solution was adjusted to pH 3.0 using Amberlite IR-120(H^+). The resin was removed by filtration, the solution was decolorized with charcoal, and concentrated on the rotary evaporator. The residue was dried under high vacuum to afford the carboxylic acid as a solid.

A sample of this carboxylic acid (100 mg, 0.27 mmol) was dissolved in water and the pH of the solution was adjusted to 9.0 with 1 M aqueous NaOH. The solution was evaporated, and the residue was dried by evaporating with toluene. Pyridine (5.0 mL) was added, followed by benzoic anhydride (609 mg, 2.69 mmol) and diethyl ether (1.0 mL). The reaction was stirred at 40 °C for 19 h. The solution was then partitioned between EtOAc and 1 M aqueous HCl. The pyridine-free organic layer was washed with brine, dried, and concentrated. Chromatography of the residue (2:1 hexanes:EtOAc) afforded **4b** as an oil (108 mg, 60%).

The oily **4b** could be recrystallized from CH_2Cl_2/hexanes.

mp 181.5-182.5°C.

$[\alpha]_D^{25}$ = +34.0° (c 0. 9, $CHCl_3$)

^{1}H nmr ($CDCl_3$) δ 4.09 (d, 1H, *J* = 16.9, H-3), 4.29 (br s, 1H, H-6), 4.48 (dd, 1H, *J* = 12.3, *J* = 4.8, H-9), 4.54 (dd, 1H, Σ*J* = 19.7, H-8a), 4.63 (dd, 1H, *J* = 12.3, *J* = 2.8, H-9′), 4.89 (d, 1H, *J* = 16.9, H-3), 5.14 (d, 1H, *J* = 12.3, CH_{CBz}), 5.20 (br d, 1H, H-4a), 5.24 (d, 1H, *J* = 12.3, CH_{CBz}), 5.72 (dd, 1H, Σ*J* = 19.0, H-7), 6.01 (dd, 1H, Σ*J* = 19.0, H-8), 7.31-7.41 (m, 10 H, CH_{Ar}), 7.43-7.59 (m, 4H, CH_{Ar}), 7.89-8.11 (m, 6H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 44.3 (C-3), 62.6 (C-9), 68.6 (*C*H_{2CBz}), 69.6 (C-7), 71.7 (C-8), 74.5 (C-8a), 74.5 (C-6), 81.4 (C-4a), 127.8, 128.2, 128.3, 128.3, 128.4, 128.6, 129.4, 129.7, 129.8, 130.0 (C_{Ar}), 133.1, 133.4, 133.6 (4° C_{Bz}), 135.1 (4° C_{CBz}), 154.4 (*C*=O_{CBz}), 165.1, 165.2, 165.9, 166.3 (*C*=$O_{ester/lactone}$) ppm.

Anal. calc'd. for $C_{37}H_{31}O_{11}N$: C, 66.76; H, 4.69; N, 2.10; found: C, 66.73; H, 4.66; N, 2.01.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-4-(benzyloxycarbonyl)-6-(acetoxy)methyl-7,8-bis(acetoxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (4c).

A sample of the carboxylic acid (200 mg, 0.51 mmol) was converted to the sodium carboxylate as described above. The dried salt was dissolved in pyridine (10 mL) and acetic anhydride (0.24 mL, 2.54 mmol) was added. The mixture was stirred for 24 h, when a second portion of acetic anhydride (0.24 mL, 2.54 mmol) was added. After a further 16 h, DMAP (ca. 5 mg) was added. After a further 20 h, the reaction mixture was heated to 40°C. After a further 24 h, the reaction appeared to be complete. Workup as described above, and chromatography (3:2 hexanes:EtOAc) provided **4c** (145 mg, 60%).

$[\alpha]_D^{25}$ = +22.9° (c 0.6, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 2.05 (s, 6H, 2 × CH_3), 2.08 (s, 3H, CH_3), 3.87 (br s, 1H, H-6), 4.03 (d, 1H, *J* = 17.2, H-3), 4.06-4.12 (br m, 1H, H-9), 4.23-4.31 (m, 2H, H-8a, H-9′), 4.86 (d, 1H, *J* = 17.2, H-3′), 4.96 (d, 1H, *J* = 9.5, H-4a), 5.12 (dd, 1H, *J* = 9.9, *J* = 9.0, H-7), 5.21 (dd, 2H, *J* = 12.5, CH_{2CBz}), 5.43 (dd, 1H, *J* = 9.0, *J* = 9.8, H-8), 7.37 (m, 5H, CH_{Ar}) ppm.

Anal. calc'd. for $C_{22}H_{25}O_{11}N$: C, 55.11; H, 5.26; N, 2.92; found: C, 54.55; H, 5.46; N, 2.78.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-4-(benzyloxycarbonyl)-6-(pivaloyloxy)methyl-7,8-bis(pivaloyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (4d).

Hydrolysis of ester **3b** (2.0 g, 5.0 mmol) proceeded as previously described. The solution was adjusted to pH 8.5-9.0 with 1 M aqueous HCl. Concentration provided a crude sodium salt.

The salt was dissolved in dry pyridine (15 mL) containing DMAP (0.03 g, 0.25 mmol). Pivaloyl chloride (6.2 mL, 50 mmol) was added dropwise *via* syringe. After 1 h, the mixture was heated to 40 °C for 16 h. The solution was concentrated, and the residue was re-evaporated from toluene. The crude material was adsorbed onto silica gel (10 mL) and applied to dry silica (4 cm × 5.5 cm) in a fritted funnel. Portionwise elution (6:1 hexanes:EtOAc) gave 2.52 g of white powder, which was crystallized from methanol, yielding **4d** (83%).

mp 210-211°C.

$[\alpha]_D^{25}$ = +47.2° (c 0.50, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.16, 1.18, 1.21 (3 × s, 9H, C(CH_3)$_3$), 3.90 (br m, 1H, H-6), 4.05 (d, 1H, J = 17.0, H-3), 4.10-4.20 (m, 2H, H-9, H-9′), 4.27 (dd, 1H, J = 9.5, J = 10.1, H-8a), 4.85 (br d, 1H, J = 17.0, H-3′), 5.00 (d, 1H, J = 9.5, H-4a), 5.15-5.26 (m, 3H, CH_{2CBz}, H-7), 5.52 (dd, 1H, J = 10.1, J = 8.9, H-8), 7.30-7.40 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 26.5, 27.0, 27.1 (C(CH_3)$_3$), 38.8, 38.9 (C(CH_3)$_3$), 44.4 (C-3), 61.40 (C-9), 67.7 (C-7), 68.7 (CH_{2CBz}), 71.0 (C-8), 74.6 (C-8a), 74.9 (C-6), 81.3 (C-4a), 128.1, 128.6, 128.7 (C_{Ar}), 135.2, (4° C_{Ar}), 154.4 (C=O_{CBz}), 166.3 (C=$O_{oxazinone}$), 176.4, 176.9, 177.9 (C=O_{piv}) ppm.

Anal. calc'd. for $C_{31}H_{43}NO_{11}$: C, 61.47; H, 7.16; N, 2.31; found: C, 61.38; H, 7.24; N, 2.23.

N-(3,4,6-tri-O-benzyl-β-D-glucopyranosyl)glycine ethyl ester (2b).

A solution of 3,4,6-tri-O-benzyl-D-glucose[8] (6.42 g, 14.3 mmol) and freshly distilled glycine ethyl ester[20] (2.6 mL, *ca.* 25.7 mmol) in $CHCl_3$ (25 mL) was gently boiled under reflux for 22.5 h. The solution was concentrated to a brown oil, which solidified on standing under high vacuum. This solid was recrystallized from di(isopropyl)ether. The residue obtained from the mother liquors was chromatographed (hexanes:EtOAc 4:1 → 1:1) to obtain additional product. A second recrystallization of the combined products from di(isopropyl)ether and hexanes afforded **2b** (6.08 g, 79%).

An analytical sample had mp 74-75 °C.

$[\alpha]_D^{25}$ = +5.0° (c 0.6, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2, CH_3), 2.27 (br s, 1H, NH), 3.07 (s, 1H, OH), 3.35-3.47(m, 2H), 3.55 (d, 1H, J = 17.4, CHC=O), 3.57-3.61 (m, 2H), 3.64-3.72 (m, 2H), 3.70 (d, 1H, J = 17.4, CHC=O), 3.87 (d, 1H, J = 8.7, H-1), 4.19 (q, 2H, CH_2CH_3), 4.51 (d, 1H, J = 12.2, CH_{Bn}), 4.52 (d, 1H, J = 10.8, CH_{Bn}), 4.59 (d, 1H, J = 12.2, CH_{Bn}), 4.83 (d, 1H, J = 11.3, CH_{Bn}), 4.85 (d, 1H, J = 10.8, CH_{Bn}), 5.01 (d, 1H, J = 11.3, CH_{Bn}), 7.10-7.40 (m, 15 H, CH_{Ar}) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz)[21] δ 14.2 (CH_3), 46.4 (CH_2C=O), 61.1 (CH_2CH_3), 69.0, 73.5, 74.3, 75.0, 76.3 (C-2, C-4, C-5, C-6, CH_{2Bn}), 85.5 (C-3), 89.7 (C-1), 127.6, 127.6, 127.7, 127.8, 128.0, 128.4 (C_{Ar}), 138.0, 138.2, 138.8 (4° C_{Ar}), 172.4 (C=O) ppm.

Anal. calc'd. for $C_{31}H_{37}NO_7$: C, 69.51; H, 6.96; N, 2.61; found: C, 69.27; H, 7.02; N, 2.59.

N-(3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-N-(benzyloxycarbonyl)glycine ethyl ester (3b).

A solution of **2b** (4.90 g, 9.16 mmol) and N,N-diisopropylethylamine (3.20 mL, 18.8 mmol) in $CHCl_3$ (10.0 mL) was chilled to 0°C. Benzyl chloroformate (2.00 mL, 14.0 mmol) was added dropwise over 10 min. The solution was allowed to come to room temperature, and stirring was continued for 3 h. Water (70 mL) was added, and the mixture was partitioned with ether (265 mL). The ether layer was washed with 1 M aqueous HCl (2 × 35 mL), saturated aqueous $NaHCO_3$ (35 mL), and brine (35 mL). Concentration of the dried solution afforded a clear oil. Passage through a 4.5 cm × 8 cm dry column of silica gel, eluting with a hexanes:EtOAc gradient, provided **3b** as a viscous oil (5.85 g, 95%) which crystallized very slowly on seeding or scratching.

An analytical sample recrystallized from di(isopropyl) ether had mp 75.5-77 °C.

$[\alpha]_D^{25}$ = +15.7° (c 0.6, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.15 (t, 3H, J = 7.1, CH_3), 3.45 (dd, 1H, J = 9.1, H-4), 3.54-3.59 (m, 2H, H-2, H-5), 3.61-3.69 (m, 3H, H-3, H-6, H-6′), 3.94 (d, 1H, J = 17.4, CHC=O), 4.06-4.10 (m, 3H, CHC=O, CH_2CH_3), 4.47 (d, 1H, J = 12.3, CH_{CBz}), 4.51 (d, 1H, J = 12.3, CH_{CBz}), 4.56 (d, 1H, J = 11.2, CH_{Bn}), 4.68 (d, 1H, J =

5.0, O*H*), 4.74 (d, 1H, *J* = 11.2, C*H*$_{Bn}$), 4.76 (d, 1H, *J* = 11.5, C*H*$_{Bn}$), 4.94 (d, 1H, *J* = 11.5, C*H*$_{Bn}$), 5.13 (d, 1H, *J* = 12.8, C*H*$_{Bn}$), 5.15 (d, 1H, *J* = 9.1, H-1), 5.16 (d, 1H, *J* = 12.8, C*H*$_{Bn}$), 7.14-7.18 (m, 2H, C*H*$_{Ar}$), 7.22-7.37 (m, 18H, CH$_{Ar}$) ppm.

^{13}C nmr (CDCl$_3$)[22] δ 13.1 (*C*H$_3$), 43.4 (*C*H$_2$C=O), 60.0 (*C*H$_2$CH$_3$), 66.4 (*C*H$_{2Bn}$), 68.9 (C-6), 70.30 (C-2), 72.1, 73.0, 73.3 (*C*H$_{2Bn}$), 76.2 (C-5), 76.8 (C-4), 84.4 (C-3), 84.9 (C-1), 126.4, 126.6, 126.7, 126.8, 127.1, 127.3, 127.4, 127.6 (C$_{Ar}$) ppm.

Anal. calc'd. for $C_{39}H_{43}NO_9$: C, 69.94; H, 6.47; N, 2.09; found: C, 69.81; H, 6.51; N, 2.07.

_N_-(3,4,6-tri-_O_-benzyl-β-_D_-glucopyranosyl)-_N_-(_p_-toluenesulfonyl)glycine ethyl ester (3c).

A solution of ester **2b** (1.71 g, 3.2 mmol) in CH_2Cl_2 (15.9 mL) and pyridine (8.5 mL, 32 eq.) was cooled to < 0 °C. Tosyl chloride (3.66 g, 19.2 mmol) was added in portions over 10 minutes. The reaction was allowed to come to room temperature over 1 h, and was then stirred for 1 h more. Water (24 mL) was added slowly, and the mixture was stirred until the excess TsCl was hydrolyzed. The reaction mixture was poured into diethyl ether (80 mL), the phases were separated, and the organic layer was washed with 1 M aqueous HCl (2 × 24 mL), saturated aqueous $NaHCO_3$ (24 mL), and brine (24 mL). The dried organic solution was concentrated, and the residue was purified by chromatography (3:1 hexanes:EtOAc) to provide **3c** (1.29 g, 59%).

mp 116-118 °C.

$(\alpha)_D^{25}$ = -3.2° (c 0.5, $CHCl_3$).

^{1}H nmr (CDCl$_3$) δ 1.32 (t, 3H, *J* = 7.1, CH$_2$C*H*$_3$), 2.33 (s, 3H, ArC*H*$_3$), 3.39 (dd, 1H, *J* = 9.1, *J* = 8.8, H-2), 3.45-3.60 (m, 4H, H-4, H-5, H-6, H-6′), 3.78 (dd, 1H, *J* = 8.8, *J* = 8.5, H-3), 3.82 (d, 1H, *J* = 18.9, C*H*C=O), 3.94 (d, 1H, *J* = 18.9, C*H*C=O), 4.18-4.34 (m, 2H, OC*H*$_2$CH$_3$), 4.40 (d, 1H, *J* = 12.2, C*H*$_{Bn}$), 4.44 (d, 1H, *J* = 12.2, C*H*$_{Bn}$), 4.55 (br s, 1H, O*H*), 4.56 (d, 1H, *J* = 11, C*H*$_{Bn}$), 4.83 (d, 1H, *J* = 11, C*H*$_{Bn}$), 4.89 (d, 1H, *J* = 11, C*H*$_{Bn}$) , 5.08 (d, 1H, *J* = 9.1, H-1), 5.15 (d, 1H, *J* = 11, C*H*$_{Bn}$), 7.14 (d, 2H, *J* = 8.2, C*H*$_{Ar,tosyl}$), 7.22-7.41 (m, 15 H, C*H*$_{Ar,Bn}$), 7.76 (d, 2H, *J* = 8.2, CH$_{Ar,tosyl}$) ppm.

^{13}C nmr (CDCl$_3$) δ 14.0 (OCH$_2$*C*H$_3$), 21.5 (Ar*C*H$_3$), 43.3 (*C*H$_2$C=O), 62.4 (O*C*H$_2$CH$_3$), 68.9 (C-6), 72.3 (C-2), 73.2, 75.0, 75.5 (*C*H$_{2Bn}$), 76.8 (C-4, C-5), 84.6 (C-3), 86.9 (C-1), 127.4, 127.5, 127.7, 127.8, 128.1, 128.3, 129.5 (C$_{Ar}$), 135.8, 138.1, 138.6, 143.5 (4° C$_{Ar}$), 171.5 (*C*=O) ppm.

Anal. calc'd. for $C_{38}H_{43}O_9NS$: C, 66.16; H, 6.28; N, 2.03; found: C, 65.84; H, 6.17; N, 2.00.

(4a_R_, 6_R_, 7_R_, 8_S_, 8a_R_)-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7,8-bis(benzyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (4e).

Hydrolysis of ester **3b** (1.19 g, 1.77 mmol) was performed as described above, using THF as cosolvent, to give a sodium salt. The salt was dissolved in dry pyridine (30 mL), and a solution of benzoic anhydride (0.50 g, 2.21 mmol) in pyridine (6 mL) was added. The mixture was stirred at 23 °C for 3.5 h. Water was then added to obtain a clear solution, which was stirred for 30 min more. The solution was evaporated, the residue was dissolved in ether (100 mL) and washed with water (30 mL), 1 M aqueous HCl (2 × 15 mL) and saturated $NaHCO_3$ (2 × 15 mL). The thick oil which was obtained on evaporation of the dried solution was dissolved in a small amount of 3:1 hexanes:EtOAc and applied to dry silica gel (4 cm × 5.5 cm) in a fritted funnel. Portionwise elution (1:0 → 3:1 hexanes:EtOAc) afforded 0.96 g of a chromatographically homogeneous oil. This material was crystallized from di(isopropyl)ether with vigorous scratching, yielding **4e** (0.89 g, 80%).

mp 85-86 °C.

$[\alpha]_D^{25}$ = +26.1° (c 0.66, $CHCl_3$).

^{1}H nmr (DMSO-d_6, 383 K) δ 3.63-3.72 (m, 4H, H-6, H-7, H-9, H'-9), 4.09 (dd, 1H, *J* = 9.5, *J* = 8.0, H-8), 4.40 (d, 1H, *J* = 16.5, H-3), 4.46 (dd, 1H, *J* = 9.5, *J* = 8.1, H-8a), 4.47 (d, 1H, *J* = 12.2, C*H*$_{Bn}$), 4.49 (d, *J* = 16.5, H-3'), 4.51 (d, 1H, *J* = 12.2, C*H*$_{Bn}$), 4.59 (d, 1H, *J* = 11.3, C*H*$_{Bn}$), 4.77 (app. d, 2H, $J_{app.}$ = 11.6, 2 × C*H*$_{Bn}$), 4.88 (d, 1H, *J* = 11.4, C*H*$_{Bn}$), 4.99 (d, 1H, *J* = 9.5, H-4a), 5.15 (d, 1H, *J* = 12.7, C*H*$_{CBz}$), 5.21 (1H, d, *J* = 12.7, C*H*$_{CBz}$), 7.29 (m, 20H, C*H*$_{Ar}$) ppm.

^{13}C nmr (DMSO-d_6, 383 K) δ 43.7 (C-3), 66.8 (*C*H$_{2CBz}$), 68.4 (C-9), 72.0 (C$_{Bn-9}$), 73.2 (C$_{Bn-8}$), 73.4 (C$_{Bn-7}$), 76.2 (C-8a), 76.3 (C-6), 77.5 (C-7), 80.0 (C-4a), 80.7 (C-8), 126.7, 126.8, 126.9, 127.2, 127.5, 127.6 (C$_{Ar}$), 135.6 (4° C$_{CBz}$), 137.6, 137.7 (4° C$_{Bn}$), 154.1 (*C*=O$_{CBz}$), 167.1 (*C*=O$_{oxazinone}$) ppm.

Anal. calc'd. for $C_{37}H_{37}NO_8$: C, 71.25; H, 5.98; N, 2.25; found: C, 71.20; H, 5.96; N 2.21.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-4-(*p*-toluenesulfonyl)-6-(benzyloxy)methyl-7,8-bis(benzyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (4f).

As previously described, tosylate **3c** (1.01 g, 1.47 mmol) was hydrolysed to afford a sodium salt. The crude salt was dissolved in pyridine (20 mL), and acetic anhydride (0.15 mL, 1.6 mmol) was added. After 1 h, water (25 mL) was added, and the mixture was stirred for 10 min to destroy excess anhydride. The solution was poured into diethyl ether (60 mL), the phases were separated, and the organic layer was washed with 1 M aqueous HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (15 mL). Concentration of the dried solution and chromatography of the residue (hexanes:EtOAc 3:1) gave **4f** (431 mg, 44%).

mp 49-53 °C.

$[\alpha]_D^{25}$ = +39.2° (c 0.5, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 2.41 (s, 3H, ArC*H*$_3$), 3.66 (m, 1H, H-6), 3.74 (m, 3H, H-7, H-9, H-9'), 3.86 (dd, 1H, *J* = 9.3, *J* = 8.2, H-8), 4.00 (d, 1H, *J* = 17.0, H-3), 4.08 (dd, 1H, *J* = 9.4, *J* = 9.3, H-8a), 4.47 (d, 1H, *J*=17.0, H-3'), 4.48 (d, 1H, *J* = 12.2, C*H*$_{Bn}$), 4.53 (d, 1H, *J* = 10.8, C*H*$_{Bn}$), 4.58 (d, 1H, *J* = 12.2, C*H*$_{Bn}$), 4.74 (d, 1H, *J* = 10.9, C*H*$_{Bn}$), 4.82 (d, 1H, *J* = 9.4, H-4a), 4.84 (d, 1H, *J* = 10.8, C*H*$_{Bn}$), 4.94 (d, 1H, *J* = 10.9, C*H*$_{Bn}$), 7.41 (m, 2H, C*H*$_{Ar,tosyl}$), 7.26-7.35 (m, 15H, C*H*$_{Ar,Bn}$), 7.76 (d, 2H, *J* = 8.3, CH$_{Ar,tosyl}$) ppm.

^{13}C nmr ($CDCl_3$) δ 21.5 (Ar*C*H$_3$), 44.9 (C-3), 68.1 (C-9), 73.5, 75.2, 75.4 (Ar*C*H$_2$), 77.0 (C-7), 77.4 (C-6), 77.5 (C-8a), 81.7 (C-4a), 82.1 (C-8), 127.7, 127.7, 127.8, 127.8, 127.9, 128.1, 128.3, 128.4, 129.8 (C$_{Ar}$), 135.5, 137.4, 137.6, 137.7, 144.6 (4° C$_{Ar}$), 166.3 (*C*=O) ppm.

Anal. calc'd. for $C_{36}H_{37}O_8NS$: C, 67.16; H, 5.79; N, 2.17; found: C, 67.14; H, 5.76; N, 2.17.

(3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-methyl-4-(benzyloxycarbonyl)-6-(pivaloyloxy)methyl-7,8-bis(pivaloyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (5a).

A solution of oxazinone **4d** (242.3 mg, 0.4 mmol) in THF (4.5 mL) and HMPA (0.5 mL) was cooled to -95°C. A solution of LiHMDS in THF (1 M, 440 μL, 0.440 mmol) was added. The mixture was stirred at -95°C for 1 h, then methyl iodide (250 μL, 4.02 mmol) was added. After 1.5 h the reaction was quenched by pouring into water (15 mL). The aqueous layer was extracted with diethyl ether (2 × 15 mL). The ether layers were combined, washed with water (2 × 10 mL), dried, and evaporated to provide an oil. Chromatography (4:1 hexanes:EtOAc) afforded **5a** (131.5 mg, 57%, de > 98%) as a glassy solid, as well as unreacted **4d** (18.5 mg). The product yield reflects the amount of recovered **4d**.

An analytical sample had mp 152-153°C.

$(\alpha)_D^{25}$ = +53.4° (c 0.50, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.16, 1.20, 1.22 (3 × s, 9H, C(CH_3)$_3$), 1.64 (d, 3H, *J* = 7.6, CH_3), 3.86 (ddd, 1H, *J* = 10.1, *J* = 4.5, *J* = 1.7, H-6), 4.10 (dd, 1H, *J* = 4.5, *J* = 12.6, H-9), 4.19 (dd, 1H, *J* = 1.7, *J* = 12.6, H-9′), 4.31 (dd, 1H, *J* = 9.6, *J* = 10.0, H-8a), 4.95 (d, 1H, *J* = 9.6, H-4a), 4.97 (q, 1H, *J* = 7.6, H-3), 5.18 (dd, 1H, *J* = 8.9, *J* = 10.1, H-7), 5.20 (m, 2H, CH_{2Cbz}), 5.45 (dd, 1H, *J* = 10.0, *J* = 8.9, H-8), 7.35-7.45 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 19.8 (CH_3), 27.1, 27.1 (C(*C*H_3)$_3$), 38.8, 38.9 (*C*(CH_3)$_3$), 52.5 (C-3), 61.4 (C-9), 67.9 (C-7), 68.5 (*C*H_{2Cbz}), 71.3 (C-8), 73.3 (C-8a), 74.9 (C-6), 80.7 (C-4a), 128.0, 128.6, 128.7 (C_{Ar}), 135.3, (4° C_{Ar}), 154.5 (*C*=O_{CBz}), 168.4 (*C*=$O_{oxazinone}$), 176.5, 177.0, 177.8 (*C*=O_{piv}) ppm.

Anal. calc'd. for $C_{32}H_{45}NO_{11}$: C, 62.02; H, 7.32; N, 2.26; found: C, 62.07; H, 7.43; N, 2.22.

(3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-Methyl-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7,8-bis(benzyloxy)-6H-pyrano[3,2-b]-1, 4-oxazin-2-one (5b)

Oxazinone **4e** (1.00 g, 1.60 mmol) in HMPA/THF (20% v/v, 5 mL) was cooled to -100 °C. A 1 M solution of LiHMDS in THF (2.00 mL, 2.00 mmol) was added, followed 2 minutes later by CH_3I (1.00 mL, 16.0 mmol). The reaction temperature was maintained between -100 and -70 °C for 2.5 h. The reaction was quenched with water (50 mL), and the product was extracted with ether (200 mL). The organic layer was washed with water (5 × 50 mL), and brine (50 mL), dried and concentrated. Chromatography (2:1 → 3:5 hexanes:ether) provided **5b** (0.56 g, 56%). The diastereomeric excess was 92%, by ^{1}H nmr integration.

An analytical sample recrystallized from ether/pentane had m.p. 83-84.5 °C.

$(\alpha)_D^{25}$ = +38.4° (c 0.61, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.65 (d, 3H, *J* = 7.6, CH_3 **5b**), 1.83 (d, CH_3 ***epi*-5b**), 3.60 (m, 1H, H-6), 3.71 (m, 2H, H-9, H-9′), 3.80 (dd, 1H, *J* = 10.0, *J* = 8.0, H-7), 3.88 (dd, 1H, *J* = 8.0, *J* = 9.5, H-8), 4.34 (dd, 1H, *J* = 9.6, *J* = 9.5, H-8a), 4.46 (d, 1H, *J* = 12.1, CH_{Bn}), 4.50 (d, 1H, *J* = 10.8, CH_{Bn}), 4.59 (d, 1H, *J* = 12.1, CH_{Bn}), 4.78 (d, 1H, *J* = 10.9, CH_{Bn}), 4.79 (d, 1H, *J* = 9.6, H-4a), 4.83 (d, 1H, *J* = 10.8, CH_{Bn}), 4.98 (br q, 1H, *J* = 7.6, H-3), 5.02 (d, 1H, *J* = 10.9, CH_{Bn}), 5.16 (d, 1H, *J* = 12.2, CH_{CBz}), 5.21 (d, 1H, *J* = 12.2, CH_{CBz}), 7.10-7.15 (m, 2H, CH_{Ar}), 7.25-7.40 (m, 18H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 19.5 (*C*H_3), 52.3 (C-3), 67.7 (C-9), 68.2 (*C*H_{2CBz}), 73,4, 75.3, 75.5 (*C*H_{2Bn}), 76.3 (C-8a), 77.4 (C-6), 77.5 (C-7), 80.5 (C-4a), 82.5 (C-8), 127.7, 127.9, 127.9, 128.1, 128.3, 128.4, 128.4, 128.5, 128.6 (C_{Ar}), 135.4 (4° C_{CBz}), 137.5, 137.6, 137.8 (4° C_{Bn}), 154.8 (*C*=O_{CBz}), 169.4 (C=$O_{oxazinone}$) ppm.

Anal. calc'd. for $C_{38}H_{39}0_8N$: C, 71.57; H, 6.16; N, 2.20; found: C, 71.64; H, 6.35; N, 2.19.

(3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-allyl-4-(benzyloxycarbonyl)-6-(pivaloyloxy)methyl-7,8-bis(pivaloyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one, (7a) and (3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3,3-diallyl-4-(benzyloxycarbonyl)-6-(pivaloyloxy)methyl-7,8-bis(pivaloyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one, (8a)

Oxazinone **4d** (91 mg, 0.15 mmol) was dissolved in THF (1 mL). Allyl bromide (130 μL, 1.5 mmol) was added and the solution cooled to −80°C. A solution of LiHMDS in hexanes (1 M, 225 μL,.0.225 mmol) was added. The mixture was stirred for one hour, but no reaction was observed. HMPA (150 μL) was added to the vigorously stirred solution and the reaction was allowed to proceed for 20 min. The flask was removed from the cooling bath, buffer (2 mL) was added, followed by diethyl ether (5 mL). The solution was poured into ether (15 mL) and the phases were separated. The organic layer was washed with water (3 × 2 mL), dried and

evaporated. Column chromatography (9:1 hexanes:EtOAc) yielded **8a** (25.1 mg, 25%), **7a** (22 mg, 23.2%, de >98%) and unreacted **4d** (2.2 mg). The product yields reflect the amount of recovered **4d**.

7a: An analytical sample had mp 131-133°C.

$(\alpha)_D^{25}$ = +78.0° (c 0.50, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.16, 1.19, 1.22 (3 × s, 9H, C(CH_3)$_3$), 2.70 (m, 2H, CH_{2allyl}) 3.86 (m, 1H, H-6), 4.08 (dd, 1H, *J* = 4.2, *J* = 12.5, H-9), 4.19 (dd, 1H, *J* = 1.9, *J* = 12.5, H-9′), 4.37 (dd, 1H, *J* = 9.6, *J* = 10.0, H-8a), 4.90 (m, 1H, H-3), 4.95 (d, 1H, *J* = 9.6, H-4a), 5.20 (m, 5H, H-7, CH_{2Cbz}, CH_{2vinyl}), 5.44 (dd, 1H, *J* = 10.0, *J* = 8.9, H-8), 5.82 (dddd, 1H, *J*=7.3, 7.3, 10.1, 16.8, CH_{vinyl}), 7.35-7.45 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 27.0, 27.1 (C(CH_3)$_3$), 38.3 (CH_{2allyl}), 38.8, 38.9 ($C(CH_3)_3$), 56.7 (C-3), 61.2 (C-9), 67.8 (C-7), 68.5 (CH_{2Cbz}), 71.3 (C-8), 73.1 (C-8a), 74.8 (C-6), 80.7 (C-4a), 119.8 (CH_{2vinyl}), 127.9, 128.5, 128.6 (C_{Ar}), 131.5 (CH_{vinyl}), 135.3 (4° C_{Ar}), 154.8 (C=O_{Cbz}), 167.3 (C=$O_{oxazinone}$), 176.4, 176.9, 177.8 (C=O_{piv}) ppm.

Anal. calc'd. for $C_{34}H_{47}NO_{11}$: C, 63.24; H, 7.34; N, 2.17; found: C, 63.12; H, 7.46; N, 2.08.

8a: An analytical sample had mp 137.5-138.5°C.

$(\alpha)_D^{25}$ = +54.4° (c 0.32, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.13, 1.18, 1.22 (3 × s, 9H, C(CH_3)$_3$), 2.67 (dd, 1H, *J* = 13.6, *J* = 8.6, $CH_{\beta allyl}$), 2.84 (ddd, 1H, *J* = 14.3, *J* = 5.6, *J* = 1.5, $CH_{\alpha allyl}$), 3.15 (ddd, 1H, *J* = 13.6, *J* = 6.4, *J* = 1.0, $CH_{\beta allyl}$), 3.35 (dd, 1H, *J* = 14.3, *J* = 8.9, $CH_{\alpha allyl}$), 3.70 (ddd, 1H, *J* = 10.0, *J* = 3.0, *J* = 2.5, H-6), 3.95 (m, 2H, H-9), 4.23 (dd, 1H, *J* = 9.3, *J* = 10.0, H-8a), 4.80 (d, 1H, *J* = 9.3, H-4a), 4.94-5.06 (m, 2H, $CH_{2\alpha vinyl}$), 5.14 (dd, 1H, *J* = 8.9, *J* = 10.0, H-7), 5.12 (d, 1H, *J* = 12.1, CH_{CBz}), 5.22 (d, 1H, *J* = 12.1, CH_{CBz}), 5.18-5.26 (m, 2H, $CH_{2\beta vinyl}$), 5.37 (dd, 1H, *J* = 10.0, *J* = 8.9, H-8), 5.45 (dddd, 1H, *J* = 5.6, *J* = 8.9, *J* = 10.4, *J* = 16.7, $CH_{\alpha vinyl}$), 5.89 (dddd, 1H, *J* = 6.4, *J* = 8.6, *J* = 10.5, *J* = 17.0, $CH_{\beta vinyl}$), 7.35-7.45 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 27.0, 27.1 (C(CH_3)$_3$), 38.7, 38.9 ($C(CH_3)_3$), 42.1, 43.5 (CH_{2allyl}), 60.9 (C-9), 67.6 (C-7), 67.9 (CH_{2Cbz}), 69.8 (C-3), 71.2 (C-8), 72.4 (C-8a), 74.2 (C-6), 80.4 (C-4a), 120.5, 120.7 (CH_{2vinyl}), 128.2, 128.5, 128.6 (C_{Ar}), 131.3, 132.5, (CH_{vinyl}), 135.5 (4° C_{Ar}), 154.1 (C=O_{CBz}), 169.6 (C=$O_{oxazinone}$), 176.3, 177.04, 177.7 (C=O_{piv}) ppm.

Anal. calc'd. for $C_{37}H_{51}NO_{11}$: C, 64.80; H, 7.50; N, 2.04; found: C, 64.75; H, 7.65; N, 2.00.

(3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-Allyl-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis(benzyloxy)-6H-pyrano[3,2-b]-1, 4-oxazin-2-one (7b) and (4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3,3-di(allyl)-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis(benzyloxy)-6H-pyrano[3,2-b]-1, 4-oxazin-2-one (8b).

Oxazinone **4e** (0.25 g, 0.40 mmol) in HMPA/THF (20% v/v, 5 mL) was cooled to -100 °C. A 1 M solution of LiHMDS (0.54 mL, 0.54 mmol) was added, followed by allyl bromide (0.35 mL, 4.0 mmol) 2 min later. The reaction was allowed to warm gradually from -100 to -78 °C. After 2.5 h the reaction was quenched with water (15 mL), and the product was extracted into ether (50 mL). The organic phase was washed with water (5 × 15 mL) and brine (15 mL), then dried and concentrated. The residual oil was chromatographed (2:1 hexanes: ether) to obtain **7b** (0.07 g, 26%), and **8b** (0.07 g, 25%).

7b: $(\alpha)_D^{25}$ = +29.9° (c 0.66, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 2.71 (m, 2H, CH_{2allyl}), 3.58-3.65 (br m, 1H, H-6), 3.71-3.78 (br m, 2H, H-9, H-9′), 3.84 (dd, 1H, J = 10.4, J = 7.7, H-7), 3.91 (dd, 1H, J = 7.7, J = 9.8, H-8), 4.40 (dd, 1H, J = 9.2, J = 9.8, H-8a), 4.51 (d, 1H, J = 12.1, CH_{Bn}), 4.57 (d, 1H, J = 10.7, CH_{Bn}), 4.62 (d, 1H, J = 12.1, CH_{Bn}), 4.80 (d, 1H, J = 10.9, CH_{Bn}), 4.82 (d, 1H, J = 9.2, H-4a), 4.88 (d, 1H, J = 10.8, CH_{Bn}), 4.97 (m, 1H, H-3), 5.05 (d, 1H, J = 10.9, CH_{Bn}), 5.19 (d, 1H, J = 12.3, CH_{Bn}), 5.23 (d, 1H, J = 12.3, CH_{Bn}), 5.25 (br m, 2H, CH_{2vinyl}), 5.83-5.92 (m, 1H, CH_{vinyl}), 7.15 (m, 2H, CH_{Ar}), 7.30 (m, 18H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$)[22] δ 37.4 (CH_{2allyl}), 56.4 (C-3), 68.0 (C-9), 68.2 (C_{CBz}), 72.7, 75.0, 77.0 (C_{Bn}), 76.1 (C-8a), 77.3 (C-6), 77.5 (C-7), 80.3 (C-4a), 82.0 (C-8), 119.4 (CH_{2vinyl}), 128.1 (C_{Ar}), 131.9 (CH_{vinyl}) ppm.

Anal. calc'd. for $C_{40}H_{41}O_8N$: C, 72.38; H, 6.23; N, 2.11. Found: C, 72.61; H, 6.46; N, 2.24.

8b: $[\alpha]_D^{25}$ = +30.2° (c 1.43, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 2.80 (m, 1H, $CH_{\beta allyl}$), 2.93 (m, 1H, $CH_{\alpha allyl}$), 3.11 (br dd, 1H, $CH_{\beta allyl}$), 3.38-3.52 (m, 3H, $CH_{\alpha allyl}$, H-6, H-9), 3.61 (dd, 1H, J = 11.0, J = 3.5, H-9′), 3.74-3.85 (m, 2H, H-7, H-8), 4.26 (dd, 1H, J = 9.3, J = 9.0, H-8a), 4.41 (d, 1H, J = 12.1, CH_{Bn}), 4.52 (2 × d, 2H, $J \cong$ 10.8, 2 × CH_{Bn}), 4.65 (d, 1H, J = 9.2, H-4a), 4.75 (d, 1H, J = 10.9, CH_{Bn}), 4.82 (d, 1H, J = 10.9, CH_{Bn}), 5.01-5.10 (m, 5H, $CH_{2\alpha vinyl}$, 3 × CH_{Bn}), 5.20-5.26 (br m, 2H, $CH_{2\beta vinyl}$), 5.45-5.58 (m, 1H, $CH_{\alpha vinyl}$), 5.84-5.98 (m, 1H, $CH_{\beta vinyl}$), 7.30 (m, 20H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 41.4, 43.6 (CH_{2allyl}), 67.7 (C-9), 68.0 (CH_{2CBz}), 68.9 (C-3), 73.3, 75.2, 75.5 (CH_{2Bn}), 76.6 (C-8a), 77.2 (C-7), 77.5 (C-6), 80.4 (C-4a), 82.6 (C-8), 120.2, 120.5 (CH_{2vinyl}), 127.6, 127.8, 127.9, 128.2, 128.2, 128.3, 128.3, 128.4, 128.4, 128.4 (C_{Ar}), 131.8, 132.2 (CH_{vinyl}), 135.7 (4° C_{CBz}), 137.7, 137.9, 138.0 (4° C_{Bn}), 154.3 (C=O_{CBz}), 170.1 (C=$O_{oxazinone}$) ppm.

Anal. calc'd. for $C_{43}H_{45}O_8N$: C ,73.38; H, 6.45; N, 1.99; found: C, 73.25; H, 6.38; N, 1.97.

Allylation of 4e under Conditions "D".

Oxazinone **4e** (100 mg, 0.16 mmol), TMEDA (34 μL, 0.24 mmol) and HMPA (300 μL) were dissolved in THF (1 mL) and cooled to -80 °C. A solution of LiHMDS in hexanes (1.09 M, 160 μL, 0.17 mmol) was added. After stirring the solution at -80 °C for 20 minutes, allyl bromide (17 μL, 0.19 mmol) was added. After 30 min, the cooling bath was removed, the reaction was warmed to room temperature over 5 min, and then quenched with buffer (2 mL). After dilution with diethyl ether (20 mL), the phases were separated, and the organic layer was washed with water (4 × 2 mL) and brine (2 mL). The dried ether solution was concentrated, and chromatography of the residue afforded **8b** (18 mg, 18%), **7b** (18 mg, 18%), and **4e** (7.7 mg). The yields reflect the amount of recovered **4e**.

Allylation of 4e under Conditions "E", giving some (3*R*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-allyl-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis(benzyloxy)-6H-pyrano[3,2-b]-1, 4-oxazin-2-one (*epi*-7b)

A mixture of **4e** (100 mg, 0.16 mmol) and TMEDA (26 μL, 0.19 mmol) in THF (1.0 mL) was cooled in a dry ice/acetone bath. Allyl bromide (16 μL, 0.19 mmol) was added, followed by dropwise addition of a solution of LiHMDS in hexanes (1 M, 180 μL, 0.18 mmol). The solution was stirred for 10 min at -65 °C, and then HMPA (100 μL) was added while maintaining vigorous stirring. The temperature was held at -65 °C for 17 min more, and then allowed to rise to -20 °C over 1 h. The reaction was quenched with pH 7 buffer (1 mL) and then brought to room temperature. After diluting with diethyl ether (20 mL), the phases were separated, and the organic layer was washed with water (3 × 2 mL) and brine (2 mL). The dried solution was concentrated

and the residue was chromatographed (9:1 → 3:1 hexanes:EtOAc) to give **8b** (19 mg, 19%), **7b** + ***epi*-7b** (32 mg, 33%) and **4e** (9.6 mg). The yields reflect the amount of recovered **4e**. The ratio of **7b**:***epi*-7b** was 7.5:1.0. One fraction containing pure ***epi*-7b** allowed this material to be identified by ^{1}H nmr analysis.

^{1}H nmr ($CDCl_3$) δ 3.02-3.19 (m, 2H, CH_{2allyl}), 3.55 (ddd, 1H, *J* = 9.5, *J* = 3.6, *J* = 2.1, H-6), 3.66 (dd, 1H, *J* = 2.1, *J* = 11.0, H-9), 3.70 (dd, 1H, *J* = 3.6, *J* = 11.0, H-9'), 3.79 (dd, 1H, *J* = 8.4, *J* = 9.5, H-7), 3.86 (dd, 1H, *J* = 9.0, *J* = 8.4, H-8), 4.26 (dd, 1H, *J* = 9.7 , H-8a), 4.34 (dd, 1H, *J* = 6.1, *J* = 7.7, H-3), 4.45 (d, 1H, *J* = 12.1, CH_{Bn}), 4.45 (d, 1H, *J* = 10.7, CH_{Bn}), 4.60 (d, 1H, *J* = 12.1, CH_{Bn}), 4.77 (d, 1H, *J* = 11.0, CH_{Bn}), 4.82 (d, 1H, *J* = 10.7, CH_{Bn}), 4.83 (d, 1H, *J* = 9.7, H-4a), 5.00 (d, 1H, *J* = 11.0, CH_{Bn}), 5.11 (d, 1H, *J* = 12.3, CH_{CBz}), 5.14 (d, 1H, *J* = 12.3, CH_{CBz}), 5.15 (m, 1H, CH_{Evinyl}), 5.20 (m, 1H, CH_{Zvinyl}), 5.85 (m, 1H, CH_{vinyl}), 7.05-7.10 (m, 2H, CH_{Ar}), 7.20-7.40 (m, 18H, CH_{Ar}) ppm.

Allylation of 4d under Conditions "F".

Following the procedure of Pietzonka and Seebach,[14b] oxazinone **4d** (30 mg, 0.05 mmol) in THF (0.5 mL) was treated with allyl bromide (13 μL, 0.15 mmol) and a solution of P4 base in hexanes (0.055 mmol). Chromatography (6:1 hexanes:EtOAc) of the crude product gave **8a** (16.4 mg, 52.7%), **7a** (5.8 mg, 16.7%, de >98%) and recovered **4d** (2.5 mg). Product yields reflect the amount of recovered **4d**.

Allylation of 4e under Conditions "F".

Following the procedure of Pietzonka and Seebach,[14b] oxazinone **4e** (100 mg, 0.16 mmol) in THF (0.8 mL) was treated with allyl bromide (41 μL, 0.47 mmol) and a solution of P4 base in hexanes (0.175 mmol). Chromatography (9:1 → 3:1 hexanes:EtOAc) afforded **8b** (27.3 mg, 31%), **7b** (32.1 mg, 39%, d.e. >98%), and unreacted **4e** (21.6 mg). The product yields reflect the amount of recovered **4e**.

(3*S*, 4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3-ethyl-4-(benzyloxycarbonyl)-6-(pivaloyloxy)methyl-7,8-bis(pivaloyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (9) and (4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-3,3-diethyl-4-(benzyloxycarbonyl)-6-(pivaloyloxy)methyl-7,8-bis(pivaloyloxy)-6H-pyrano[3,2-b]-1,4-oxazin-2-one (10).

Following the procedure of Pietzonka and Seebach,[14b] oxazinone **4d** (60 mg, 0.1 mmol) and ethyl bromide (37 μL, 0.5 mmol) were dissolved in THF (1.0 mL) and cooled to -95°C. P4 base (0.1 mmol) was added. Chromatography (6:1 hexanes:EtOAc) yielded **9** (27.5 mg, 48%, d.e. > 98%), **10** (13.4 mg, 22%) and unreacted **4d** (5 mg). Yields reflect the amount of recovered **4d**.

9: mp 137-139 °C.

$(\alpha)_D^{25}$ = +44.4° (c 0.64,$CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 1.10 (tr, 3H, *J* = 7.4, CH_2CH_3), 1.16, 1.19, 1.21 (3 × s, 9H, $C(CH_3)_3$), 1.96 (m 2H, CH_2CH_3), 3.86 (br m, 1H, H-6), 4.06 (dd, 1H, *J* = 4.4, *J* = 12.5, H-9), 4.21 (dd, 1H, *J* = 1.8, *J* = 12.5, H-9'), 4.31 (dd, 1H, *J* = 9.6, *J* = 10.0, H-8a), 4.79 (br m, 1H, H-3), 4.96 (d, 1H, *J* = 9.6, H-4a), 5.20 (m, 3H, H-7, CH_{2Cbz}), 5.45 (dd, 1H, *J* = 10.0, *J* = 8.9, H-8), 7.30-7.45 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 10.6 (CH_2CH_3), 27.0, 27.1 ($C(CH_3)_3$), 27.4 (CH_2CH_3), 38.8, 38.9 ($C(CH_3)_3$), 58.2 (C-3), 61.3 (C-9), 67.9 (C-7), 68.5 (CH_{2Cbz}), 71.4 (C-8), 73.1 (C-8a), 74.8 (C-6), 80.9 (C-4a), 127.9, 128.5, 128.7 (CH_{Ar}), 135.3 (4° C_{Ar}), 155.0 ($C{=}O_{Cbz}$), 167.7 ($C{=}O_{oxazinone}$), 176.4, 176.9, 177.8 ($C{=}O_{piv}$) ppm.

Anal. calc'd. for $C_{33}H_{47}NO_{11}$: C, 62.54; H, 7.48; N, 2.21; found: C, 62.03; H, 7.47; N, 2.11.

10: mp 93-95 °C.

$[\alpha]_D^{25} = +36.76°$ (c 0.34, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ0.66 (t, 3H, *J*=7.5, CH_2CH_3), 1.04 (t, 3H, *J*=7.5, CH_2CH_3), 1.14, 1.20, 1.22 (3 × s, 9H, $C(CH_3)_3$), 2.10 (m 2H, CH_2CH_3), 2.25 (m 1H, CH_2CH_3), 2.55 (m 1H, CH_2CH_3), 3.75 (ddd, 1H, *J* = 10.0, *J* = 3.2, *J* = 5.7, H-6), 3.96 (m, 2H, H-9, H-9′), 4.14 (dd, 1H, *J* = 9.3, *J* = 9.9, H-8a), 4.91 (d, 1H, *J* = 9.3, H-4a), 5.18 (m, 3H, H-7, CH_{2Cbz}), 5.41 (dd, 1H, *J* = 9.9, *J* = 9.0, H-8), 7.30-7.40 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ 8.9, 9.9 (CH_2CH_3), 27.0, 27.1 ($C(CH_3)_3$), 30.7, 32.9 (CH_2CH_3), 38.8, 38.9 ($C(CH_3)_3$), 61.1 (C-9), 67.7 (C-7), 67.9 (CH_{2Cbz}), 71.3, 71.4 (C-8, C-3), 72.7 (C-8a), 74.4 (C-6), 81.0 (C-4a), 128.3, 128.5, 128.6 (CH_{Ar}), 135.6 (4° C_{Ar}), 154.2 (C=O_{Cbz}), 170.0 (C=$O_{oxazinone}$), 176.4, 177.1, 177.8 (C=O_{piv}) ppm.

Anal. calc'd. for $C_{35}H_{51}NO_{11}$: C, 63.52; H, 7.77; N, 2.12; found: C, 63.78; H, 8.00; N, 2.04.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-2-*t*-Butyldimethylsilyloxy-4-(benzyloxycarbonyl)-6-(pivaloyloxy)methyl-7, 8-bis(pivaloyloxy)-4*H*, 6*H*-(4a, 7, 8, 8a)-tetrahydro)pyrano[3,2-b]-1,4-oxazine (11a).

Oxazinone **4d** (100 mg, 0.17 mmol) was dissolved in THF (1 mL), and TBDMSCl (29.8mg, 0.198 mmol) in THF (0.2 mL) was added. The solution was cooled to -65°C and LiHMDS (1 M, 198 μL, 0.198 mmol) was added. Little reaction occurred over 20 min, so HMPA (0.1 mL) was added. After a further 5 min, the solution was quenched with buffer (2 mL) and diluted with diethyl ether (5 mL). The mixture was poured into ether (15 mL) and the phases were separated. The organic layer was washed with water (2×2 mL), brine (2 mL), dried and evaporated. to afford **11a**. ^{1}H nmr of the crude product showed the reaction to be essentially quantitative, with HMPA and excess silyl materials visible. Chromatography (7:1 hexanes:EtOAc) yielded **11a** (63%).

mp 122-123 °C.

$[\alpha]_D^{25} = -30.8°$ (c 0.50, $CHCl_3$).

^{1}H nmr ($CDCl_3$) δ 0.13 (s, 6H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.16, 1.18, 1.22 (3 × s, 9H, $C(CH_3)_3$), 3.85 (dd, 1H, *J* = 8.5, *J* = 10.1, H-8a), 3.85 (m, 1H, H-6), 4.11 (m, 2H, H-9, H-9′), 4.72 (d, 1H, *J* = 8.5, H-4a), 5.17 (dd, 1H, *J* = 9.0, *J* = 10.1, H-7), 5.11 (d, 1H, *J* = 12.4, CH_{CBz}), 5.27 (d, 1H, *J* = 12.4, CH_{CBz}), 5.42 (dd, 1H *J* = 10.1, *J* = 9.0, H-8), 5.81 (s, 1H, H-3), 7.30-7.40 (m, 5H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ -5.0, -4.6 ($SiCH_3$), 17.9 ($SiC(CH_3)_3$), 25.3 ($SiC(CH_3)_3$), 27.1, 27.1, 27.2 ($C(CH_3)_3$), 38.8, 38.9 ($C(CH_3)_3$), 61.6 (C-9), 67.8 (C-7), 68.0 (CH_{2Cbz}), 71.8 (C-8), 74.8 (C-6), 76.7 (C-8a), 81.2 (C-4a), 89.3 (C-3), 127.8, 128.2, 128.5 (C_{Ar}), 135.9 (4° C_{Ar}), 153.3 (C=O_{Cbz}), 147.4 (C=$O_{oxazinone}$), 176.5, 177.1, 178.0 (C=O_{piv}) ppm.

Anal. calc'd. for $C_{37}H_{58}NO_{11}Si$: C, 61.73; H, 7.98; N, 1.95; found: C, 61.47; H, 8.12; N, 1.91.

(4a*R*, 6*R*, 7*R*, 8*S*, 8a*R*)-2-(*t*-Butyldimethylsilyloxy)-4-(benzyloxycarbonyl)-6-(benzyloxy)methyl-7, 8-bis-(benzyloxy)-4*H*, 6*H*-(4a, 7, 8, 8a-tetrahydro)pyrano[3,2-b]-1,4-oxazine (11b).

A solution of **4e** (100 mg, 0.16 mmol) and TBDMSCl (26 mg, 0.172 mmol) in THF (1 mL) was cooled to -65 °C. TMEDA (25 μL, 0.175 mmol) was added, followed by a solution of LiHMDS in hexanes (1 M, 175 μL, 0.175 mmol). The mixture was stirred at -65 °C for 20 min, but no reaction was observed. HMPA (100 μL) was added dropwise to the vigorously stirred solution, and the reaction was allowed to proceed for 20 min. It was removed from the cold bath, quenched with buffer (1 mL), and diluted with diethyl ether (20 mL). The phases were separated, and the organic layer was washed with water (2 × 2 mL) and brine (2 mL). The dried

solution was evaporated to afford 125 mg of oily **11b** containing silyl byproducts and HMPA. Rapid chromatography on a short column (85:15 hexanes:EtOAc) afforded **11b** as an oil (92.4 mg, 78%).

^{1}H nmr ($CDCl_3$) δ 0.18 (s, 3H, SiCH_3), 0.19 (s, 3H, SiCH_3), 0.93 (s, 9H, SiC(CH_3)$_3$), 3.55-3.75, (m, 3H, H-6, H-9, H-9′), 3.80-3.90 (m, 3H, H-7, H-8, H-8a), 4.45 (d, 1H, J = 12.1, CH_{Bn}), 4.47 (d, 1H, J = 10.7, CH_{Bn}), 4.64 (d, 1H, J = 12.1, CH_{Bn}), 4.62 (br d, 1H, J = 7.7, H-4a), 4.79 (d, 1H, J = 11.1, CH_{Bn}), 4.82 (d, 1H, J = 10.7, CH_{Bn}), 5.01 (d, 1H, J = 11.1, CH_{Bn}), 5.14 (d, 1H, J = 12.4, CH_{CBz}), 5.23 (d, 1H, J = 12.4, CH_{CBz}), 5.81 (s, 1H, H-3), 7.10-7.15 (m, 2H, CH_{Ar}), 7.25-7.40 (m, 18H, CH_{Ar}) ppm.

^{13}C nmr ($CDCl_3$) δ -5.1, -4.5 (SiCH_3), 17.9 (SiC(CH$_3$)$_3$), 25.4 (SiC(CH_3)$_3$), 67.6 (CH_{2CBz}), 68.0 (C-9), 73.5, 75.1, 75.2 (CH_{2Bn}), 77.3 (C-6), 77.6 (C-7), 79.6 (C-8), 81.2 (C-4a), 82.7 (C-8a), 89.3 (C-3), 127.6, 127.7, 127.7, 127.8, 127.8, 128.0, 128.0, 128.3, 128.4 (C_{Ar}), 136.1, 137.9, 137.9, 138.1 (4° C_{Ar}), 147.8 (C-2), 153.4 (C=O) ppm.

Computational Experiments

Initial structures were created, and semi-empirical AM1[23] calculations were performed using SPARTAN (v. 3.1.4, Wavefunction Inc., Irvine CA, USA) on a Hewlett-Packard 9000/730 workstation. AM1-optimized structures were exported to an IBM RS-6000/590 system, and submitted to sequential *ab initio* optimizations with the STO-3G and 6-31G* basis sets, using GAUSSIAN 94.[24]

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