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Several Generations of Chemoenzymatic Synthesis of Oseltamivir (Tamiflu): Evolution of Strategy, Quest for a Process-Quality Synthesis, and Evaluation of Efficiency Metrics

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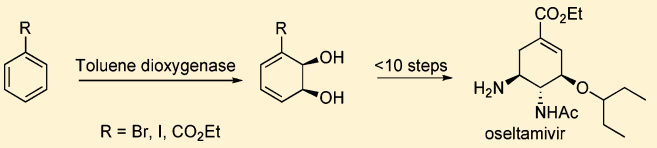
Supporting Information

ABSTRACT: Four generations of chemoenzymatic approaches to oseltamivir are presented. The first two generations relied on the use of cyclohexadiene-*cis*-diol derived enzymatically from bromobenzene. The third and fourth generation used the corresponding diol obtained from ethyl benzoate by fermentation with *E. coli* JM109(pDTG601a). Oseltamivir was obtained from ethyl benzoate by intersecting intermediate **39** (third-generation synthesis) and intermediate **45** (fourth-generation synthesis). Both of these advanced approaches benefited from symmetry considerations and translocation of the acrylate double bond with concomitant elimination of the C-1 hydroxyl. The syntheses are evaluated for overall efficiency by the use of efficiency metrics and compared with other syntheses of oseltamivir (both academic and industrial).



INTRODUCTION

Oseltamivir (**1**) is a direct precursor to the prodrug Tamiflu (**2**) administered as a phosphate. Along with other inhibitors of neuraminidase portrayed in Figure 1, it was developed based on the understanding of the mechanism of hydrolysis of sialyl glycosides. Neuraminidase is one of several essential surface glycoproteins required for the efficient replication of the virus and serves to cleave sialic acid from virions in order to avoid their aggregation, which would make further progress in replication inefficient. Thus, the mechanism-based inhibition of the neuraminidase action would constitute an effective strategy in combating influenza infections. The compounds pictured in Figure 1 all act as transition-state mimic inhibitors of glycolysis and appear to be effective to some degree in reducing the spread of infection. The mechanism of influenza infection and neuraminidase inhibition[1] as well as effective pharmaceutical approaches to drug development[2] have been reviewed on numerous occasions.

From the perspective of a synthetic chemist, oseltamivir should not present itself as a particularly challenging target. It is a relatively simple molecule, yet a particularly efficient design for its synthesis has not materialized despite numerous attempts by academic researchers.[3] The current production route employed by Roche seems to be the most efficient despite a 13-step preparation from shikimic acid, which provides the necessary chirality. Other commercial routes exist[4] and have been reviewed as well as evaluated for overall effectiveness by using green metrics.[5]

Interest in the synthesis of oseltamivir continues despite the fact that the compound seems to be less effective against recent mutations of the influenza virus.[6] Thus, new approaches to this molecule continue to appear regularly in the literature. In this paper, we report the evolution of a chemoenzymatic strategy toward oseltamivir through four generations of design. In addition, an evaluation of overall efficiency and comparison with existing syntheses is provided for the successful approaches.

RESULTS AND DISCUSSION

The first-generation approach to oseltamivir was based on the recognition that the structure represents a special case of a "dideoxy diamino" analogue of a cyclitol.[7] Given the many successful syntheses of amino cyclitols and amino inositols from cyclohexadiene-*cis*-1,2-diols[8] via further stereoselective aminations and/or hydroxylations, it seemed logical to approach oseltamivir from acetonide **10**,[9] obtained from the corresponding diol, which is produced by fermentation of bromobenzene with *E. coli* JM 109(pDTG601a) on a medium to large scale.[10] Application of Corey's protocol[11] provided the acetamido bromide **11**, which was transformed to aziridine **12**, as shown in

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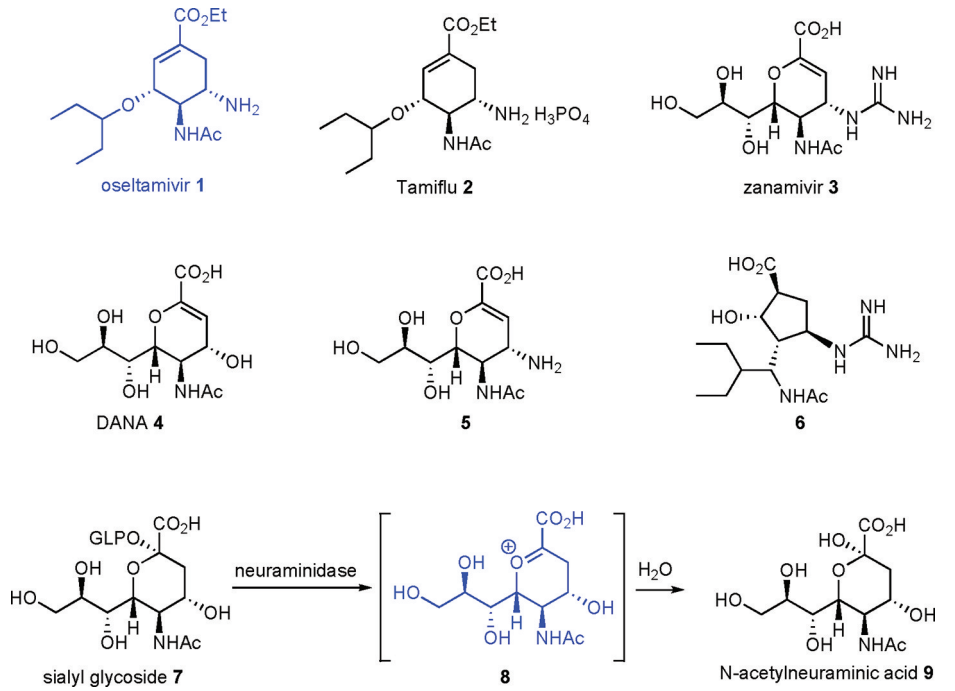
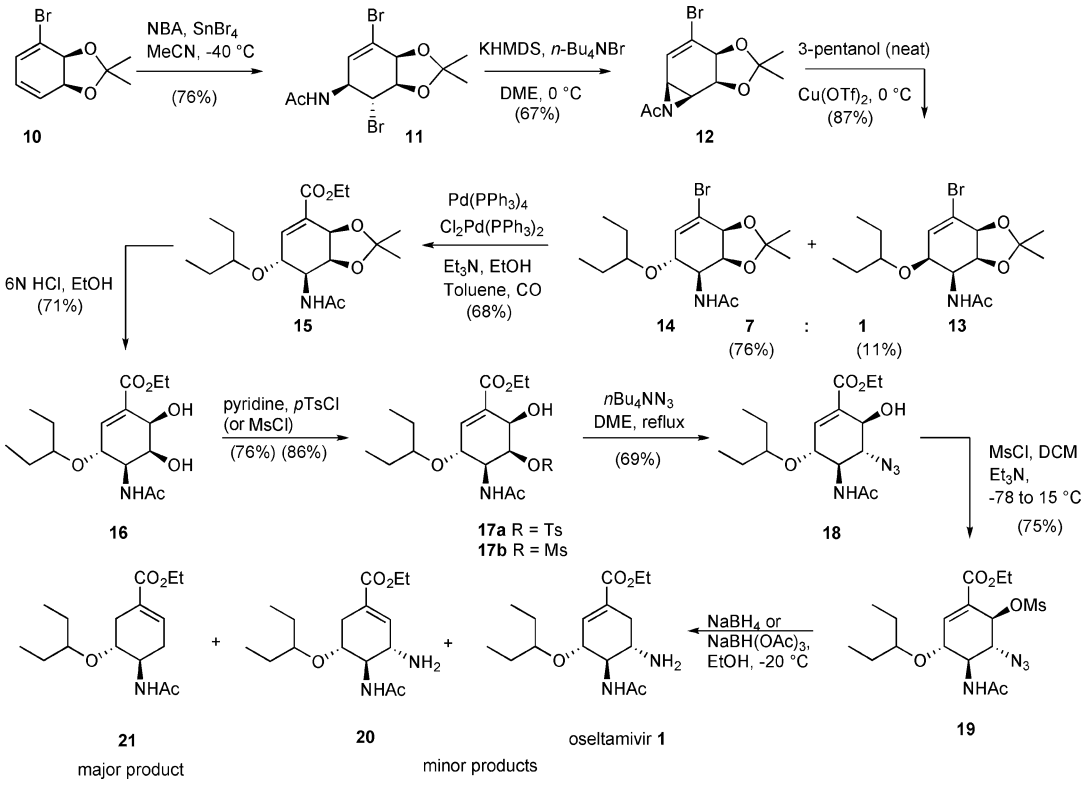


Figure 1. Oseltamivir, Tamiflu, and other neuraminidase inhibitors based on the transition state for sialyl glycoside hydrolysis.

Scheme 1. [a]



[a]Abbreviations: DCM = dichloromethane, DME = dimethoxyethane, KHMDS = potassium hexamethyldisilazane, NBA = *N*-bromoacetamide.

Scheme 1. Opening of the aziridine ring with 3-pentanol provided a 7:1 ratio of the *trans*- and *cis*-ethers **14** and **13**, respectively, in a combined yield of 87%. The major isomer **14** was subjected to palladium-catalyzed carbonylation protocol to provide the acrylate ester **15** in 68% yield. Acid-catalyzed hydrolysis yielded the free diol **16**, and a tosylation of the distal hydroxyl furnished tosylate **17a** in 76% yield. Displacement of the tosyl group with azide gave the azidohydrin **18**, which was converted to the mesylate **19** in anticipation of the reduction of azide as well as the regioselective reduction of the mesylate to oseltamivir **1**.

Unfortunately, all of our attempts to displace the mesylate group with hydride reagents resulted only in the 1,4-displacement

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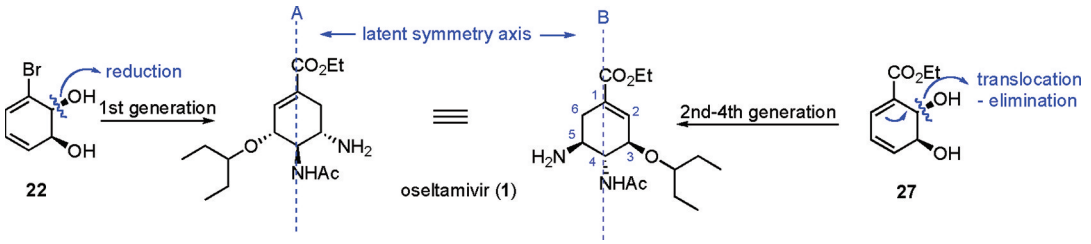
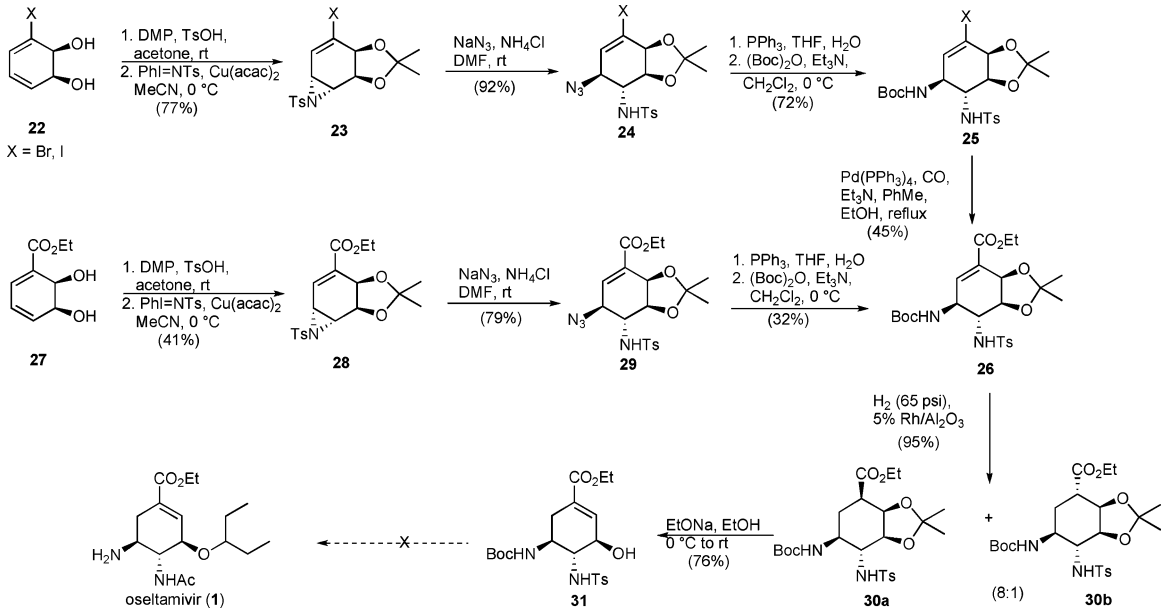


Figure 2. Symmetry analysis of oseltamivir.

Scheme 2. [a]



[a]Abbreviations: DMF = dimethylformamide, DMP = 2,2-dimethoxypropane, THF = tetrahydrofuran.

of the mesylate and the reduction of the azide. The major product of these attempts was the fully reduced compound **21**. Amine **20** was isolated as a minor product along with at best only traces of oseltamivir. On the basis of these disappointing results, the approach was abandoned, despite the fact that azide **19** was obtained in only 10 steps from bromobenzene.

The second approach to oseltamivir also began with the enzymatically derived diols **22** (X = Br or I) but would take into account observation of latent symmetry in oseltamivir. As noted above, the first-generation synthesis relied on the reductive removal of the C-2 hydroxyl. The initial observation of the 1,4-reduction of the mesylate in **19** and the concomitant translocation of the olefin ultimately led to the recognition of the latent symmetry and design of an approach that would take advantage of a more flexible introduction of the nitrogen and oxygen substituents.

Oseltamivir possesses a latent axis of functional symmetry with respect to the carboxylate and acetamido groups, as shown in Figure 2. This implies that the synthesis could start with *either* diastereomer of vinyl aziridine, which could be opened with *either* oxygen *or* nitrogen nucleophiles and lead to either representation of **1** as depicted below.

The order of introduction of nucleophiles into either aziridine **12** (Scheme 1) or **23** (Scheme 2) depends on the eventual translocation of the olefin from the initial C-1/C-6 position to C-1/C-2 placement.

The known vinyl aziridine **23**,[12] prepared in two steps from diol **22**, was treated with sodium azide to produce the vinyl azide **24**, whose Staudinger reduction followed by protection furnished the Boc-protected amine **25** in 72% yield, as shown in Scheme 2. Palladium-catalyzed carbonylation then provided the acrylate **26** in 45% yield. Comparable results were also obtained from the corresponding vinyl iodide derived from iodobenzene by fermentation.

An alternative route to this compound was also developed from diol **27**, derived enzymatically from ethyl benzoate as shown in Scheme 2. We thought that starting with ethyl benzoate, which contains the carboxylate group of oseltamivir, would avoid the carbonylation step and would ultimately be shorter that the route utilizing either bromo- or iodobenzene. However, the former route produced acrylate **26** in 23% yield as compared to an overall yield of 10% for the route from ethyl benzoate. Encouraged by the rapid access to the protected diamine **26** (seven steps from bromobenzene), we attempted the reductive removal exchange of the tosyl group. Acetylation of **26** followed by the usual sodium naphthalide detosylation was unsuccessful.

Hydrogenation of **26** provided the saturated esters **30a** and **30b** in an 8:1 ratio, and treatment of these esters with sodium ethoxide in ethanol led cleanly to the allylic alcohol **31** in 76% yield. When PtO_2 was used as a catalyst in 95% EtOH only the fully saturated alcohol resulting from the overhydrogenation of **31** was isolated in 92% yield, indicating that the collapse of

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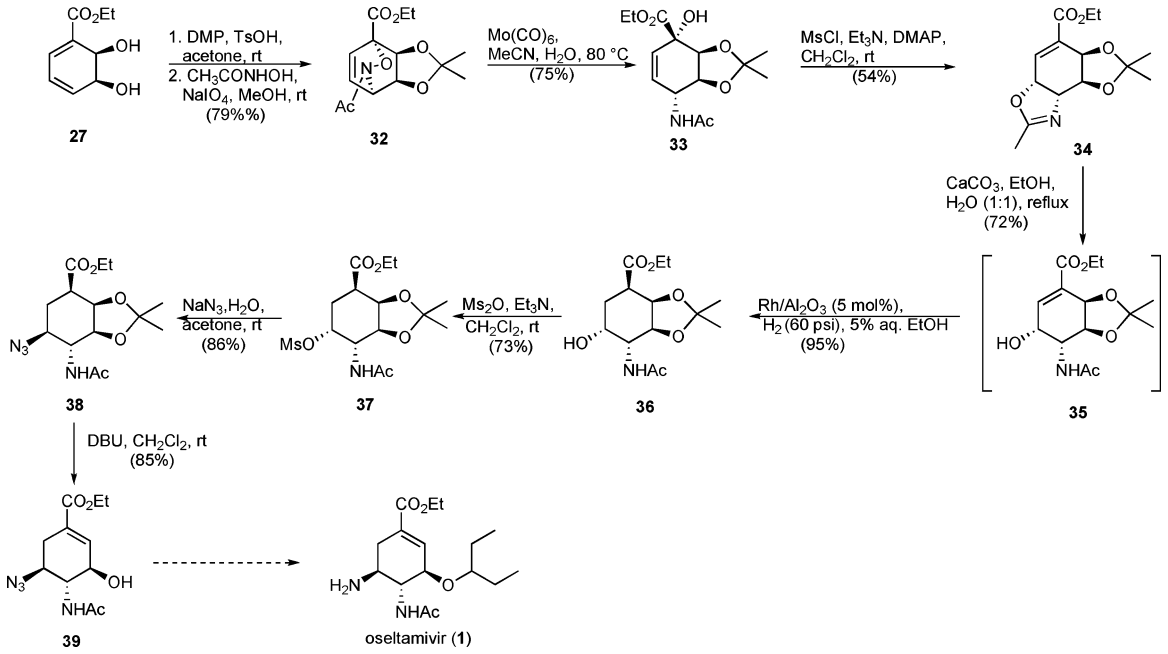
Scheme 3. [a]



[a]Abbreviations: DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-*N*,*N*-dimethylaminopyridine, DMP = 2,2-dimethoxypropane.

the acetonide occurs under these conditions. The reductive detosylation was attempted with this compound as well to no avail. In addition, attempts to alkylate **31** with various electrophilic reagents derived form 3-pentanol, such as the trichloracetimidate reported by Fang,[3p] were unsuccessful, and further efforts were abandoned.

The third-generation synthesis, which ultimately proved successful, was also based on the recognition that oseltamivir possesses a latent axis of functional symmetry with respect to the carboxylate and acetamido groups, as shown in Figure 2, and assumed the translocation of the acrylate olefin at a late stage of synthesis.

To avoid potential issues inherent in the removal of the tosyl group or reduction of C-2 hydroxyl, we decided to introduce the acetamido group by a hetero-Diels–Alder cycloaddition (inverse electron demand) of acyl nitroso group to the polarized diene in diol **27**. Thus, diol **27** was protected as an acetonide and treated with acetylhydroxamic acid in the presence of sodium periodate to afford cleanly the oxazine **32** as a single stereoisomer in 79% yield, as shown in Scheme 3. Reduction of the oxazine with $Mo(CO)_6$[13] produced the allylic alcohol **33** in 75% yield. Treatment of this alcohol with mesyl chloride led to the allylic displacement to furnish oxazoline **34**, which was directly hydrolyzed with aqueous calcium carbonate in ethanol to the amino alcohol derivative **35**.

Hydrogenation over rhodium on alumina then provided the fully saturated ester **36** in 95% yield. At this stage what remained was the introduction of the remaining nitrogen functionality, installation of pentan-2-ol moiety, and regeneration of the acrylate moiety. This was accomplished by conversion of the alcohol to its mesylate **37** and displacement of the mesylate with sodium azide in acetone to give azide **38** in 86% yield, Scheme 3. The formal synthesis of oseltamivir was completed by treatment of ester **38** with DBU in methylene chloride, leading to the elimination of the C-2 ether with concomitant collapse of the acetonide to produce the penultimate intermediate, the allylic alcohol **39**, which was reported by Fang in his synthesis of oseltamivir.[14]

The third-generation synthesis was relatively short and reasonably efficient but still relied on the use of azide for the introduction of the second nitrogen functionality. The translocation of the acrylate double bond proved to be a much more convenient way of removing the C-2 hydroxyl than the attempted reduction during the first-generation synthesis. In addition, starting the synthesis with the diol derived from ethyl benzoate greatly improved the overall efficiency as the three carbons of the ester are retained in the product. Thus, the only further improvement sought was one that would avoid the use of azide as means of introducing the nitrogen functionality.

The fourth-generation synthesis also began with diol **27**[15] derived by fermentation of ethylbenzoate with *E. coli* JM109(pDTG601a)[16] leading to the diol in space–time yields of 1 g/L/hour. The diol was converted in three steps to the amino alcohol derivative **33** as described previously.[17] We have discovered, quite fortuitously, that the well-known Dauben–Michno oxidative transposition[18] (previously applied only to allylic alcohols substituted with electron-donating groups)[19] can also be used to convert allylic alcohols substituted with electron-withdrawing groups to the corresponding enones. Thus, treatment of alcohol **33** with chromium oxide and acetic anhydride provided enone **40** in excellent yields, Scheme 4. This reaction was found to be quite general and was later exploited in the synthesis of β-cyanoenones from allylic cyanohydrins in good yields.[20] On a larger scale, the enone was directly converted to oxime **41** in 75–82% yield from **33**. Hydrogenation of the oxime over rhodium on alumina provided the saturated ester **42** along with ~10% of the over-reduced product lacking the C-2 oxygen functionality. Similar results were also obtained when palladium on alumina and/or $Pd(OH)_2$ were used in the hydrogenation. This mixture was converted to the Boc-protected derivatives **43** and **44** in 50% yield over the two steps. Eventually, it was found that

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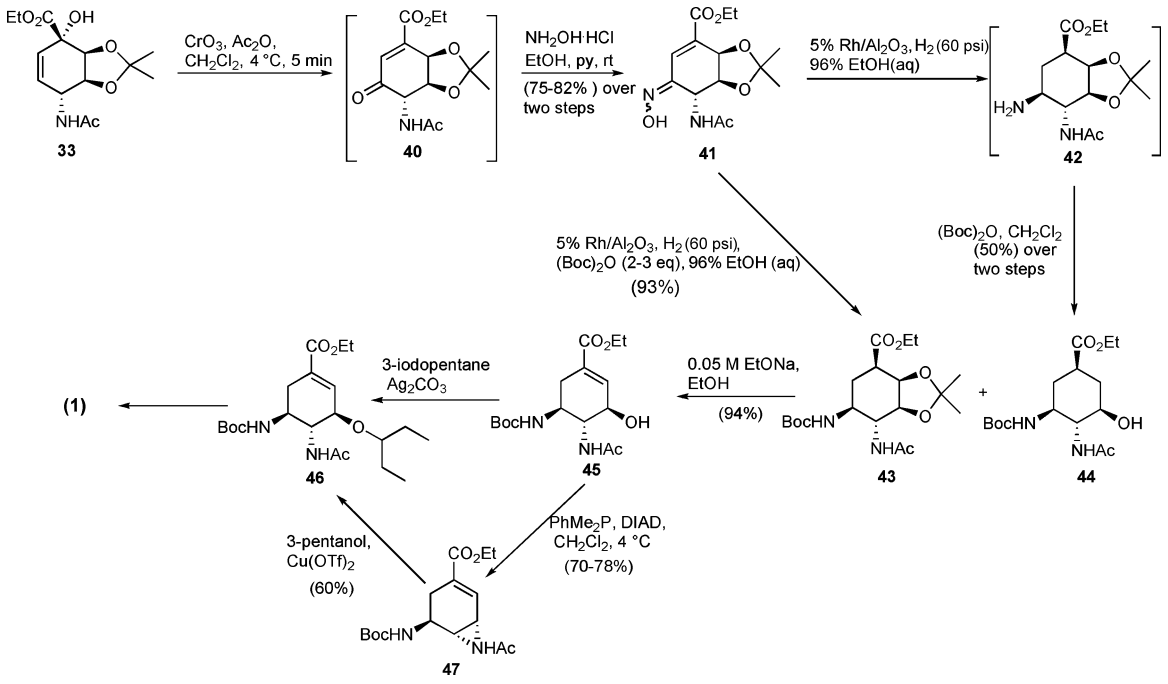
Scheme 4. [a]



[a]Abbreviations: DIAD = diisopropyl azodicarboxylate.

performing the hydrogenation in the presence of Boc anhydride led directly to carbamate **44** in 93% yield, Scheme 4.

The collapse of the acetonide and the generation of the required acrylate unit was accomplished with sodium ethoxide in ethanol to provide the allylic alcohol **45** in 94% yield, thus formalizing the synthesis.[21] On a small scale, we have converted this material to Boc-protected oseltamivir **46** in two ways: by intersecting Corey's[3g] or Shibasaki's[3u] protocols via aziridine **47** and its opening with 3-pentanol and by a low-yielding (~10%) alkylation with 3-iodopentane.[22] In our hands, the repetition of Corey's procedure provided **46** in 21% yield from the allylic alcohol. Repetition of Shibasaki's protocol gave **46** in 47% yield. Deprotection then provided the title compound matched by TLC and HPLC with an authentic sample.

In summary, the fourth-generation approach provided for a very efficient synthesis of allylic alcohol **45**: 52% overall yield from diol **27**. The advantage of this latest design is, in addition to brevity, the fact that the 10 chemical steps may be reduced to just five operations, and on larger scales no chromatography is needed. In any future ameliorations of this synthesis improvements need to be discovered in the introduction of the 3-pentanyl side chain. As of this writing there are no direct high-yielding alkylation-based methods available for this transformation.

Evaluation of Efficiency Metrics for Third- and Fourth-Generation Synthesis. In order to better gauge the material efficiencies of our two successful synthesis routes to oseltamivir phosphate against published syntheses prior to ours we determined their green metrics performances according to the previously described Andraos algorithm which was used to test the "greenness" of six industrial and nine academic plans to this target molecule.[5] The essential metrics examined were as follows: number of steps (*N*), number of input materials (*I*), percent overall yield, percent overall atom economy (AE),[23] and overall *E*-factor.[24] The overall *E*-factor in turn was subdivided into its waste components arising from byproducts and side products (*E*-kernel), excess reagent consumption (*E*-excess), and auxiliary material consumption arising from reaction solvent, catalysts, all workup materials, and all purification materials (*E*-aux). OP = oseltamivir phosphate.

The basis scale for all calculations is 1 mol of target oseltamivir phosphate product so that standardized comparisons of plan performances can be made. Overall yields were determined by multiplying all reported reaction yields along the longest linear sequence of a plan. The list below shows in words how each of the other metrics is evaluated. Masses of all materials given here are appropriately scaled to meet the objective of getting to the 1 mol basis scale of the final target product. Hence, the *E*-factor values are interpreted formally as mass units of associated waste per mol of target product. Using the molecular weight of oseltamivir phosphate these are then converted to standard *E*-factor units of mass of waste in grams per gram of target product.

(1) % overall AE = [molecular weight of OP/sum of molecular weights of all stoichiometric reagents used] × 100%
(2) *E*-kernel = [sum of masses of all stoichiometric reagents − mass of 1 mol OP]/mass of 1 mol OP
(3) *E*-excess = sum of masses of excess reagents/mass of 1 mol OP
(4) *E*-aux = sum of masses of reaction solvents, catalysts, and workup and purification materials/mass of 1 mol OP
(5) Overall *E*-factor = [sum of masses of all reagents, catalysts, reaction solvents, and workup and purification materials − mass of 1 mol OP]/mass of 1 mol OP = *E*-kernel + *E*-excess + *E*-aux

The *E*-kernel contribution is a good metric to probe the intrinsic chemical efficiency of synthesis plans since it depends on the number of steps, reaction yields, and atom economies for each step. These parameters are directly linked to the core synthesis design strategy employed. An important insight

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Table 1. Comparison of Material Efficiency Green Metrics for Syntheses toward Fang's Intermediate 39

plan	*N*	*I*	% yield	% AE	*E*-kernal	*E*-excess	*E*-aux	*E*-total
Scheme 3	7	15	11.6	17.1	28.5	109.5	1105.6	1243.6
Fang[a]	11	18	26.5	14.7	12.6	59.1	1656.7	1728.3
Scheme 3b	8	17	6.9	16.8	34.3	1241.4	1206.8	2482.5
Fang[c]	14	29	18.9	8.6	32.0	291.8	2342.5	2666.4
Chen–Liu[d]	17	27	4.4	7.3	124.7	178.8	7626.7	7930.2
Scheme 3e	8	17	5.5	16.8	37.3	5990.9	5484.1	11512.2

[a]See ref 3p; starting material is (*S*,*S*)-3-bromocyclohexa-3,5-diene-*cis*-1,2-diol; final target product is oseltamivir phosphate. [b]Includes enzymatic *cis*-dihydroxylation step to compound **27** from ethyl benzoate assuming maximum yield of 60% for this step, aqueous reaction solvent not included, and 10-fold reduction in ethyl acetate workup solvent. [c]See ref 3j; starting material is D-xylose. [d]See ref 3hh. [e]Includes enzymatic *cis*-dihydroxylation step to compound **27** from ethyl benzoate assuming: 48% yield for this step, all reaction and workup solvents included.

Table 2. Summary of Material Efficiency Green Metrics for Scheme 3 to Oseltamivir Phosphate[a]

step	reaction	% yield	% AE	*E*-kernel	*E*-excess	*E*-aux	*E*-total
1	**27** → **32**	70	51	1.8	11.5	57.5	70.8
2	**32** → **33**	72	71	0.9	1.5	10.2	12.5
3	**33** → **34**	54	46	3.0	1.7	136.5	141.3
4	**34** → **35**	72	100	0.4	6.4	6.0	12.8
5	**35** → **36**	95	100	0.06	0.7	12.3	13.1
6	**36** → **37**	73	66	1.1	1.7	88.2	91.0
7	**37** → **39**	85	42	1.8	3.8	148.7	154.2
8	**39** + 3-pentyl trichloroacetimidate	78	68	0.9	0.2	0	1.1
8*	3-pentyl trichloroacetimidate synthesis	69	81	0.8	0.7	2.4	3.9
9	hydrogenation	99	92	0.1	0.6	101.8	102.5
10	H_3PO_4 salt formation	92	100	0.09	0.3	33.8	34.1
overall		8.2	21	28	107	1137	1272

[a]Steps 8, 8*, 9, and 10 pertain to Fang's synthesis (see ref 3j); the asterisk designates that this step was performed in the second branch of the convergent synthesis.

concerning metrics analysis is that it is most useful in a comparative rather in an absolute sense, that is, when various plans to a common target molecule are compared head-to-head according to some criteria. Such a comparison is fairest if such a set of plans also begin from a common starting material; however, this is a rare situation since most plans begin from different kinds of starting materials. More importantly, the recognition that true optimization has been achieved is realized when "best values" of all metrics parameters gravitate to the same synthesis plan.

We first examined the synthesis of Fang's intermediate, compound **39**, according to Scheme 3 and two prior plans for this target by Fang[3j,p] and Chen-Liu[3hh] whose plans began from D-xylose and D-glucal, respectively. The results are summarized in Table 1 where the entries are ranked in ascending order with respect to *E*-total. From these data we note that the plan given in Scheme 3 is superior in material efficiency performance over the others mainly because of a dramatic reduction in the number of steps and a high overall atom economy. Though the Fang plan had the highest overall yield at 19%, it had about the same *E*-kernel value as the plan in Scheme 3 because its atom economy was halved. This is a good example of non-orchestrated optimization where a gain in one metric is offset by a poorer performance in another. Overall, it is clear that the best values of all eight metrics listed in Table 1 are linked to Scheme 3 (see the first row), and hence, we may conclude that this is indeed optimal relative to the other plans. However, when the chemoenzymatic step to produce the *cis*-diol **27** is included in the analysis for Scheme 3 so that the initial starting material is now ethyl benzoate, the overall yield and *E*-factor performances drop significantly (see the last row). The yield for this chemoenzymatic step is 48%.[17] Since it is the lowest yield in the sequence and it appears in the first step where the scale of reaction is necessarily the highest in the plan, it results in a 31% increase in *E*-kernel compared to when this step is excluded. Also, the greatest contributor to *E*-total arises from the aqueous nutrient broth used as a reaction solvent. Both of these apparent shortcomings in metrics performance can be overcome on two fronts. First, the chemoenzymatic transformation may be repeated over several cycles to convert as much of the starting amount of ethyl benzoate as possible to product. From a practical perspective three cycles are sufficient to increase the reaction yield for this step to a maximum of 60%. This results in a best *E*-kernel value of 34.3 compared to 37.3. Second, the aqueous broth is relatively nontoxic compared to other solvents used once it has been autoclaved prior to disposal after the *E. coli* JM109(pDTG601a) cells are spent. This type of evaluation conforms to the calculations of effective mass yield (EMY) proposed by Hudlicky some time ago for bioctalytic processes in which the mass of those components judged benign do not enter into final calculations.[25] If the mass of solvent is not included in the calculation then the *E*-total value improves to 3392, which is close in magnitude to Fang's value of 2666. A further 10-fold reduction in ethyl acetate consumption as a workup solvent can potentially lead to a best value of *E*-total of 2483, which surpasses the Fang performance.

Next, we examined in detail the green metrics performances of Schemes 3 and 4 toward the oseltamivir phosphate target product. In carrying out these calculations, the amounts of purification materials, in particular chromatographic solvents and silica gel, were not included since estimates of their masses were not made consistently in all steps. Therefore, the *E*-aux contributions arise from masses of catalysts, reaction solvents, and workup extraction solvents/washes only. Tables 2 and 3

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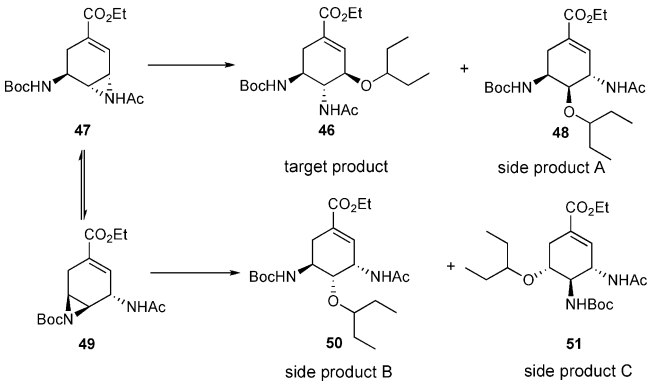
Table 3. Summary of Material Efficiency Green Metrics for Scheme 4 to Oseltamivir Phosphate

step	reaction	% yield	% AE	*E*-kernel	*E*-excess	*E*-aux	*E*-total
1	**27** → **32**	70	51	1.8	11.5	57.5	70.8
2	**32** → **33**	72	71	0.9	1.5	10.2	12.5
3	**33** → **41**	82	58	1.1	5.3	257.5	263.9
4	**41** → **43**	93	75	0.4	1.8	19.1	21.3
5[a]	**43** → **45**	95	86	0.2	0	43.5	43.8
6[a]	**45** → **47**	67	44	2.4	1.4	50.5	54.4
7[a]	**47** → **46**	59	100	0.7	67.6	9.1	77.3
8[b]	**46** → **1**	73	66	1.1	4.6	31.0	36.7
overall		10.5	22	24	183	1416	1623

[a]See ref 21. [b]See ref 3u.

summarize the results for each reaction in each scheme as well as the overall performances. From these data, it is possible to identify bottlenecks in each plan by pinpointing which steps contribute the most waste and what parameters in particular are responsible. This allows for further iterative improvements that could be made to the plans so that the goal of orchestrated and directed optimization is achieved. In effect, a metrics analysis guides further meaningful optimization. Both plans were evaluated from the common starting material *cis*-diol **27**. Since Scheme 3 represents a formal synthesis of **1**, the remaining steps from Fang's plan were used to complete the analysis from intermediate **39** to the final target product. From Table 2 we observe that in Scheme 3, step 3 (**33** → **34**) has the lowest yield and steps 1 (**27** → **32**), 3, and 7 (**37** → **39**) have the lowest atom economies. With respect to *E*-factors, steps 1 and 3 contribute the largest *E*-kernel values, steps 1 and 4 (**34** → **35**) have the largest *E*-excess contributions, and steps 3, 7, and 9 (azide hydrogenation) have the largest auxiliary material consumption. Overall, steps 3, 7, and 9 are the major waste producers in this plan. We suggest the following recommendations for further improvements: increase the yield of step 3, reduce excess reagent consumption for steps 1 and 4, and reduce solvent demand for steps 3 and 7. From Table 3 we observe that in Scheme 4, step 7 (**47** → **46**) has the lowest yield and steps 1 (**27** → **32**) and 6 (**45** → **47**) have the lowest atom economies. Steps 1 and 6 contribute the most waste from byproducts and side products. Steps 1 and 7 contribute the most excess reagent consumption. Step 3 (**33** → **41**) has by far the largest auxiliary material consumption. Overall, step 3 is the main waste producer in this plan. As before, we may suggest the following recommendations for further improvements: increase the yield of step 7, reduce excess reagent consumption for steps 1 and 7, and reduce solvent demand for step 3. The first option may be challenging due to the propensity of competing side reactions as shown in Scheme 5. On comparing the overall performances of plans in Schemes 3 and 4 we note that when all auxiliary materials are excluded, the latter plan is indeed better performing than the former one at the kernel level. This is consistent with the Scheme 4 plan being shorter by two steps and having a 3% higher overall yield (11% versus 8%). The overall atom economies are about the same for both plans. This result reinforces the conclusion that the synthesis strategy employed in Scheme 4 is superior to that in Scheme 3. However, when auxiliary materials are taken into account (reaction solvents, catalysts, and workup materials) the overall *E*-factor for Scheme 4 is now higher than that for Scheme 3 which goes against the direction of optimization achieved by the intrinsic chemical performance. Hence, further optimization of the plan in

Scheme 5



Scheme 4 will necessarily involve auxiliary material reduction in order to maintain its overall higher rank. Such a scenario is confirmed when the workup solvent demand due to ethyl acetate for step 3 is eliminated from the calculation of *E*-total. This makes sense since that step was already identified as having the largest *E*-aux contribution and largest *E*-total value overall (see row 3 in Table 3). Indeed, a recalculation of *E*-total results in a value of 1214 if this improvement were to be implemented, corresponding to a 25% reduction in overall waste from an original value of 1623. An *E*-total of 1214 is now less than the estimate of 1272 for Scheme 3 if no further optimization is made to that plan.

Finally, we may examine the overall ranking of both plans in Schemes 3 and 4 against all prior plans published to date according to intrinsic chemical performance. The results shown graphically in Figure 3 display *E*-kernel profiles in ascending order for academic and industrial plans separately. This is an update of the analysis from the previously published review[5] and includes more recent plans from Chen–Liu,[3hh] Fang G2,[3p] Fang G3,[3p] Hayashi G1,[3t] Hayashi G2,[3ii] Hayashi G3,[3ii] Kamimura,[3jj] Ko,[3kk] Kongkathip,[3nn] Lu,[3ll] Mandai G1,[3v] Mandai G2,[3v] Roche G6,[3ee] Shibasaki G4,[3u] Shibasaki G5,[3x] Shiniogi & Co., Ltd.,[3mm] and Wu.[3ff] Superimposed on these bar graphs is the fractional contribution to kernel waste from target bond forming reactions and sacrificial reactions. Target bond forming reactions pertain to those in a synthesis plan that are involved in the skeletal building up of the target molecule structure. Sacrificial reactions, on the other hand, are those in a plan that involve protection group chemistry, redox adjustments to atoms for further elaboration in subsequent target bond forming steps, and chiral directing group chemistry. Low overall *E*-kernel factor values and a lower proportion of waste arising from sacrificial reactions characterize well-strategized plans. An interesting case comparison is that between the Banwell[3o] plan and our own, which utilizes the same chemoenzymatic dihydroxylation reaction, albeit the starting material in the Banwell plan is bromobenzene instead of ethyl benzoate. In our plans, about 40% of the kernel waste arises from sacrificial reactions, whereas the Banwell strategy affords 70%, yet both plans have similar *E*-kernel values between 21 and 28. Among academic plans, Schemes 3 and 4 rank among the best disclosed so far; however, there is little difference in *E*-kernel performance between the top ranking dozen plans in this group. For example, the *E*-kernel values range from 7 (Shi) to 24 (Hayashi G2). However, the overall yields range from 48% over eight steps (Shi, linear) to 31% over four steps (Hayashi G2, convergent) corresponding to average yields per

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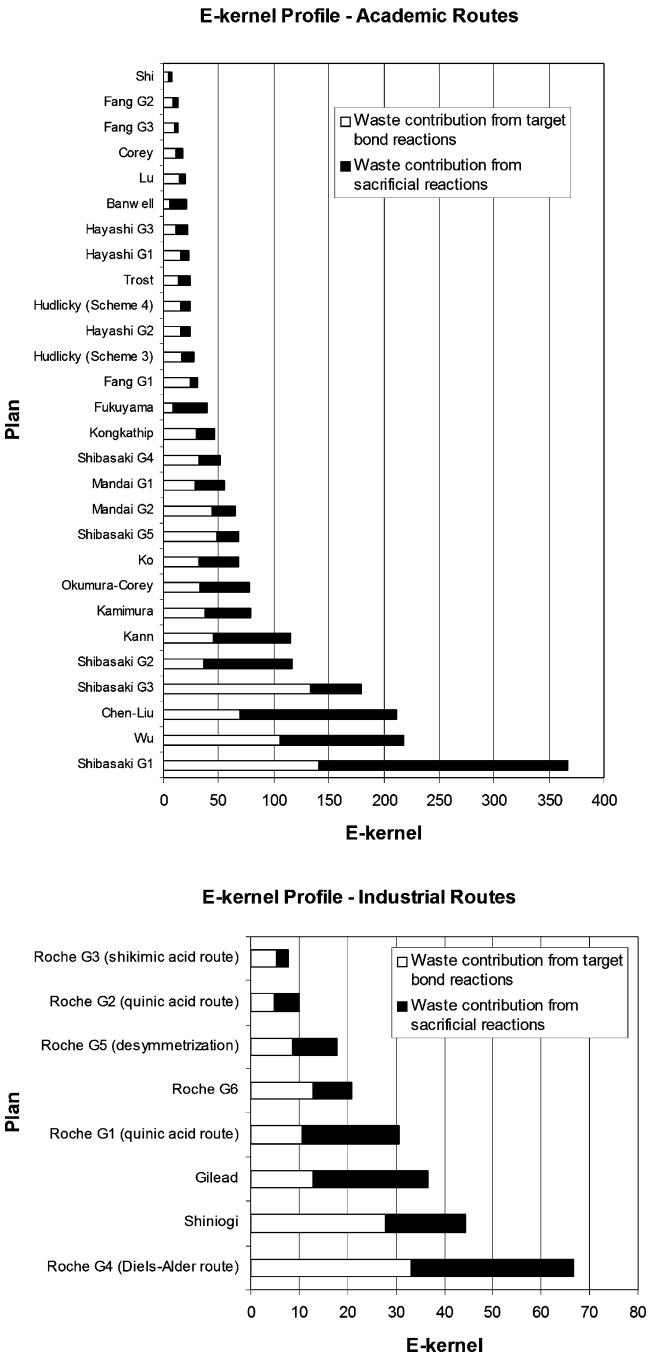


Figure 3. E-kernel profiles for various academic and industrial synthesis plans to oseltamivir phosphate showing proportion of waste originating from target bond forming and sacrificial reactions.

step of 91 and 75%, respectively. A caveat is that all estimates of metrics are based on the veracity of reported reaction yields in the literature for these plans.[26] Despite these advances and claims, the industrial plans are still well ahead in performance as evidenced by the 5-fold decrease in the scale of the *E*-kernel axis for the industrial plan profile. The best performing Roche G3 plan from shikimic acid has 13 steps, an overall yield of 39%, and an *E*-kernel value of 8. When reaction solvents, catalysts, and auxiliaries are included the *E*-total is 231, which is half the value of the best performing academic Shi plan (*E*-total =465). It should be noted that the solvent demand for chromatographic purification in the Shi plan was not disclosed in all steps, which is also true of the majority of academic plans. This means that the *E*-total value of 465 for the Shi plan should be considered a lower limit of the true *E*-total value. In general the details of overall solvent usage for the industrial plans was better disclosed in published procedures. Another important point is that none of the published academic plans were conducted on a scale large enough to demonstrate their feasibility for industrial processes. It remains to be seen whether their performances can be replicated at larger kilogram scales comparable to those used in the best performing industrial plan (Roche G3 plan from shikimic acid).[3d,f] Of particular note in this regard is the extreme telescoping of reaction steps without isolation of intermediates achieved by the Hayashi plans.[3t,ii] The Roche G3 plan requires 446 g of shikimic acid starting material to produce 1 mol or 410 g of oseltamivir phosphate along with 95 kg of total waste and was conducted on a 5 mol scale of shikimic acid. The Hayashi G2 plan, on the other hand, requires 289 g of starting 3-pentanol to produce 1 mol or 312 g of oseltamivir along with 191 kg of total waste and was conducted on a 46 mmol scale of 3-pentanol. By comparison, our Scheme 4 plan requires 1.8 kg of *cis*-diol **27** to produce 1 mol or 410 g of oseltamivir phosphate along with 666 kg of total waste and was conducted on 27 mmol scale of *cis*-diol. Clearly, these results show that in principle telescoping of steps can go a long way in reducing overall waste. In terms of strategy, 69% of the kernel waste generated in the Roche G3 plan originates from target bond forming reactions whereas the comparable value for our Scheme 4 plan is 65% which indicates that they are evenly matched. Buoyed by the results of the green metrics analysis described in this work we are confident that further directed optimizations as described earlier for key steps, are possible using our synthesis strategy, particularly at higher scale and using telescoping techniques.

CONCLUSION

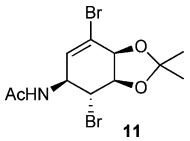
We have described four generations of approaches to oseltamivir, two of which were successful and two of which resulted in oseltamivir derivatives and/or isomers. The successful syntheses were analyzed in terms of efficiency metrics and compared with other academic as well as industrial preparations of this important compound. Our latest synthesis compared well with academic efforts in terms of overall efficiency. The metrics calculations were in each case based on conditions and yield values *as reported* in the literature. It should be noted that yield values reported in publications from academic groups are frequently subject to wide fluctuations for a variety of reasons that have recently been analyzed.[26] Thus only the industrial protocols that have been subjected to focused optimization and have been performed on large scales can be taken as reliable in terms of the reported values. We continue to address further improvements in our quest for a truly practical synthesis of oseltamivir and will report on future accomplishments in due course.

EXPERIMENTAL SECTION

All nonaqueous reactions were conducted in an inert (nitrogen or argon) atmosphere using standard Schlenk techniques for the exclusion of moisture and air. All solvents were distilled unless otherwise noted. Analytical thin-layer chromatography was performed on silica gel 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using silica gel (230−400 mesh). Melting points are uncorrected. IR spectra were obtained on a FT-IR spectrometer. Optical rotation was measured on a polarimeter

at a wavelength of 589 nm. ^{1}H and ^{13}C spectra were recorded on 300 MHz and/or 600 MHz spectrometers. All chemical shifts are referenced to TMS or residual nondeuterated solvent. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (C). Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University. Combustion analyses were performed by Atlantic Microlabs, Atlanta, GA.

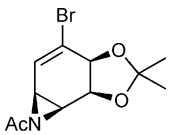
***N*-[(3a*R*,4*R*,5*S*,7a*S*)-4,7-Dibromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl]acetamide (11).**



11

To a solution of *N*-bromoacetamide (309 mg, 2.25 mmol) in 40 mL of acetonitrile was added 0.28 mL $SnBr_4$ (0.4 M in CH_2Cl_2, 0.11 mmol) at −40 °C in the dark. Diene **10**[9] (432 mg; 1.87 mmol) in acetonitrile (20 mL) was added slowly to the reaction mixture by syringe pump at the same temperature over 4 h. The resulting reaction mixture was stirred for 1 h, before saturated aqueous $NaHCO_3$ (10 mL) and Na_2SO_3 (10 mL) were carefully added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on neutral alumina (CH_2Cl_2) to afford bromo amide **11** (526 mg, 76%) as colorless crystals: R_f 0.71 (CH_2Cl_2/MeOH 96:4); mp 181 °C; $[\alpha]^{23}_D$ +188.2 (*c* 0.50, $CHCl_3$); IR (film) ν 3684, 3019, 2400, 1676, 1498, 1425, 1216, 1064, 929, 757, 669, 497, 478, 472 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, *J* = 9.0 Hz, 1H), 4.93 (m, 1H), 4.68 (d, *J* = 5.1 Hz, 1H), 4.60 (t, *J* = 4.5 Hz, 1H), 4.21 (t, *J* = 3.6 Hz, 2H), 1.97 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 128.0, 124.7, 112.0, 77.8, 75.8, 50.3, 44.4, 27.8, 26.5, 23.3; MS (EI) *m*/*z* 366 (M), 354(6), 313 (6), 294 (6), 255 (6), 253 (12), 251 (7), 232 (33), 230 (34), 190 (11), 189 (6), 188 (12), 187 (5), 174 (6), 173 (10), 172 (8), 171 (9), 165 (8), 163 (8), 151 (6), 109 (22), 108 (9), 93 (7), 81 (8), 80 (10), 65 (8), 59 (11), 55 (8), 43 (100), 42 (11), 41 (6); HRMS (EI) calcd for $C_{11}H_{15}O_3NBr_2$ 366.9419, found 366.9418. Anal. Calcd: C, 35.80; H, 4.10. Found: C, 35.77; H, 4.11.

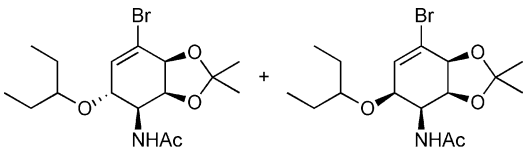
(3a*S*,4*S*,5*S*,7a*S*)-8-Acetyl-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-4,5-epimino-1,3-benzodioxole (12).



12

To a solution of amide **11** (17.61 g, 47.72 mmol) in dimethoxyethane (400 mL) was added *n*-Bu_4NBr (16.33 g, 52.49 mmol) at 0 °C under argon. At this temperature, potassium bis(trimethylsilyl)amide (100 mL, 0.5 M in toluene, 52.49 mmol) was added dropwise. The reaction mixture was stirred for 3 h at 0 °C and then quenched by the addition of potassium phosphate monobasic sodium hydroxide (350 mL, set to pH 7). The two-phase mixture was extracted with ethyl acetate (3 × 150 mL), and then the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a solvent gradient of 2:1 then 1:1 (hexanes−ethyl acetate) to afford **12** (9.21 g, 67%) as colorless crystals: R_f 0.44 (1:1, hexanes−ethyl acetate); mp 128 °C; $[\alpha]^{23}_D$ −57.6 (*c* 0.75, $CHCl_3$); IR (film) ν 3017, 2938, 1704, 1423, 1383, 1372, 1289, 1267, 1216, 1161, 1063, 994, 967, 894, 868, 819, 756, 668, 619, 554, 510, 485, 468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, *J* = 4.8 Hz, 1H), 4.72 (dd, *J* = 0.9, 6.9 Hz, 1H), 4.46 (dd, *J* = 4.2, 6.9 Hz, 1H), 3.19 (dd, *J* = 5.1, 6.0 Hz, 1H), 3.11 (ddd, *J* = 0.9, 6.0, 6.1 Hz, 1H), 2.17 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 129.9, 122.8, 108.5, 76.6, 71.9, 39.6, 36.7, 27.0, 24.9, 23.2; MS (EI) *m*/*z* 272 ($M^+ - CH_3$), 232 (9), 230 (9), 208 (5), 190 (9), 189 (8), 188 (9), 187 (7), 172 (6), 170 (5), 160 (13), 158 (13), 150 (18), 109 (18), 108 (45), 100 (23), 85 (10), 84 (5), 81 (9), 80 (17), 79 (7), 78 (7), 59 (9), 53 (7), 52 (6), 51 (10), 43 (100), 42 (6), 41 (6); HRMS (EI) calcd for $C_{11}H_{14}O_3NBr$ 287.0157, found 287.0161. Anal. Calcd: C, 45.85; H, 4.90. Found: C, 45.84; H, 4.95.

***N*-((3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-2,2-dimethyl-5-(pentan-3-yloxy)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)acetamide (14) and *N*-((3a*S*,4*S*,5*S*,7a*S*)-7-Bromo-2,2-dimethyl-5-(pentan-3-yloxy)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)-acetamide (13).**



14 **7** : **1** **13**

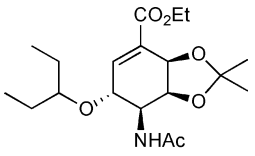
To a solution of aziridine **12** (7.78 g, 27.0 mmol) in 3-pentanol (30 mL) was added copper(II) trifluoromethanesulfonate (976 mg, 2.70 mmol) at 0 °C. The reaction mixture was stirred for 16 h before being concentrated under reduced pressure. The crude residue was dissolved in methylene chloride (20 mL), washed with satd $NaHCO_3$ (3 × 5 mL) and brine (1 × 10 mL), and then dried over Na_2SO_4. The residue was purified by flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes−diethyl ether) to afford **13** (1.09 g, 11%) and **14** (7.64 g, 76%) as clear oils.

13: R_f 0.45 (diethyl ether); $[\alpha]^{23}_D$ +41.5 (*c* 1.0, $CHCl_3$); IR (film) ν 3439, 3019, 2971, 2936, 2879, 1675, 1514, 1463, 1384, 1373, 1342, 1514, 1463, 1384, 1373, 1342, 1216, 1163, 1095, 1046, 965, 931, 888, 865, 758, 669, 502 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.35 (d, *J* = 8.7 Hz, 1NH), 6.31 (d, *J* = 5.3 Hz, 1H), 4.57 (d, *J* = 5.3 Hz, 1H), 4.40−4.44 (m, 2H), 3.90 (t, *J* = 5.3 Hz, 1H), 3.19 (quint, *J* = 5.8 Hz, 1H), 2.03 (s, 3H), 1.41−1.55 (m, 4H), 1.46 (s, 3H), 1.36 (s, 3H), 0.88 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 129.0, 127.5, 111.1, 81.6, 76.7, 75.3, 70.6, 46.6, 27.5, 26.6, 26.4, 25.9, 23.3, 9.8, 9.6; MS (EI) *m*/*z* 375 (M), 232 (8), 231 (7), 230 (9), 229 (5), 190 (21), 189 (16), 188 (22), 187 (13), 166 (6), 164 (6), 143 (22), 142 (100), 137 (9), 136 (8), 126 (6), 125 (6), 110 (5), 109 (32), 108 (7), 100 (30), 85 (6), 84 (61), 83 (9), 80 (9), 71 (8), 70 (9), 60 (9), 59 (12), 43 (73), 41 (7); HRMS (EI) calcd for $C_{16}H_{26}BrNO_4$ 375.1045, found 375.1045.

14: R_f 0.40 (diethyl ether); $[\alpha]^{23}_D$ −100.0 (*c* 1.0, $CHCl_3$); IR (film) ν 3439, 3019, 2971, 2936, 2879, 1675, 1514, 1463, 1384, 1373, 1342, 1514, 1463, 1384, 1373, 1342, 1216, 1163, 1095, 1046, 965, 931, 888, 865, 758, 669, 502 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.14 (d, *J* = 1.5 Hz, 1H), 5.83 (d, *J* = 9.0 Hz, 1H), 4.57 (dd, *J* = 1.5, 5.3 Hz, 1H), 4.40 (dd, *J* = 2.4, 5.1 Hz, 1H), 4.30 (dt, *J* = 2.4, 8.9 Hz, 1H), 3.89 (dd, *J* = 1.5, 8.9 Hz, 1H), 3.24 (quint, *J* = 5.6 Hz, 1H), 2.00 (s, 3H), 1.43−1.49 (m, 4H), 1.38 (s, 3H), 1.34 (s, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 132.5, 122.7, 110.2, 82.4, 77.3, 76.0, 73.6, 51.2, 27.4, 26.3, 26.1, 25.6, 23.5, 9.6, 9.2; MS (EI) *m*/*z* 375 (M), 232 (8), 231 (7), 230 (9), 229 (5), 190

(21), 189 (16), 188 (22), 187 (13), 166 (6), 164 (6), 143 (22), 142 (100), 137 (9), 136 (8), 126 (6), 125 (6), 110 (5), 109 (32), 108 (7), 100 (30), 85 (6), 84 (61), 83 (9), 80 (9), 71 (8), 70 (9), 60 (9), 59 (12), 43 (73), 41 (7); HRMS (EI) calcd for $C_{16}H_{26}BrNO_4$ 375.1045, found 375.1045. Anal. Calcd: C, 51.07; H, 6.96. Found: C, 51.07; H, 6.98.

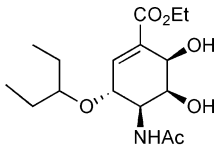
Ethyl (3a*R*,6*R*,7*S*,7a*S*)-7-Acetamido-2,2-dimethyl-6-(pentan-3-yloxy)-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-4-carboxylate (15).



15

To a solution of vinyl bromide **14** (6.50 g, 17.3 mmol) in toluene (300 mL) and ethanol (82 mL) was passed CO gas (1 atm). After 10 min, triethylamine (84.2 mL, 604.6 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (998 mg, 0.864 mmol) at room temperature. The resulting solution was heated to 60 °C while a continuous flow of CO gas (1 atm) was passed. After 2 h, dichlorobis(triphenylphosphine)palladium(II) (1.21 g, 1.73 mmol) was added in two portions over 15 min. The reaction mixture was brought to reflux for 4 h, cooled to room temperature, and filtered through a plug of Celite. The crude material was purified by flash column chromatography with a solvent gradient of 2:1 then 1:1 (hexanes-ethyl acetate) to yield **15** (4.34 g, 68%) as a colorless solid: R_f 0.22 (96:4, methylene chloride/methanol); mp 112–115 °C; $[\alpha]^{23}_D$ −122.7 (*c* 1.0, $CHCl_3$); IR (film) ν 3383, 3022, 2975, 2879, 1711, 1663, 1576, 1464, 1374, 1254, 1218, 1094, 1068, 929, 776, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.90 (d, J = 1.9 Hz, 1H), 5.82 (d, J = 8.7 Hz, 1NH), 5.03 (dd, J = 0.76, 5.7 Hz, 1H), 4.49 (dd, J = 2.6, 5.7 Hz, 1H), 4.22–4.31 (m, 3H), 4.04 (d, J = 9.0 Hz, 1H), 3.34 (quint, J = 5.6 Hz, 1H), 2.03 (s, 3H), 1.48–1.56 (m, 4H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 165.5, 141.1, 129.9, 109.5, 82.6, 74.7, 72.0, 71.6, 61.1, 51.9, 27.3, 26.1, 25.9, 25.5, 23.6, 14.2, 9.6, 9.3; MS (EI) m/z (%) 369 (M^+-CH_3), 228 (10), 182 (12), 181 (11), 154 (6), 153 (8), 143 (8), 142 (88), 136 (10), 112 (8), 110 (7), 109 (7), 100 (17), 88 (6), 87 (13), 86 (32), 85 (8), 84 (100), 83 (9), 80 (6), 71 (12), 70 (11), 69 (5), 60 (8), 59 (13), 58 (5), 57 (11), 55 (11), 49 (10), 47 (11), 43 (87), 42 (6), 41 (13); HRMS (EI) calcd for $C_{18}H_{28}NO_6$ 354.1917, found 354.1919.

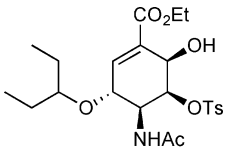
Ethyl (3*R*,4*R*,5*S*,6*R*)-4-Acetamido-5,6-dihydroxy-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (16).



16

To a solution of ester **15** (1.13 g, 3.06 mmol) in ethanol (20 mL) was added 6 M HCl (500 μL) at room temperature. The resulting solution was stirred for 5 h at 60 °C before the addition of H_2O (500 μL). The reaction was stirred for an additional 1 h at 60 °C before being cooled to room temperature and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a solvent system of 24:1 (methylene chloride/methanol) to yield **16** (715 mg, 71%) as white solid: R_f 0.71 (9:1, methylene chloride/methanol); $[\alpha]^{23}_D$ −44.1 (*c* 0.47, $CHCl_3$); mp 154 °C; IR (film) ν 3380, 3020, 2970, 2937, 2879, 1715, 1661, 1576, 1464, 1374, 1244, 1217, 1094, 1060, 929, 756, 667 cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 7.36 (d, J = 6.4 Hz, 1NH), 6.78 (d, J = 3.8 Hz, 1H), 4.86 (d, J = 4.2 Hz, 1OH), 4.64 (t, J = 3.9 Hz, 1H), 4.21–4.25 (m, 1H) 4.21 (dq, J = 1.1, 7.2 Hz, 2H), 4.01–4.15 (m, 2H), 3.96 (dd, J = 4.3, 6.6 Hz, 1H), 3.56 (quin, J = 5.8 Hz, 1H), 1.87 (s, 3H), 1.44–1.58 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ 169.2, 165.9, 137.7, 132.6, 81.4, 73.4, 67.0, 65.7, 60.4, 53.1, 26.1, 26.0, 22.4, 13.6, 9.2, 8.8; MS (FAB) m/z 330 (M^+), 260 (21), 242 (25), 224 (13), 182 (23), 178 (14), 152 (11), 136 (13), 112 (11), 110 (21), 109 (16), 81 (13), 71 (13), 69 (17), 67 (10), 60 (19), 57 (19), 55 (31), 43 (100), 41 (34), 39 (16), 29 (45); HRMS calcd for $C_{16}H_{28}NO_6^+$ 330.1917, found 330.1919.

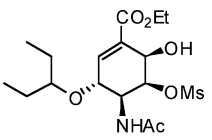
Ethyl (3*R*,4*S*,5*S*,6*R*)- 4-Acetamido-6-hydroxy-3-(pent-3-yloxy)-5-(tosyloxy)cyclohex-1-enecarboxylate (17a).



17a

To a solution of diol **16** (2.32 g, 7.04 mmol) in dry pyridine (15 mL) was added 4-toluenesulfonyl chloride (1.48 g, 7.74 mmol) portionwise over 5 min. The reaction mixture was stirred at room temperature for 48 h and then diluted with methylene chloride (10 mL). The organic layer was washed with cold 1 N HCl (3 × 5 mL) and brine (1 × 10 mL) and dried over Na_2SO_4. The crude mixture was purified by flash column chromatography with a solvent system gradient of 99:1 then 96:4 (methylene chloride/methanol) to yield **17** (1.76 g, 76%, based on 0.587 g of recovered starting material) as a clear oil: R_f 0.71 (96:4, methylene chloride/methanol); $[\alpha]^{23}_D$ −36.6 (*c* 2.5, $CHCl_3$); IR (film) ν 3375, 2971, 2937, 2879, 2733, 2458, 2252, 1920, 1716, 1660, 1598, 1527, 1463, 1444, 1372, 1248, 1218, 1190, 1178, 1121, 1096, 1059, 1002, 970, 915, 848, 815, 769, 704, 666, 556, 486 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 6.8 Hz, 1NH), 6.87 (d, J = 4.9 Hz, 1H), 4.95 (t, J = 3.5 Hz, 1H), 4.76 (t, J = 3.8 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.15 (dt, J = 3.2, 6.8 Hz, 1H), 4.08 (dd, J = 2.6, 4.9 Hz, 1H), 3.45 (quint, J = 5.8 Hz, 1H), 3.25 (d, J = 3.4 Hz, 1OH), 2.45 (s, 3H), 1.92 (s, 3H), 1.45–1.51 (m, 2H), 1.34–1.40 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H), 1.24–1.26 (m, 1H), 0.84 (t, J = 7.4, 3H), 0.70 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 165.3, 145.4, 137.4, 132.9, 131.2, 130.1 (2 × C), 128.0 (2 × C), 82.2, 74.6, 72.6, 64.6, 61.6, 50.9, 26.3, 25.9, 23.4, 21.7, 14.2, 9.8, 8.9; MS (FAB) m/z 484 (M^+), 29 (13), 39 (10), 41 (13), 43 (27), 55 (12), 57 (8), 69 (6), 77 (5), 91 (8), 136 (8), 178 (5), 224 (7), 396 (5); HRMS (FAB) calcd for $C_{23}H_{34}NO_8S$ 484.2005, found 484.1998.

Ethyl (3*R*,4*S*,5*S*,6*R*)-4-Acetamido-6-hydroxy-5-(methylsulfonyloxy)-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (17b).



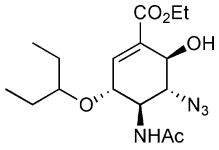
17b

To a stirred solution of **16** (20 mg, 0.061 mmol) in pyridine (0.5 mL) was added mesyl chloride (5 μL, 0.06 mmol) at 0 °C.

dx.doi.org/10.1021/jo2018872 | *J. Org. Chem.* 2011, 76, 10050–10067

The resulting solution was stirred for 24 h before being diluted with Et_2O (1 mL) and H_2O (1 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 × 0.2 mL). The combined organic layers were washed with brine (1 × 1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 1:20 then 1:10 (hexane−ethyl acetate) to yield mesylate **17b** (21 mg, 86%) as a white solid: R_f 0.47 (1:15 hexanes−ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, J = 4.1 Hz, 1H), 6.83 (d, J = 6.8 Hz, 1NH), 5.09 (t, J = 3.6 Hz, 1H), 4.95 (d, J = 4.2 Hz, 1H), 4.42 (dt, J = 3.7, 7.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.14 (t, J = 4.2 Hz, 1H), 3.69 (br s, 1OH), 3.53 (qn, J = 5.7 Hz, 1H), 3.13 (s, 3H), 1.98 (s, 3H), 1.48−1.60 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H); MS (EI) m/z 362 ($M - C_2H_5O^+$), 43 (100), 112 (66), 136 (39), 149 (25), 158 (32), 181 (29), 182 (21), 228 (44); HRMS calcd for $C_{15}H_{24}NO_7S$ 362.1270, found 362.1278.

Ethyl (3*R*,4*R*,5*R*,6*R*)-4-Acetamido-5-azido-6-hydroxy-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (18). *A. From Tosylate **17a**.*



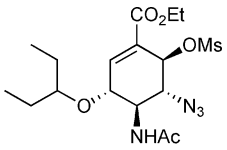
18

To a stirred solution of tosylate **17a** (24 mg, 0.049 mmol) in dimethoxyethane (2 mL) was added tetrabutylammonium azide (141 mg, 0.49 mmol). The resulting suspension was heated to reflux for 16 h, cooled, and concentrated under reduced pressure. The crude material was purified by flash column chromatography with a solvent system of 2:1 (hexanes−ethyl acetate) to yield **18** (12 mg, 69%) as a pale yellow oil.

*B. From Mesylate **17b**.* A similar protocol from mesylate **17b** furnished **18** in comparable yield.

18: R_f 0.27 (1:1 hexanes−ethyl acetate); $[\alpha]^{23}_D$ −39.71 (c 1.00, $CHCl_3$); mp 112−115 °C (hexanes−ethyl acetate); IR (film) ν 3382, 2966, 2927, 2863, 1719, 1653 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (dd, J = 0.94, 2.8 Hz, 1H), 6.10 (d, J = 7.9 Hz, 1NH), 4.71 (ddd, J = 0.94, 1.1, 6.4 Hz, 1H), 4.48 (dd, J = 6.4, 9.4 Hz, 1H), 4.43 (ddd, J = 2.1, 2.7, 6.8 Hz, 1H), 4.28 (dq, J = 2.7, 7.1 Hz, 2H), 3.82 (ddd, J = 6.7, 7.9, 9.4 Hz, 1H), 3.47 (quint, J = 5.8 Hz, 1H), 2.01 (s, 3H), 1.48−1.56 (m, 4H), 1.33 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 166.0, 139.4, 130.3, 82.5, 73.0, 71.3, 61.5, 58.9, 55.9, 26.1, 25.8, 23.5, 14.2, 9.6, 9.4; MS (FAB) m/z 348 ($M^+ - 7$), 29 (57), 43 (100), 77 (27), 107 (16), 136 (26), 172 (15), 224 (23), 242 (31), 260 (64), 278 (26).

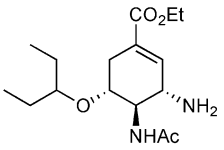
Ethyl (3*R*,4*R*,5*R*,6*R*)-4-Acetamido-5-azido-6-(methylsulfonyloxy)-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (19).



19

To a stirred solution of alcohol **18** (23 mg, 0.065 mmol) in methylene chloride (1 mL) was added triethylamine (72 mL, 0.52 mmol). The resulting solution was cooled to −78 °C prior to the addition of methanesulfonyl chloride (15 mL, 0.19 mmol). The reaction mixture was allowed to warm to 15 °C slowly over 3 h, quenched by the addition of satd $NaHCO_3$ (1 mL), extracted into methylene chloride (3 × 1 mL), and dried over Na_2SO_4. The crude material was purified by flash column chromatography with a solvent gradient of 2:1 and then 1:1 (hexanes−ethyl acetate) to yield **19** (21 mg, 75%) as a white solid: R_f 0.40 (1:1 hexanes−ethyl acetate); $[\alpha]^{23}_D$ −3.88 (c 0.50, $CHCl_3$); mp 96−98 °C; IR (film) ν 3345, 2968, 2932, 2877, 1717, 1655, 1558, 1362, 1264 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, J = 3.4 Hz, 1H), 6.14 (d, J = 8.5 Hz, 1NH), 5.65 (d, J = 4.14 Hz, 1H), 4.73 (dd, J = 4.2, 5.8 Hz, 1H), 4.26−4.31 (m, 3H), 4.22 (ddd, J = 3.4, 5.3, 8.5 Hz, 1H), 3.58−3.62 (m, 1H), 3.18 (s, 3H), 2.00 (s, 3H), 1.49−1.56 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 164.4, 143.1, 125.5, 82.5, 72.4, 65.8, 61.9, 54.5, 53.4, 38.9, 26.1, 25.8, 23.4, 14.1, 9.9, 9.2; MS (EI) m/z 425 ($M^+ - 7$), 43 (100), 55 (11), 79 (12), 120 (15), 136 (37), 152 (29), 201 (40), 224 (21), 242 (79), 300 (17), 329 (7), 360 (5).

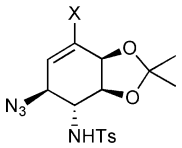
Ethyl (3*S*,4*R*,5*R*)-4-Acetamido-3-amino-5-(pentan-3-yloxy)-cyclohex-1-enecarboxylate (20).



20

A 32 mg portion of carboxylate **19** (0.07 mmol) was dissolved in 0.5 mL of ethanol and 0.1 mL of THF. Sodium borohydride (14 mg, 0.37 mmol) was added in small portions at rt. The reaction was stirred for 12 h, concentrated on high vacuum, and partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and evaporated. After a pipet column (CH_2Cl_2/MeOH 96:4 to 8:2), 2 mg of the double bond regioisomer of oseltamivir was isolated (0.01 mmol, 9%): R_f 0.40 (8:2 CH_2Cl_2/MeOH); ^{1}H NMR (600 MHz, MeOD-d_4) δ 6.61 (s, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 3.83 (m, 1H), 3.72 (m, 1H), 3.68 (m, 1H), 3.39 (quint, J = 5.7 Hz, 1 H), 2.87 (dd, J = 5.1 Hz, J = 17.1 Hz, 1 H), 2.25 (m, 1H), 1.96 (s, 3H), 1.40 (m, 4H), 1.19 (t, J = 7.2 Hz, 3H), 0.76 (t, J = 7.2 Hz, 3H), 0.75 (t, J = 7.2 Hz, 3H).

***N*-[(3a*S*,4*R*,5*S*,7a*S*)-5-Azido-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]-4-methylbenzenesulfonamide (24, X = Br) and *N*-[(3a*S*,4*R*,5*S*,7a*S*)-5-Azido-7-iodo-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]-4-methylbenzenesulfonamide (24, X = I).**

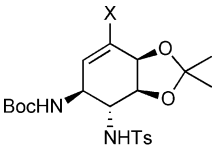


24

To a stirred solution of aziridine **23** (X = Br)[12] (200 mg, 0.499 mmol) in DMF (2 mL) was added NH_4Cl (400 mg) and NaN_3 (324 mg, 4.99 mmol) at 0 °C. The reaction mixture was stirred for 12 h, extracted into Et_2O (5 × 1 mL), washed with H_2O (20 × 0.5 mL), washed with brine (1 × 1 mL) and dried over Na_2SO_4. The crude material was recrystallized from $CHCl_3$-hexanes to yield **24** (X = Br) (203 mg, 92%) as a white solid: R_f 0.53 (2:1 hexanes-ethyl acetate); mp 119−120 °C ($CHCl_3$−hexanes); $[\alpha]^{23}_D$ +82.36 (c 3.5, $CHCl_3$); IR (film) ν 3435, 2108, 1645, 1599, 1219, 1159 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 6.14 (d, J = 3.4 Hz, 1H), 5.61 (d, J = 8.3 Hz, 1H), 4.58 (d, J = 5.6 Hz, 1H),

4.19 (dd, J = 5.8, 6.9 Hz, 1H), 3.73 (dd, J = 3.0, 6.4 Hz, 1H), 3.56 (q, J = 7.5 Hz, 1H), 2.45 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 137.6, 129.7, 128.9, 127.2, 124.2, 111.4, 75.9, 75.7, 60.5, 55.2, 27.5, 25.9, 21.6; MS (EI) m/z 442 (M), 43 (47), 91 (100), 155 (35); HRMS calcd for $C_{15}H_{16}N_4O_4BrS^{\bullet}$ 442.0076, found 442.0072.

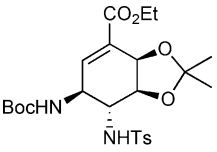
tert-Butyl (3a*S*,4*R*,5*S*,7a*S*)-7-Bromo-2,2-dimethyl-4-([(4-methylphenyl)sulfonyl]amino)-3a,4,5,7a-tetrahydro-l,3-benzodioxol-5-yl)carbamate (25, X = Br) and _tert_-Butyl (3a*S*,4*R*,5*S*,7a*S*)-7-Bromo-2,2-dimethyl-4-([(4-methylphenyl)sulfonyl]amino)-3a,4,5,7a-tetrahydro-l,3-benzodioxol-5-yl)carbamate (25, X = I).



25

To a stirred solution of azide **24** (X = Br) (41 mg, 0.092 mmol) in 12:1 THF/H_2O (1 mL) was added triphenylphosphine (48 mg, 0.18 mmol). The reaction mixture was stirred for 12 h, extracted into Et_2O (5 × 0.5 mL), washed with brine (1 × 1 mL), and dried over Na_2SO_4. To a stirred solution of the crude Staudinger intermediate (0.092 mmol) in DCM (1 mL) and triethylamine (50 μL) was added $(Boc)_2O$ (29 mg, 0.14 mmol) at 0 °C. The reaction mixture was stirred for 12 h, extracted into $CHCl_3$ (5 × 0.5 mL), washed with satd NH_4Cl (2 × 1 mL), washed with brine (1 × 1 mL), and then dried over Na_2SO_4. The crude material was purified by flash column chromatography with a solvent gradient of 10:1, 6:1 then 3:1 (hexane−ethyl acetate) to yield **25** (X = Br) (36 mg, 77%): R_f 0.31 (2:1 hexanes−ethyl acetate); mp 153−154 °C (EtOAc−hexanes); $[\alpha]^{23}_D$ +15.467 (c 2.1, $CHCl_3$); IR (film) ν 3408, 2090, 1642, 1161 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 7.9 Hz, 2H), 6.17 (d, J = 3.4 Hz, 1H), 5.32 (d, J = 8.9 Hz, 1H), 5.26 (d, J = 8.2 Hz, 1H), 4.60 (d, J = 5.6 Hz, 1H), 4.23 (dd, J = 6.2, 6.9 Hz, 1H), 4.08−4.13 (m, 1H), 3.46 (q, J = 7.4 Hz, 1H), 2.40 (s, 3H), 1.43 (s, 9H), 1.29 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 143.5, 137.5, 132.7, 129.6, 127.32, 121.4, 110.9, 80.3, 76.4, 76.3, 55.0, 51.2, 28.3, 27.3, 25.9, 21.5; MS (EI) m/z 516 (M), 57 (46), 91 (81), 98 (62), 99 (97), 139 (48), 254 (100); HRMS calcd for $C_{21}H_{29}N_2O_6SBr$ 516.0930, found 516.0940.

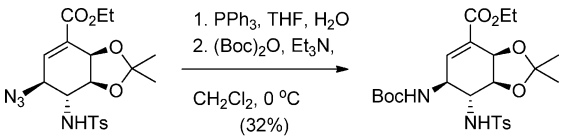
Ethyl (3a*R*,6*S*,7*R*,7a*S*)-6-[(_tert_-Butoxycarbonyl)amino]-2,2-dimethyl-7-{ [(4-methylphenyl)sulfonyl]amino}-3a,6,7,7 a-tetrahydro-l,3-benzodioxole-4-carboxylate (26). *A. From Vinyl Bromide **25**.* A solution of vinyl bromide **25** (X = Br, I) (2.00 g,



26

3.86 mmol), ethanol (15 mL), and triethylamine (15 mL) in toluene (70 mL) was purged with CO (g) for 10 min. The solution was charged with CO(g) and $Pd(PPh_3)_4$ (223 mg, 0.193 mmol) and then heated to 60 °C for 1 h before the addition of $Pd[(PPh_3)_2(Cl)_2]$ (271 mg, 0.386 mmol). The reaction was then heated to reflux for 6 h, cooled to room temperature, and filtered through a plug of SiO_2. The crude material was purified by flash column chromatography to yield acrylate **26** (888 mg, 45%) as a yellow oil.

*B. From Azide **29**.*

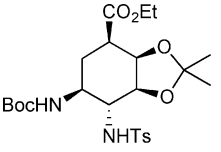


(29) **(26)**

To a stirred solution of **29** (110 mg, 0.252 mmol) in 12:1 THF/H_2O (1.5 mL) was added triphenylphosphine (132 mg, 0.504 mmol). The reaction mixture was stirred for 12 h, extracted into Et_2O (3 × 1 mL), washed with brine (1 × 1 mL), and dried over Na_2SO_4. To a stirred solution of the crude Staudinger intermediate (0.252 mmol) in DCM (1.5 mL) and triethylamine (200 μL) was added $(Boc)_2O$ (275 mg, 1.26 mmol) at 0 °C. The reaction mixture was stirred for 16 h, extracted into $CHCl_3$ (5 × 1 mL), washed with satd NH_4Cl (2 × 1 mL), washed with brine (1 × 1 mL), and then dried over Na_2SO_4. The crude material was purified by flash column chromatography to yield **26** (41 mg, 32%).

26: R_f 0.46 (1:1 hexanes−ethyl acetate); $[\alpha]^{23}_D$ −11.77 (c 0.72, $CHCl_3$); IR (film) ν 3434, 2099, 1647, 1160 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 2.2 Hz, 1H), 5.36 (d, J = 8.2 Hz, 1H), 5.23 (d, J = 8.3 Hz, 1H), 4.92 (d, J = 5.6 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 4.10 (dd, J = 6.0, 8.9 Hz, 1H), 3.38 (q, J = 8.7 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 143.5, 136.7, 129.6, 127.6, 109.5, 78.3, 74.0, 60.7, 42.9, 28.7, 27.4, 26.0, 21.5, 20.5, 14.1; MS (EI) m/z 510 (M), 43(100), 57(52), 84(54); HRMS calcd for $C_{24}H_{34}N_2O_8S$ 510.2036, found 510.2038.

Ethyl (3a*R*,4*R*,6*S*,7*R*,7a*S*)-6-[(_tert_-Butoxycarbonyl)amino]-2,2-dimethyl-7-{[(4-methylphenyl)sulfonyl]amino}hexahydro-l,3-benzodioxole-4-carboxylate (30a).



30a

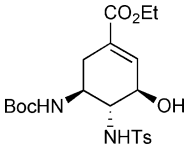
A hydrogenation vial was charged with acrylate **26** (240 mg, 0.470 mmol), 5% Rh/Al_2O_3 (60 mg), and 85% ethanol (1.5 mL) before evacuation with H_2. The reaction was stirred at room temperature and 55 psi for 144 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography with a solvent gradient of 3:1 then 1:1 (hexanes−ethyl acetate) to yield **30a** and **30b** (8:1) (228 mg, 95%) as a white solid:

*Major isomer **30a**:* R_f 0.49 (1:1 hexanes−ethyl acetate); mp 246−247 °C ($CHCl_3$); IR (film) ν 3434, 2099, 1647, 1160 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 5.30 (d, J = 8.6 Hz, 1H), 5.12 (d, J = 8.3 Hz, 1H), 4.46 (t, J = 4.3 Hz, 1H), 4.18−4.25 (m, 1H), 4.09−4.15 (m, 1H), 3.86 (dd, J = 5.1, 8.8 Hz, 1H), 3.40 (dq, J = 1.3, 10.2 Hz, 1H), 3.21 (q, J = 9.3 Hz, 1H), 2.81 (dt, J = 3.8, 12.6 Hz, 1H), 2.42 (s, 3H), 2.13 (dt, J = 3.7, 13.5 Hz, 1H), 1.80 (q, J = 12.8 Hz, 1H), 1.45 (s, 9H), 1.22 (t, J = 6.9 Hz, 3H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 156.4, 142.8, 138.6, 129.1, 127.4, 109.4, 80.1, 79.2, 73.8, 60.9, 60.2, 50.4, 41.2, 28.5, 28.4, 27.7, 26.0, 21.4, 14.1; MS (EI) m/z 497 (M − CH_3), 41 (52), 43 (44), 57 (100), 91 (99), 100 (35), 155 (44), 182 (46), 240 (47), 257 (79); HRMS calcd for $C_{23}H_{33}N_2O_8S$ 497.1958, found 497.1962.

The minor isomer **30b** was not fully characterized, identified only by NMR in the mixtures. In preparative runs, the mixture of the two isomers was used in the next step without separation.

dx.doi.org/10.1021/jo2018872 | J. Org. Chem. 2011, 76, 10050−10067

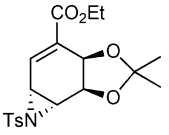
Ethyl (3*R*,4*R*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-4-(4-methylphenylsulfonamido)cyclohex-1-ene carboxylate (31).



31

The allylic alcohol **31** was generated on a small scale by base-catalyzed elimination (EtOH, EtONa, room temperature).

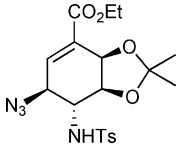
Ethyl (3a*S*,4*R*,5*R*,7a*R*)-2,2-Dimethyl-8-[(4-methylphenyl)-sulfonyl]-3a,4,5,7a-tetrahydro-4,5-epimino-1,3-benzodioxole-7-carboxylate (28).



28

To a stirred solution of acetonide **27** (500 mg, 2.23 mmol) and $Cu(acac)_2$ (58 mg, 0.22 mmol) in MeCN (1 mL) was added PhI=NTs (832 mg, 2.23 mmol) at 0 °C. The resulting solution was stirred for 5 h before being filtered through SiO_2 and concentrated. The crude material was purified via flash column chromatography with a solvent gradient of 10:1, 6:1, then 3:1 (hexane−ethyl acetate) to yield aziridine **28** (359 mg, 41%) as colorless crystals: R_f 0.46 (2:1 hexanes−ethyl acetate); mp 106−107 °C (MeOH−hexanes); $[\alpha]^{23}_D$ −52.5 (*c* 0.62, $CHCl_3$); IR (film) ν 3434, 2099, 1647, 1160 cm^{-1}; ^1H NMR (600 MHz, $(CO(CD_3)_2)$ δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 4.5 Hz, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.62 (dd, *J* = 0.9, 6.9 Hz, 1H), 4.14−4.21 (m, 2H), 3.56 (dd, *J* = 4.5, 6.2 Hz, 1H), 3.34 (dd, *J* = 1.1, 6.4 Hz, 1H), 2.45 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 145.2, 134.7, 134.1, 131.2, 130.0 (2 × C), 127.9 (2 × C), 110.3, 70.0, 68.6, 60.7, 37.5, 35.3, 27.0, 24.9, 20.8, 13.6; MS (EI) *m*/*z* 393 (M), 43 (38), 47 (29), 49 (24), 47 (100), 86 (80), 91 (20); HRMS calcd for $C_{19}H_{23}NO_6S$ 393.1246, found 393.1239.

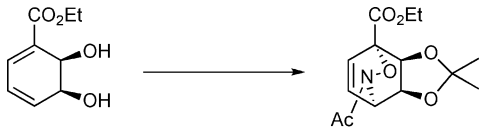
Ethyl (3a*R*,6*S*,7*R*,7a*S*)-6-Azido-2,2-dimethyl-7-{[(4-methylphenyl)sulfonyl]amino}-3a,6,7,7a-tetrahydro-l,3-benzo-dioxole-4-carboxylate (29).



29

To a stirred solution of **28** (25 mg, 0.064 mmol) and NH_4Cl (51 mg, 0.95 mmol) in DMF (0.5 mL) was added NaN_3 (8 mg, 0.127 mmol) at 0 °C. The resulting suspension was stirred for 3 h before being diluted with Et_2O (1 mL) and H_2O (1 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 × 0.2 mL). The combined organic layers were washed with brine (1 × 1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent gradient of 4:1 then 2:1 (hexane−ethyl acetate) to yield **29** (22 mg, 79%) as a white solid: R_f 0.43 (1:1 hexanes−ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 2.6 Hz, 1H), 4.99 (d, *J* = 7.8 Hz, 1H), 4.91 (d, *J* = 5.5 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.10 (dd, *J* = 5.7, 9.1 Hz, 1H), 3.93 (dd, *J* = 2.6, 9.0 Hz, 1H), 3.45−3.54 (m, 1H), 2.42 (s, 3H), 1.32−1.37 (m, 4H), 1.28−1.32 (m, 5H); MS (FAB) *m*/*z* 437 ($M + H^+$), 43 (18), 91 (100), 136 (20), 139 (39), 152 (23), 155 (72), 167 (24), 168 (22), 181 (27), 196 (38), 437 (27); HRMS calcd for $C_{19}H_{25}N_4O_6S$ 437.1495, found 437.1494

Ethyl (3a*S*,4*S*,7*R*,7a*S*)-8-Acetyl-2,2-dimethyl-7,7a-dihydro-4,7-(epoxyimino)-1,3-benzodioxole-4(3a*H*)-carboxylate (32).



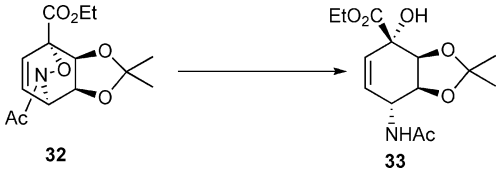
27 **32**

To a stirred solution of *cis*-dihydrodiol 27[15] (5.00 g, 27.1 mmol) in 2,2-dimethoxypropane (80 mL) was added *p*-toluenesulfonic acid (catalytic amount) at room temperature. After complete consumption of starting material (TLC analysis), the solution was cooled 0 °C before the addition of H_2O (10 mL). On a preparative scale, the intermediate acetonide was not isolated (analytical samples were purified via flash column chromatography with a solvent system of 3:1 (hexanes−ethyl acetate)).

Data for the intermediate acetonide, **ethyl (3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole-4-carboxylate**:[15] colorless oil; R_f 0.56 (1:1 hexanes/ethyl acetate); $[\alpha]^{23}_D$ +74.6 (*c* 4.02, $CHCl_3$); IR (film) ν 3018, 2987, 2936, 1712, 1651, 1425, 1380, 1259, 1155, 1031, 917, 856, 697, 667, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 5.3, *J* = 3.1 Hz, 1H), 4.84 (d, *J* = 5.7 Hz, 1H), 4.28−4.41 (m, 1H), 4.07−4.26 (m, 2H), 2.21−2.45 (m, 1H), 1.99−2.16 (m, 1H), 1.86−1.99 (m, 1H), 1.58−1.72 (m, 1H), 1.33 (d, *J* = 10.2 Hz, 6H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 142.3, 130.0, 108.5, 72.6, 70.4, 60.5, 27.8, 26.2, 25.1, 20.9, 14.2; MS (EI) *m*/*z* 226 ($M^+ - CH_3$), 211 (77), 181 (15), 169 (17), 123 (100), 105 (17), 95 (13), 83 (11), 79 (76), 67 (14), 59 (10), 55 (11), 43 (82), 41 (14); HRMS ($M^+ - CH_3$) calcd for $C_{12}H_{16}O_4$ 211.0970, found 211.0969. Anal. Calcd: C, 64.27; H, 7.19. Found: C, 64.52; H, 7.08.

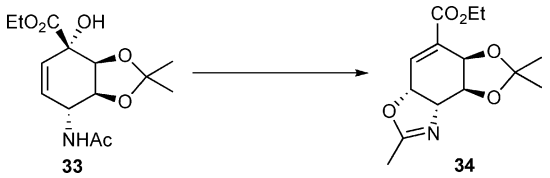
$NaIO_4$ (5.80 g, 27.1 mmol) was added to the reaction vessel prior to the addition of a solution of acetohydroxamic acid (2.03 g, 27.1 mmol) in MeOH (25 mL) dropwise over 5 min. The resulting solution was stirred at room temperature for 16 h, quenched by the slow addition of satd $NaHSO_3$ (10 mL) and extracted into Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 2:8 (hexanes−ethyl acetate) to yield **32** (5.65 g, 70% over two steps) as a white solid: R_f 0.33 (3:7 hexanes−ethyl acetate); mp 89−90 °C (hexanes−ethyl acetate); $[\alpha]^{23}_D$ −18.0 (*c* 0.54, $CHCl_3$); IR (film) ν 3466, 2938, 2987, 1747, 1684, 1620, 1372, 1275, 1086 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.57−6.65 (m, 2H), 5.47−5.52 (m, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.56 (dd, *J* = 4.7, 6.6 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.01 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 166.6, 132.4, 128.4, 111.7, 79.2, 76.1, 72.8, 62.7, 50.0, 25.6, 25.4, 21.7, 14.1; MS (EI) *m*/*z* 297 (M), 43(100), 96(30), 100(32), 105(35), 124(52); HRMS calcd for $C_{14}H_{19}NO_6$ 297.1212, found 297.1215. Anal. Calcd: C, 56.56; H, 6.44. Found: C, 56.67; H, 6.45.

Ethyl (3a*S*,4*S*,7*R*,7a*S*)-7-(Acetylamino)-4-hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (33).



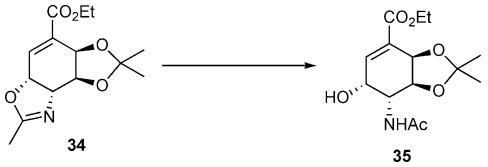
To a stirred solution of oxazine **32** (955 mg, 3.21 mmol) in 15:1/CH_3CN:H_2O (10 mL) was added molybdenum hexacarbonyl (848 mg, 3.21 mmol) at room temperature. The reaction was brought to reflux for 3 h and then cooled before the addition of activated charcoal (spatula tip). The resulting suspension was stirred for 30 min and then filtered through a plug of Celite. The crude material was purified via flash column chromatography with a solvent system of 1:9 (hexanes−ethyl acetate) to yield **33** (720 mg, 75%) as a white solid: R_f 0.20 (ethyl acetate); mp 97−99 °C (hexanes−ethyl acetate); $[\alpha]^{23}_D$ −94.3 (*c* 0.79, $CHCl_3$); IR (film) ν 3433, 2094, 1644, 1271, 1217, 1060 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.25 (d, *J* = 8.7 Hz, 1NH), 5.98 (dd, *J* = 3.8, 9.8 Hz, 1H), 5.94 (dd, *J* = 0.9, 9.9 Hz, 1H), 4.77−4.81 (m, 1H), 4.37 (t, *J* = 8.3 Hz, 1H), 4.34 (dd, *J* = 4.3, 7.7 Hz, 1H), 4.22−4.29 (m, 2H), 4.12 (s, 1OH), 1.99 (s, 3H), 1.35 (s, 3H), 1.32 (t, *J* = 7.4 Hz, 3H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 170.0, 132.9, 129.6, 109.3, 81.0, 76.3, 74.5, 62.8, 48.8, 26.2, 24.2, 23.5, 14.0; MS (EI) *m*/*z* 284 (M − CH_3^+), 43 (90), 83 (47), 84 (100), 86 (61), 96 (37), 125 (36), 153 (38), 199 (99); HRMS calcd for $C_{13}H_{18}NO_6$ 284.1130, found 284.1137. Anal. Calcd: C, 56.18; H, 7.07. Found: C, 56.27; H, 7.11.

Ethyl (3a*R*,5a*R*,8a*R*,8b*S*)-2,2,7-Trimethyl-3a,5a,8a,8b-tetrahydro[1,3]dioxolo[4,5-*e*][1,3]benzoxazole-4-carboxylate (34).



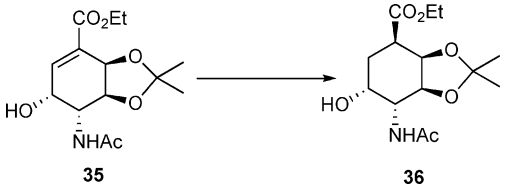
To a stirred solution of allylic alcohol **33** (400 mg, 1.33 mmol) in methylene chloride (5 mL) was added NEt_3 (0.74 mL, 4.0 mmol), DMAP (catalytic amount) and methanesulfonyl chloride (0.16 mL, 2.1 mmol) at room temperature. The resulting solution was stirred for 4 h before being quenched by the slow addition of sat. $NaHCO_3$ (5 mL), and then extracted into ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (1 × 2 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent system of 1:2 (hexanes−ethyl acetate) to yield **34** (204 mg, 54%) as a white yellow solid: R_f 0.40 (1:4 hexanes−ethyl acetate); mp 54−55 °C (hexanes−ethyl acetate); $[\alpha]^{23}_D$ +150.4 (*c* 1.25, $CHCl_3$); IR (film) ν 3543, 2986, 1722, 1667, 1372, 1218 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.0 Hz, 1H), 5.14 (dd, *J* = 2.9, 8.5 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.86 (dd, *J* = 2.7, 5.1, Hz, 1H), 4.58 (d, *J* = 8.4 Hz, 1H), 4.27−4.34 (m, 2H), 1.97 (d, *J* = 1.3 Hz, 3H), 1.42 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 165.6, 133.3, 130.5, 109.1, 73.6, 73.2, 68.9, 64.3, 61.2, 27.8, 26.3, 14.2, 14.1; MS (EI) *m*/*z* 266 (M − CH_3^+), 43 (52), 136 (19), 266 (100); HRMS calcd for $C_{13}H_{16}NO_5$ 266.1028, found 266.1032.

Ethyl (3a*R*,6*R*,7*R*,7a*S*)-7-(Acetylamino)-6-hydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole-4-carboxylate (35).



To a stirred solution of oxazoline **34** (800 mg, 2.86 mmol) in 1:1/ethanol/water (8 mL) was added calcium carbonate (570 mg, 5.69 mmol) at room temperature. The reaction mixture was brought to reflux for 48 h before concentrating. The crude residue was dissolved in ethyl acetate and then filtered through a plug of Celite. The crude material was purified via flash column chromatography with a solvent system of 1:4 (hexanes−ethyl acetate) to yield **35** (616 mg, 72%) as a white solid: R_f 0.23 (96:4 methylene chloride−methanol); mp 115−118 °C (hexanes−ethyl acetate); $[\alpha]^{23}_D$ −54.33 (*c* 1.7, $CHCl_3$); IR (film) ν 3307, 2624, 2247, 1718, 1655, 1541, 1247, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 3.1 Hz, 1NH), 5.76 (br s, 1NH), 5.01 (d, *J* = 5.6 Hz, 1H), 4.73 (t, *J* = 3.4 Hz, 1H), 4.53 (q, *J* = 5.9 Hz, 1H), 4.47 (t, *J* = 5.8 Hz, 1H), 4.26−4.31 (m, 2H), 3.07 (bs, 1OH), 2.04 (s, 3H), 1.42 (s, 6H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 165.4, 141.0, 130.3, 109.9, 73.8, 69.8, 68.8, 61.3, 52.3, 27.48, 25.7, 23.4, 14.2; MS (FAB) *m*/*z* 299 (M^+), 29(34), 43(71), 136(29), 182(23), 242(100); MS (EI) *m*/*z* 284 (M^+ − CH_3), 43 (100), 84 (25), 142 (23), 284 (17); HRMS calcd for $C_{13}H_{18}NO_6$ 284.1134, found 284.1132. Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07. Found: C, 56.22; H, 7.17.

Ethyl (3a*R*,4*R*,6*R*,7*R*,7a*S*)-7-(Acetylamino)-6-hydroxy-2,2-dimethylhexahydro-1,3-benzodioxole-4-carboxylate (36).



A hydrogenation vial was charged with ethyl acrylate **35** (150 mg, 0.501 mmol), 5% Rh/Al_2O_3 (60 mg), and 85% ethanol (2 mL) before evacuation with H_2. The reaction was stirred at room temperature and 60 psi for 144 h before being filtered through a plug of SiO_2 and concentrated. The crude material was purified via flash column chromatography with a solvent gradient of 1:1 (hexanes−ethyl acetate) and then methanol to yield **36** (143 mg, 95%) as a white solid: R_f 0.66 (90:10 $CHCl_3$−methanol); mp 156−158 °C ($CHCl_3$); $[\alpha]^{23}_D$ −90.15 (*c* 1.1, $CHCl_3$); IR (film) ν 3305, 2986, 1722, 1666, 1553, 1374, 1219, 1066, 771 cm^{-1}; ^1H NMR (600 MHz, $CO(CD_3)_2$) δ 7.17 (d, *J* = 7.7 Hz, 1NH), 4.59 (t, *J* = 4.1 Hz, 1H), 4.38 (br s, 1OH), 4.21 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.14 (dd, *J* = 4.6, 9.0 Hz, 1H), 4.11 (dq, *J* = 3.3, 7.0 Hz, 1H), 4.00−4.03 (m, 1H), 3.85 (td, *J* = 2.2, 4.5 Hz, 1H), 3.24 (dt, *J* = 4.3, 12.6 Hz, 1H), 1.92(s, 3H), 1.88−2.00 (m, 2H), 1.42 (s, 3H), 1.28 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); MS (EI) *m*/*z* 301 (M), 43 (38), 47 (29), 49 (24), 47 (100), 86 (80), 91 (20); HRMS calcd for $C_{14}H_{23}NO_6$ 301.1525, found 301.1524.

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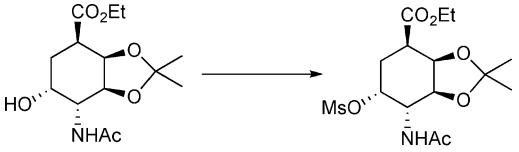
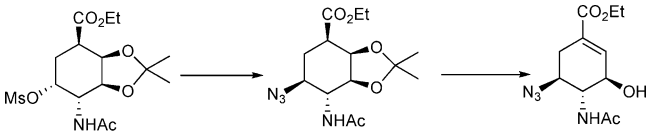
Ethyl (3a*R*,4*R*,6*R*,7*S*,7a*S*)-7-(Acetylamino)-2,2-dimethyl-6-[(methylsulfonyl)oxy]hexahydro-1,3-benzodioxole-4-carboxylate (37).



36 37

To a stirred solution of alcohol **36** (50 mg, 0.17 mmol) and triethylamine (93 μL, 0.66 mmol) in methylene chloride (100 μL) was added methanesulfonic anhydride (58 mg, 0.33 mmol) at 0 °C. The reaction temperature was slowly raised to room temperature over 24 h before the solution was diluted with methylene chloride (500 μL) and then washed with 1 N HCl (2 × 500 μL), satd $NaHCO_3$ (2 × 500 μL), and brine (1 × 1 mL). The crude material was purified via flash column chromatography with a solvent gradient of 1:2 then 1:5 (hexanes−ethyl acetate) to yield **37** (46 mg, 73%) as a white solid: R_f 0.47 (1:10 hexanes−ethyl acetate); mp 101−102 °C ($CHCl_3$); $[\alpha]^{23}_D$ −49.91 (*c* 1.21, $CHCl_3$); IR (film) ν 3307, 2628, 1719, 1651, 1361 cm cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.15−5.17 (m, 1H), 4.74 (d, *J* = 8.9 Hz, 1NH), 4.62 (t, *J* = 4.1 Hz, 1H), 4.22−4.28 (m, 1H), 4.15−4.19 (m, 1H), 4.03 (dd, *J* = 4.6, 8.6 Hz, 1H), 3.58 (dt, *J* = 2.7, 8.8 Hz, 1H), 3.12 (s, 3H), 2.92 (dt, *J* = 4.2, 13.3 Hz, 1H), 2.25 (dt, *J* = 4.2, 14.9 Hz, 1H), 2.09−2.13 (m, 1H), 2.08 (s, 3H), 1.55 (s, 3H), 1.37 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.7, 109.9, 77.7, 73.8, 73.3, 61.1, 56.4, 42.6, 37.6, 28.1, 26.2, 25.2, 21.0, 14.1; MS (FAB) *m*/*z* 380 (M + H^+), 43(23), 257(100); HRMS calcd for $C_{15}H_{26}NO_8S^+$ 380.1379, found 380.1366.

Ethyl (3*R*,4*R*,5*S*)-4-(Acetylamino)-5-azido-3-hydroxycyclohex-1-ene-1-carboxylate (39).

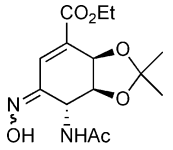


37 38 39

To a stirred solution of **37** (25 mg, 0.066 mmol) in acetone/H_2O 10:1 (0.5 mL) was added sodium azide (43 mg, 0.66 mmol). The resulting solution was stirred at room temperature for 12 h and then concentrated under reduced pressure to provide azide **ethyl (3a*R*,4*R*,6*S*,7*R*,7a*S*)-7-(acetylamino)-6-azido-2,2-dimethylhexahydro-1,3-benzodioxole-4-carboxylate (38)**, which was used without further purification. Data for **38**: R_f 0.41 (1:10 hexanes−ethyl acetate); IR (film) ν 3583, 3284, 2987, 2108, 1720, 1655, 1540, 1372, 1248, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (d, *J* = 7.5 Hz, 1NH), 4.58 (dd, *J* = 4.0, 4.8 Hz, 1H), 4.43 (dd, *J* = 4.8, 8.6 Hz, 1H), 4.13−4.29 (m, 2H), 3.91 (dt, *J* = 3.4, 11.7 Hz, 1H), 3.20 (dd, *J* = 8.1, 11.1 Hz, 1H), 2.85 (dt, *J* = 3.9, 13.2 Hz, 1H), 2.17 (dt, *J* = 3.9, 13.2 Hz, 1H), 2.02 (s, 3H), 1.91 (q, *J* = 13.1 Hz, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H); MS (FAB) *m*/*z* 327 (M+ H^+), 43(23), 257(100), 299 (33); HRMS calcd for $C_{14}H_{23}N_4O_5$ 327.1668, found 327.1670.

To a stirred solution of crude azide **38** in methylene chloride (150 μL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (15 μL, 0.1 mmol) at 0 °C. The resulting solution was stirred until complete consumption of starting material (TLC analysis, ~12 h). The reaction was diluted with methylene chloride (500 μL), washed with 1 N HCl (3 × 250 μL) and brine (1 × 500 μL), and then dried over Na_2SO_4. The crude material was purified by flash column chromatography with a solvent system of 1:7 (hexanes−ethyl acetate) to yield **39** (15 mg, 86% over two steps) as a yellow oil: R_f 0.22 (1:10 hexanes−ethyl acetate); $[\alpha]^{23}_D$ +44.3 (*c* 0.65, $CHCl_3$); IR (film) ν 3509, 2103, 1701, 1690, 1510, 1214 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.83 (t, *J* = 2.4 Hz, 1H), 5.96 (br s, 1NH), 5.28 (br s, 1OH), 4.39 (d, *J* = 2.8 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.59−3.66 (m, 2H), 2.98 (dd, *J* = 4.3, 15.9 Hz, 1H), 2.42−2.49 (m, 1H), 2.10 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 165.6, 138.1, 127.6, 71.2, 61.4, 57.9, 57.6, 29.5, 23.2, 14.1; MS (FAB) *m*/*z* 269 (M + H^+), 41 (44), 43 (100), 56 (54), 57 (46), 84 (22), 227 (55); HRMS calcd for $C_{11}H_{17}N_4O_4$ 269.1250, found 269.1248.

Ethyl (3a*R*,7*R*,7a*S*) 7-Acetamido-6-(hydroxyimino)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-4-carboxylate (41).



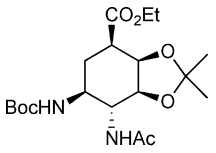
41

The oxidizing agent was prepared by stirring CrO_3 (835 mg; 8.35 mmol) in Ac_2O (2 mL) at 80 °C. After 7 min the resulting slurry was allowed to cool to room temperature diluted with 6 mL of DCM and cooled in ice-bath. This solution was added over 30 s to a cooled (4 °C) solution of tertiary alcohol **33** (1 g; 3.34 mmol) in DCM (20 mL). After 5 min of stirring the reaction was quenched by addition of 8 mL EtOH, pyridine (0.4 mL) and solid $NaHCO_3$ (2 g). Reaction mixture was then stirred additional 5 min in ice bath and 30 min at room temperature. On a preparative scale the intermediate enone **ethyl (3a*R*,7*S*,7a*S*) −7-acetamido-2,2-dimethyl-6-oxo-3a,6,7,7a-tetrahydrobenzo[d]-[1,3]dioxole-4-carboxylate (40)** was not isolated and taken directly to the next step. Analytical sample was purified via flash column chromatography (ethyl acetate). Analytical data for intermediary enone **40**: Colorless oil: R_f 0.6 (ethyl acetate); $[\alpha]^{20}_D$ +19.35 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3385, 2988, 1724, 1712, 1662, 1543, 1383, 1253, 1077, 1024; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.10 (d, *J* = 5.4 Hz, 1H), 5.13 (d, *J* = 4.8 Hz, 1H), 4.82 (m, 1H), 4.39 (m, 1H), 4.35 (q, *J* = 7.2 Hz, 1H), 2.10 (s, 3H), 1.61 (s, 3H), 1.48 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 170.8, 164.5, 140.7, 134.5, 112.0, 70.3, 62.3, 58.3, 27.7, 26.4, 23.2, 14.0; MS (EI) *m*/*z* 297 (M^+), 239 (4), 221 (4), 197 (14), 175 (13), 151 (11), 84 (100), 43 (34); HRMS calcd for $C_{14}H_{19}NO_6$ 297.1212, found 297.1218.

The above reaction mixture was again cooled in ice bath, and $NH_2OH{\cdot}HCl$ (2.32 g; 33.43 mmol) was added in one portion. After 1 h of stirring in the ice bath, the reaction mixture was allowed to warm to room temperature and stirred for additional 16 h. The mixture was then diluted with ethyl acetate (130 mL) and extracted 4 × 8 mL with saturated $NaHCO_3$ solution. Combined aqueous layers were re-extracted with ethyl acetate (30 mL). The combined organic layer was dried with $MgSO_4$ and evaporated. Chromatography of residue [hexane−ethyl acetate (1:1) → ethyl acetate, 30 g silica] afforded 860 mg (82%) of oxime **41** as a greenish oil which solidified on trituration with 2-propanol. Recrystallization from 2-propanol−hexane provided **41** as white solid: mp 106−116 °C (2-propanol); R_f 0.30 (ethyl acetate); $[\alpha]^{20}_D$ −52.63 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3367, 2988, 1720, 1659, 1547, 1382, 1246, 1069, 1023; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (bs, 1H), 7.77 (s, 1H), 6.29 (d, *J* = 8.4 Hz, 1H), 5.04 (d, *J* = 5.4 Hz, 1H), 5.02 (dd, *J* = 8.4, 8.1 Hz, 1H), 4.32 (m, 1H), 4.30 (m, 2H), 2.06 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 165.4, 148.9, 132.4, 124.8, 111.1, 76.0, 70.6, 61.7, 49.9, 27.9, 26.4, 23.3, 14.1; MS (FAB+) *m*/*z*

313 (M + H)$^+$, 255 (73), 195 (76), 150 (16), 43 (38); HRMS calcd for $C_{14}H_{21}N_2O_6$ [M$^+$ + 1] 313.1400, found 313.1406. Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45. Found: C, 54.80; H, 7.52 (crystals contain 15 mol % of 2-propanol).

(3a*R*,6*S*,7*R*,7a*S*)-7-Acetylamino-6-*tert*-butoxycarbonylamino-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[1,3]dioxole-4-carboxylic Acid Ethyl Ester (43). *Procedure A ("Stepwise").*



43

Suspension of oxime **41** (400 mg; 1.27 mmol) and 100 mg of Rh/Al_2O_3 (5%) in EtOH (96%, 45 mL) was hydrogenated in the Parr apparatus (60 pound/in.^{2}). After 16 h, the reaction mixture was filtered through a short bed of Celite and evaporated. On a preparative scale, the amine **ethyl (3a*R*,4*R*,6*S*,7*R*,7a*S*)-7-acetamido-6-amino-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxole-4-carboxylate (42)** was not isolated but taken directly to the next step. The analytical sample was purified via flash column chromatography [dichloromethane−methanol (1:1)] to yield amine **42** as colorless oil: R_f 0.26 (1:1 dichloromethane−methanol); $[\alpha]^{20}_D$ −11.54 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3445, 2984, 1733, 1654, 1556, 1384, 1222, 1144, 1049; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.52 (d, *J* = 8.4 Hz, 1H), 4.58 (dd, *J* = 4.8, 4.2 Hz, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 4.05 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.56 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.81 (ddd, *J* = 13.2, 4.2, 4.2 Hz, 1H), 2.76 (m, 1H), 2.06 (s, 3H), 2.04 (m, 1H), 1.85 (ddd, *J* = 13.2, 11.9, 11.9 Hz, 1H), 1.55 (s, 3H), 1.36 (s, 3H), 1.28 (t, *J* = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.8, 109.7, 77.9, 74.0, 60.9, 59.7, 50.8, 41.4, 30.9, 28.1, 26.2, 23.8, 14.1; MS (FAB) *m*/*z* 301 (M$^+$ + H), 273 (8), 226 (7), 184 (13), 151 (7), 110 (9), 43 (13); HRMS calcd for $C_{14}H_{24}N_2O_5$ 300.1685, found 300.1800.

Minor overhydrogenated product: ethyl (1R,3S,4R,5R)-4-acetamido-3-amino-5-hydroxycyclohexanecarboxylate: white solid; mp 158−162 °C ($CHCl_3$); R_f 0.10 (1:1 dichloromethane−methanol); $[\alpha]^{20}_D$ dynamic −12 to +7 (*c* 1, $CHCl_3$/MeOH 1:1); IR (KBr, cm^{-1}) ν 3444, 3422, 3279, 3093, 2982, 2932, 2900, 2865, 2846, 2798, 1731, 1640, 1592, 1562, 1453, 1383, 1320, 1276, 1244, 1222, 1191, 1155, 1101, 1048, 1031, 977, 956, 855, 744, 609; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.2 Hz, 2H), 3.50−3.42 (m, 2H), 3.33 (dddd, *J* = 4 × ∼1.5 Hz, 1H), 2.62 (m, 1H), 2.50 (dddd, *J* = 3.3, 3.3, 12.6, 12.6 Hz, 1H), 2.27−2.16 (m, 2H), 2.05 (s, 3H), 1.57−1.48 (m, 1H), 1.44 (ddd, *J* = 6.3, 6.3, 6.3, 1H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 173.5, 70.4, 60.8, 60.5, 52.0, 38.7, 36.1, 35.1, 21.8, 13.2; MS (FAB+) *m*/*z* 245 (100), 168 (12); HRMS calcd for $C_{11}H_{21}N_2O_4$ 245.1467, found 245.1501.

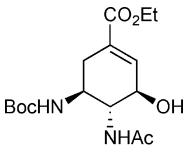
The crude mixture containing **42** and the minor overhydrogenated product was dissolved in dichloromethane (20 mL), Boc_2O (800 mg; 3.66 mmol) was added, and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (ethyl acetate−hexane 1:1). After 6 h, the reaction mixture was diluted with DCM (45 mL) and washed with saturated solution of $NaHCO_3$ (5 mL + 1 g of solid $NaHCO_3$). The organic layer was dried with $MgSO_4$ and evaporated. Chromatography of residue [ethyl acetate−hexane (3:1)→ ethyl acetate, 15 g silica] afforded 260 mg (50%) of protected amide **43** as white solid and ∼10% of overhydrogenated byproduct **ethyl (1*R*,3*S*,4*R*,5*R*)-4-acetamido-3-(*tert*-butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate (44)**.

Analytical data for major product **43**: white solid; mp 174−175 °C (ethyl acetate−hexane); R_f 0.3 (ethyl acetate); $[\alpha]^{20}_D$ −33.5 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3349, 2978, 2930, 2885, 2360, 2340, 1731, 1682, 1656, 1528, 1459.87, 1384, 1371, 1346, 1289, 1253, 1219, 1166, 1120, 1092, 1064, 1044, 1024, 1008, 988, 969, 958, 929, 905, 870, 800, 781, 755, 715, 696, 653, 624, 586, 545, 514, 464, 431; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.63 (d, *J* = 9.3 Hz, 1H), 4.96 (d, *J* = 8.7 Hz, 1H), 4.57 (dd, 2 × *J* = 3.9, 3.9 Hz, 1H), 4.33−4.18 (m, 2H), 4.00 (ddd, *J* = 11.4, 9.3, 9.0 Hz, 1H), 3.86 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.38 (m, 1H), 2.83 (ddd, *J* = 4.2, 4.2, 8.7 Hz, 1H), 2.12 (ddd, *J* = 3.9, 3.9, 9.6 Hz, 1H), 2.01 (s, 3H), 1.92 (ddd, *J* = 13.2, 13.2, 13.2 Hz, 1H), 1.43 (s, 9H), 1.36 (s, 3H), 1.28 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 170.4, 109.9, 79.7, 78.7, 73.8, 61.0, 55.2, 50.8, 41.4, 29.7, 28.3, 28.0, 26.2, 23.4, 14.2; MS (EI+) *m*/*z* (M$^+$ −CH_3) 385(3), 341(11), 329(15), 311(20); HRMS calcd for $C_{18}H_{29}N_2O_7$ 385.1975, found 385.1983. Anal. Calcd for $C_{19}H_{32}N_2O_7$: C, 56.99; H, 8.05; N, 7.00. Found: C, 57.13; H, 8.19; N, 6.93.

Ethyl (1*R*,3*S*,4*R*,5*R*)- 4-acetamido-3-(*tert*-butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate (44). Analytical data for minor product **44**: waxy solid; mp 180 °C (ethyl acetate−hexane); R_f 0.1 (ethyl acetate); $[\alpha]^{20}_D$ −90.0 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3357, 2979, 2936, 2871, 1725, 1686, 1654, 1569, 1559, 1526, 1457, 1384, 1340, 1328, 1317, 1284, 1244, 1171, 1129, 1079, 1023, 999; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (bs, 1H), 5.01 (d, *J* = 7.2 Hz, 1H), 4.16 − 4.11 (m, 2H), 3.55 (m, 2H), 3.48 (m, 1H), 2.44 (dddd, *J* = 12.0, 12.0, 3.6, 3.6 Hz, 1H), 2.34 (m, 1H), 2.18 (m, 1H), 2.00 (s, 3H), 1.56−1.50 (m, 2H), 1.49 (s, 9H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.64, 173.5, 80.4, 73.4, 62.0, 60.9, 50.6, 38.7, 36.2, 33.6, 28.3, 23.2, 14.1; MS (FAB+) *m*/*z* 345 (M$^+$ + H), 289 (45), 245 (100), 168 (26); HRMS calcd for $C_{16}H_{29}N_2O_6$ 345.2053, found 345.2026. Anal. Calcd for $C_{16}H_{28}N_2O_6$: C,55.80; H, 8.19; N, 8.13. Found: C, 55.25; H, 8.24; N, 7.56.

Procedure B ("One Pot"). A suspension of oxime **41** (73 mg; 0.24 mmol), Boc_2O (0.105 mg; 0.48 mmol) and 20 mg of Rh/Al_2O_3 (5%) in EtOH (96%, 2 mL) was hydrogenated in a Parr apparatus (60 pound/in.^{2}). After 16 h, the reaction mixture was filtered through a short bed of Celite and concentrated. Chromatography (ethyl acetate, 6 mL of silica) yield 87 mg (93%) of amide **43** as a white solid.

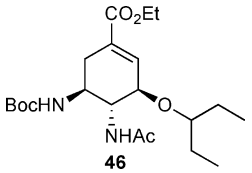
Ethyl (3*R*,4*R*,5*S*)-4-Acetylamino-5-*tert*-butoxycarbonylamino-3-hydroxycyclohex-1-enecarboxylate (45).



45

Acetonide **43** (534 mg; 1.33 mmol) was dissolved in EtOH (10 mL), and 12.4 mL of ethanolic sodium ethoxide solution (0.05 M) was added dropwise over period 1 min. After 5 min of stirring at room temperature, the reaction mixture was quenched by addition of 1 g of silica and then filtered and evaporated. Chromatography [ethyl acetate → ethyl acetate−ethanol (1:1), 5 g of silica] of the residue afforded 432 mg (94%) of allyl alcohol **45** as a white solid: mp 177−178 °C (ethyl acetate−hexane); R_f 0.2 (ethyl acetate); $[\alpha]^{20}_D$ −9.14 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3341, 2926, 2854, 2360, 2326, 1726, 1680, 1654, 1626, 1530, 1460, 1319, 1295, 1249, 1165, 1127, 1091, 1046, 1025, 992, 946, 908, 863, 782, 755, 735, 644, 607, 590, 571, 543, 491, 460, 437; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 5.8 Hz, 1H), 6.83 (dd, *J* = 2.4, 2.4 Hz, 1H), 5.07 (bs, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 4.36 − 4.29 (m, 1H), 4.27 − 4.16 (m, 2H), 3.85 − 3.83 (m, 1H), 3.77 − 3.73 (m, 1H), 2.84 (dd, 1H, *J* = 17.4, 5.1 Hz, 1H), 2.21 (dddd, *J* = 17.4, 11.0, 2 × ≈ 3 Hz, 1H), 2.03 (s, 3H), 1.47 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 165.9, 157.6, 139.1, 127.7, 80.9, 73.6, 61.1, 60.6, 48.1, 30.8, 28.2, 23.1, 14.2; MS (FAB+) *m*/z 343 (M$^+$ + H), 287(100), 243(25), 208(30); HRMS calcd for $C_{16}H_{27}N_2O_6$ 343.1870, found 343.1842. Anal. Calcd for $C_{16}H_{27}N_2O_6$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.31; H, 7.83; N, 8.17.

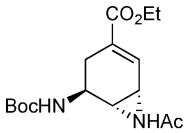
Ethyl (3*R*,4*R*,5*S*)-4-Acetamido-5-(*tert*-butoxycarbonylamino)-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (46).



46

To a solution of aziridine **47** (16 mg; 0.05 mmol) in 3-pentanol (1 mL) was added $Cu(OTf)_2$ (3 mg; 0.008 mmol). After 16 h, the reaction mixture was quenched by addition of saturated solution of $NaHCO_3$ (0.1 mL) and concentrated. Chromatography of the residue [hexane−ethyl acetate (3:1) → (2:1), 4.5 mL of silica] afforded 12 mg (60%) of compound **46** as a white solid: mp 144−145 °C ($CHCl_3$); R_f 0.3 (ethyl acetate−hexane 1:2); $[\alpha]^{20}_D$ −21.54 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) ν 3324, 2976, 3966, 2933, 2877, 2855, 1720, 1687, 1658, 1587, 1536, 1459, 1384, 1297, 1250, 1176, 1146, 1130, 1086, 1054, 1019, 948; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81 (s, 1H), 5.80 (d, J = 9.6 Hz, 1H), 5.11 (d, J = 9.0 Hz, 1H), 4.22 (m, 2H), 4.08 (ddd, J = 2 × ≈ 4.8, 9.3 Hz, 1H), 3.97 (m, 1H), 3.81 (ddd, J = 5.1, 2 × 9.6 Hz, 1H), 3.37 (quint, J = 5.7 Hz, 1H), 2.76 (dd, J = 4.8, 17.7 Hz, 1H), 2.31 (m, 1H), 2.00 (s, 3H), 1.51 (m, 4H), 1.44 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H), 0.90 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 166.0, 156.4, 137.7, 129.3, 82.2, 79.7, 76.0, 61.0, 54.5, 49.0, 31.0, 28.3, 26.1, 25.7, 23.4 14.2, 9.5, 9.2; MS (EI+) *m*/z 325 (M^+ + H), 269 (63), 243 (19), 149 (49); HRMS calcd for $C_{21}H_{36}N_2O_6$: 412.2571. Found: 412.2573.

Ethyl (1*S*,5*S*,6*R*)-7-Acetyl-5-(*tert*-butoxycarbonylamino)-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (47).



47

To a cooled (4 °C) solution of $PhMe_2P$ (71 mg; 0.52 mmol) in dichloromethane (1 mL) was added dropwise during 1 min DIAD (104 mg; 0.52 mmol). After an additional 5 min of stirring, a solution of alcohol **45** (84 mg; 0.24 mmol) and Et_3N (7 μL; 0.05 mmol) in dichloromethane (1 mL) was added dropwise. After 10 min, the reaction mixture was directly loaded on a silica column. Chromatography [hexane−ethyl acetate (3:1) → (2:1), 6 mL of silica] afforded 53 mg (70%) of aziridine **47** as a colorless oil: R_f 0.70 (ethyl acetate−hexane 1:1); $[\alpha]^{20}_D$ −81.47 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3352, 2980, 2933, 2876, 1708, 1645, 1525, 1455, 1384, 1386, 1263, 1196, 1170, 1097, 1048, 1024, 756; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (dd, J = 4.2, 3.0 Hz, 1H), 4.57 (m, 1H), 4.48 (d, J = 7.8 Hz, 1H), 4.22 (m, 2H), 3.15 (m, 1H), 3.13 (m, 1H) 2.75 (d, J = 17.4 Hz, 1H), 2.34 (m, 1H), 2.16 (s, 3H), 1.45 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.3, 165.9, 155.0, 133.8, 130.3, 80.1, 61.1, 42.0, 41.0, 31.9, 28.3, 28.3, 26.7, 23.2, 14.2; MS (EI+) *m*/z 324 (M^+), 268(8), 251(6), 222(19), 207(45), 165(80); HRMS calcd for $C_{16}H_{24}N_2O_5$ 324.1678, found 324.1685.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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