Organic Process Research & Development **2007**, *11*, 44–51

An Epoxidation Approach to a Chiral Lactone: Application of the Shi Epoxidation

David J. Ager,*,† Ken Anderson,‡ Eric Oblinger,‡ Yian Shi,§ and James VanderRoest‡

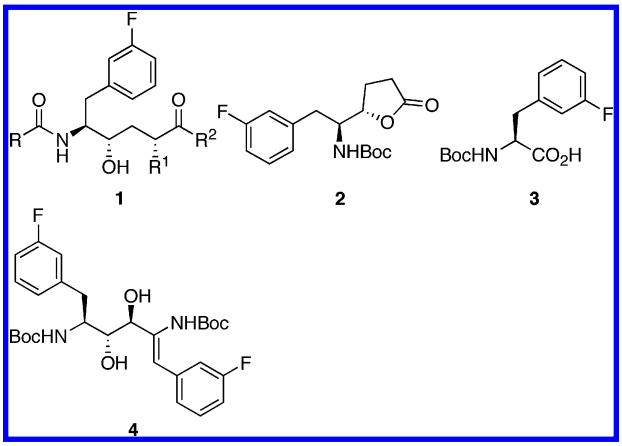
DSM Pharma Chemicals, PMB 150, 9650 Strickland Road Suite 103, Raleigh, North Carolina 27615, U.S.A., DSM Pharma Chemicals, 1421 Kalamazoo Street, South Haven, Michigan 49090, U.S.A., and Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, U.S.A.

Abstract:

The large-scale epoxidation of the alkene 7 with the organocatalyst, Epoxone (10), and Oxone as the oxidant is described. This is the first large-scale application of the Shi epoxidation methodology. The large-scale preparation of the catalyst 10 is also described. The potassium salt of the unsaturated acid precursor 7 was prepared by a Suzuki coupling from 3-fluorobenzyl chloride and the vinylborane 8 derived from 4-pentynoic acid.

Introduction

There has been interest in compounds of type **1** as dipeptide isosteres for applications as treatments for HIV as aspartyl protease inhibitors[1] and for blood pressure through modulation of rennin receptors.[2] Two approaches to the lactone **2** have been described[3] that eliminated the problems of a low temperature addition to the aldehyde derived from the Boc protected amino acid **3** and formation of the dimer **4**.[4] The two approaches that can be scaled are outlined in Scheme 1.[3]



The approach adopted by us was slightly different as the nitrogen moiety would be introduced after the stereogenic centres had been established. The route b of Scheme 1, which proceeds through an oxazolidinone showed that substitution reactions can be used with this system. Our sub-target became the lactone **5**. The nitrogen would then be introduced by an S_N2 reaction with the hydroxy group converted to an appropriate leaving group.

The key reaction to introduce the two stereogenic centres was seen as an epoxidation method. Under basic conditions, the carboxylate group of **6** would cyclise to form the lactone **5** (Scheme 2). The alkene precursor **7** can be disconnected by a Suzuki reaction to the vinylborane **8** that, in turn, can be accessed by borane addition to 4-pentynoic acid (**9**). The sequence was performed without isolation of intermediates, and the experience from the epoxidation step has given rise to independent work and improvements (vide infra).

Epoxide Formation. The fructose-derived ketone **10**, known as Epoxone, allows for the epoxidation of *trans*-alkenes with high enantioselectivity.[5,6] The method has found application in a number of syntheses.[7] As this would be the first large-scale use of the method, we had to address the preparation of the catalyst **10** as well as the epoxidation itself. In addition, because a large amount of work was involved in the process research of the epoxidation step, it was advantageous that the success of the key reaction could be considered on paper before any experimental work was performed.

The active epoxidation agent is the dioxirane **11** derived from **10**.[5] From experimental results, it has been shown that the oxygen is delivered in a spiro-fashion to the alkene rather than in a planar mode. Thus, the dioxirane's oxygen is perpendicular to the plane of the π-bond in **7**.[8] Molecular modeling indicated that the aryl group of the alkene **7** was slightly skewed compared to the plane of the alkene π-bond. This suggested that the mode of approach labeled a in Scheme 3 was energetically more favourable than the alternative approach, b, as the aryl group did not have significant interactions with the substituents of the catalyst itself. The alkene **7** is not symmetrical about the carbon−carbon double bond, and the pathway b would lead to the enantiomeric product.

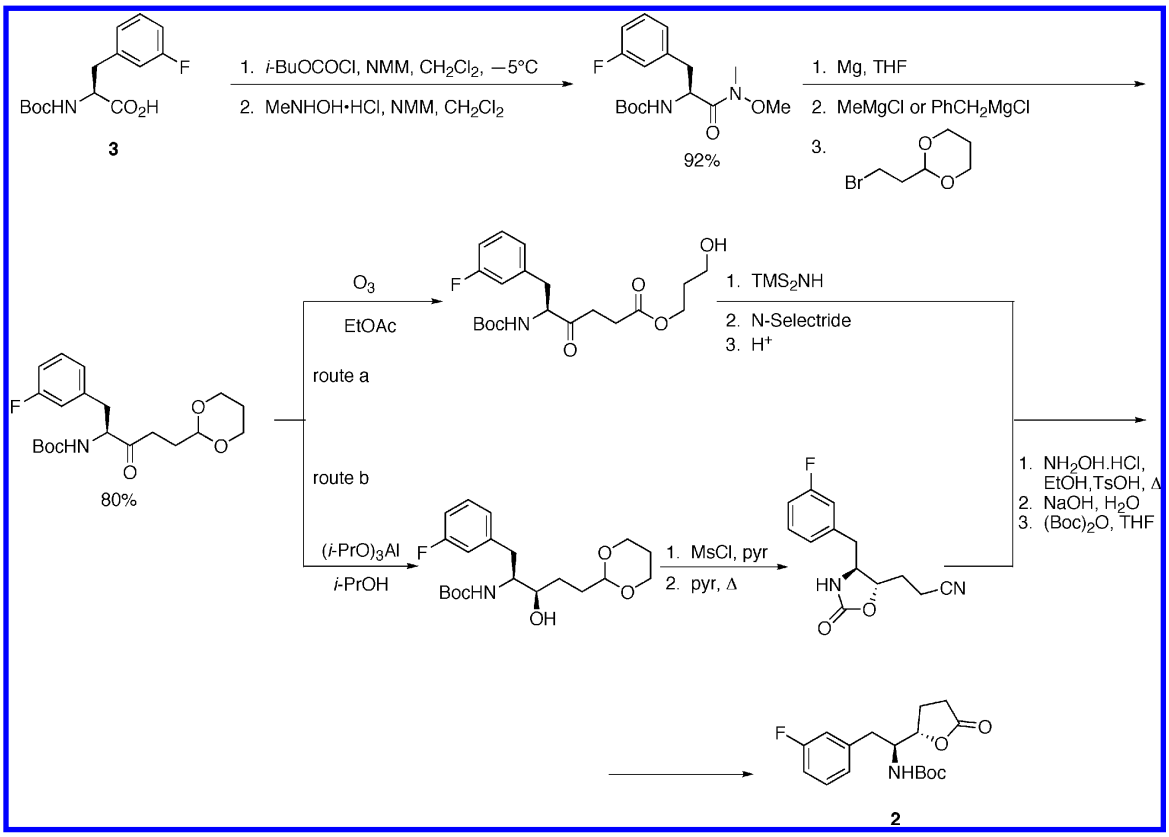
The experimental results described below show that the prediction was correct and that the major isomer of the lactone resulted from the approach described as a in Scheme

* To whom correspondence should be addressed. E-mail: david.ager@dsm.com.
† DSM Pharma Chemicals, Raleigh, North Carolina.
‡ DSM Pharma Chemicals, South Haven, Michigan.
§ Department of Chemistry, Colorado State University, Fort Collins, Colorado.

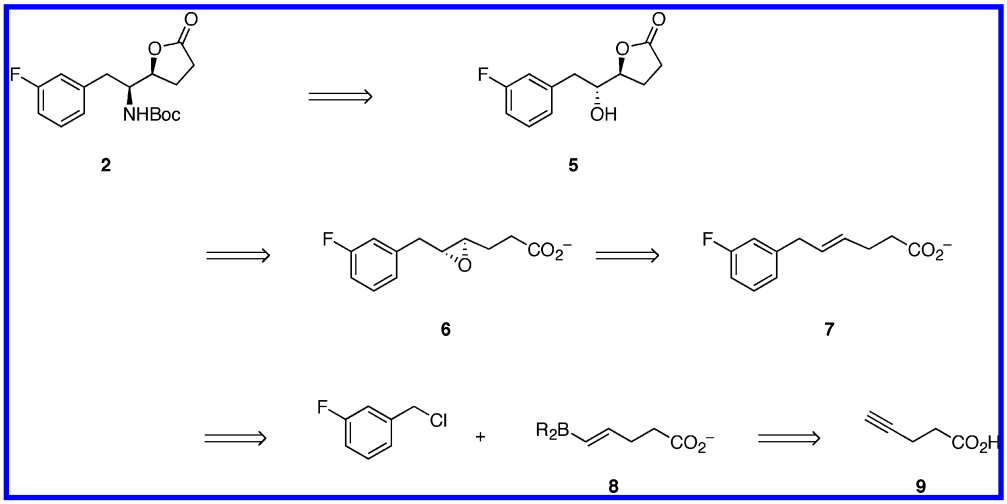
(1) Huff, J. R. *J. Med. Chem.* **1991**, *38*, 2305.
(2) Greenlee, W. J. *J. Med. Res. Rev.* **1990**, *10*, 173.
(3) Urban, F. J.; Jasys, V. J. *Org. Process Res. Dev.* **2004**, *8*, 169.
(4) Jasys, V. J.; Urban, F. J. *Tetrahedron: Asymmetry* **2001**, *12*, 361.
(5) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979.
(6) Wang, Z.-X.; Tu, F.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
(7) Shi, Y. In *Handbook of Chiral Chemistry*; Ager, D. J., Ed.; CRC, Taylor Francis: Boca Raton, 2005; pp 147−163.
(8) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794.

Published on Web 12/23/2006
10.1021/op060140e CCC: $37.00

Scheme 1



Scheme 2



3. The stereochemistry of the product was shown to be that of the desired product **6** through conversion to the amino lactone **2** prepared by alternative routes (cf. Scheme 1).

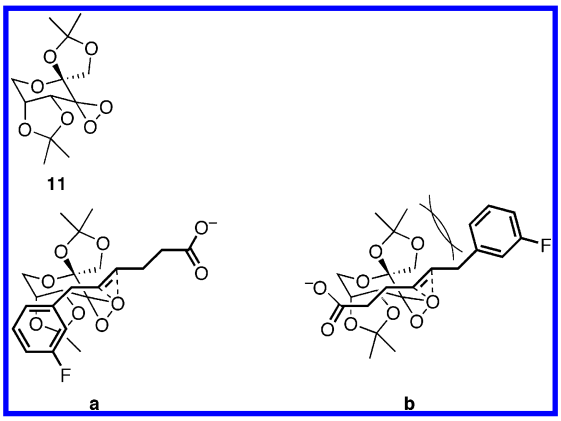
With some confidence that the epoxidation would provide high stereoselectivity, we had to address the synthesis of Epoxone (**10**) at scale, as reasonable amounts would be needed. It was known that the Baeyer−Villiger reaction competes with dioxirane formation and that a large charge of **10** would be required for the reaction to go to completion.[5] In addition, process research had to be carried out on the synthesis of the alkene **7** and the epoxidation reaction itself. The goal was to prepare over 100 kg of the lactone **5**.

Synthesis of Epoxone. The original route to the ketone **10** from D-fructose (**12**) is shown in Scheme 4.[6] This procedure has been described in detail.[9] There were a number of concerns with this methodology to prepare multikilograms of **10**, but the use of perchloric acid and a chromium-based oxidation were the ones that immediately needed to be addressed.

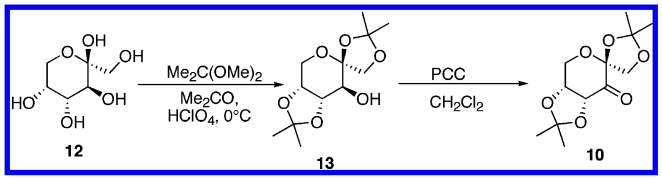
The first step was to replace the use of perchloric acid. The bis-ketal **13** is produced by the acid-catalysed reaction of D-fructose (**12**) with 2,2-dimethoxypropane. Early work had shown that the use 13 mol % of 70% $HClO_4$ as the catalyst was optimal, although hydrochloric or *p*-toluene-sulphonic (tosic) acid worked equally well. The only real problem with this reaction was when to stop it. To maximise

(9) Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1.

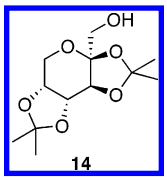
Scheme 3



Scheme 4



the yield, all of the monosaccharide **12** should react, but the amount of the thermodynamically more stable isomer **14** increases significantly if the reaction mixture is held under acidic conditions for extended periods of time.



Tosic acid was investigated in varying amounts as the catalyst. The reaction was slower than that for the analogous reaction catalysed by $HClO_4$ (8 h vs 2 h), and the yield was lower (35−40% vs 50−55%). The product was pure, however, by GC. With perchloric acid a yield of 50% or greater could be attained, but the product contained at least 15% of **14**. Although the tosic acid-catalysed reaction seemed to run a little slower, it was less likely to form **14**. Indeed, attempts to prepare significant quantities of **14** with tosic acid catalysis, so that it could be separated and purified, proved unsuccessful. As the tosic acid catalysis provided a more robust reaction, this replaced the potentially hazardous perchloric acid.

Our attention then turned to optimisation of the reaction time, since extended times seemed to do no harm. Initially a TLC system (toluene/methanol = 4:1) was tried in order to monitor the disappearance of **12** in the reaction mixture. This was unsuccessful due to the low solubility of fructose in acetone. Even when significant **12** remained as a slurry in the reaction mixture, none was seen on a TLC of the reaction solution. Furthermore, GC showed that even when **12** had been consumed, further reaction time was necessary to convert the monoacetonide intermediates to **13**. Typically, the reaction mixture contained four peaks; **13** and three intermediates or impurities, whose ratio changed over time. Typical results are summarised in Table 1. The fructose was

Table 1. **Constituents of the Reaction mixture as determined by HPLC during formation of 13 from 12 catalysed by tosic acid**

time (h)	fructose seen?	**13** (area %)	**14** (area %)	unknown I (area %)	unknown II (area %)
2	yes	49.0	15[a]	32[a]	3.9
4	yes	58.9	17.0	17.5	6.5
6	yes	62.7	17.3	12.2	7.7
8	no	63.7	17.5[a]	10[a]	8.8
24	no	66.5	17[a]	6[a]	10.6
24[b]	no	71.4	17.4[a]	4[a]	7.2

[a] Approximate values as the peaks were not baseline resolved. [b] Amount of 2,2-dimethoxypropane used was increased to 5.2 equiv. The reaction was also held for 16 h.

consumed after 8 h at 0−5 °C. Holding the mixture for another 16 h increased the amount of the desired product **13** a few percent while Unknown I declined, Unknown II increased, and the amount of **14** remained approximately the same. With perchloric acid the amount of **14** increases over the course of the reaction to the detriment of **13**.

Since a complex set of equilibria is involved in the overall desired reaction, an experiment was performed to see if increasing the amount of 2,2-dimethoxypropane from 2.2 equiv to 5.2 equiv would be advantageous. The hold period was still 16 h. These results are included as the last row of Table 1. There was an improvement in the amount of **13** formed, but not enough to justify the cost of the extra reagent.

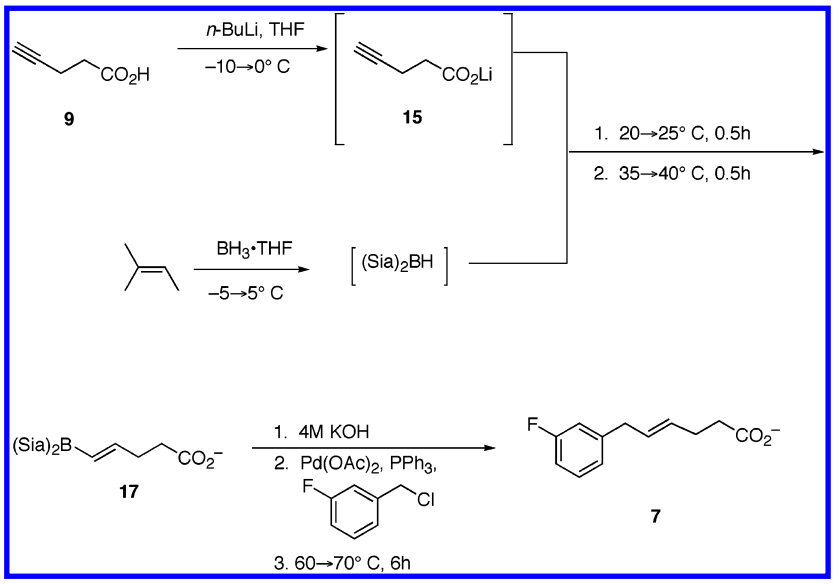
The goal for the oxidation step was to circumvent the use of a chromium reagent. The first series of experiments used pyridine/sulphur trioxide complex as the oxidant. Oxidations with this reagent can be run at ambient temperature rather than the cryogenic temperatures needed for a classic Swern oxidation. Laboratory experiments were successful with the pyr·SO_3 reagent. During preliminary scale-up experiments one lot of the alcohol **13** was produced that still contained 14% of the isomer **14**. The oxidation of the impure **13** produced the aldehyde analogue of **14** that could be removed by a sodium bisulphite wash during the oxidation work up. Although white, crystalline ketone **10** was produced after carbon treatment, there was an odour to the product. Although recrystallisation did reduce the sulphurous smell, it was never removed. As a consequence, other oxidation methods were investigated.

The use of TEMPO with bleach as the oxidant has been described for the oxidation of a wide variety of primary and secondary alcohols.[10,11] However, with the alcohol **13** as substrate little conversion was observed. The addition of phase transfer catalysts did not improve the situation. Presumably, the alcohol **13** is too hindered for reaction to occur. This steric problem has also been noted by others.[12]

Our attention turned to ruthenium-catalysed oxidations. In all our experiments ruthenium(III) chloride hydrate was used as a cheap source of the metal. The first method used bleach (10−12% NaOCl) as the oxidizing agent, while the

(10) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
(11) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212.
(12) Gonsalvi, L.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Lett.* **2002**, *4*, 1659.

Scheme 5



second used sodium periodate. The first approach turned out to be problematic. A number of process problems were identified such as the rate of addition of the bleach solution; deviations in addition rate caused the catalyst to prematurely shut down, resulting in incomplete reaction. In addition, attempts to "restart" the oxidation by adding more bleach and/or ruthenium catalyst did not effectively rectify the situation. There was also evidence that the bleach caused degradation of the product. As this approach would require a high degree of sophistication in terms of pH control, bleach addition rate, and precise temperature control, it was abandoned. It should be noted that after this decision, a report appeared using [(*i*-Pr)$_4$N](RuO$_4$) (TPAP) with bleach in buffered biphasic systems with an ether as the organic solvent;[12] however, the problems associated with the use of bleach were still apparent.

It was known that **13** could be oxidised with RuCl$_3$ as catalyst precursor in water/chloroform using NaIO$_4$ as oxidant and in the presence of a phase transfer catalyst.[13] These experiments could be repeated with high yields. We looked at replacing chloroform as the solvent. Although ethyl acetate did provide the desired ketone **10** in good yield, the reaction was complicated by the solvent instability under the reaction conditions. Some hydrolysis of the ethyl acetate occurred during the reaction, and the resultant ethanol consumed some of the oxidant. It was thought that this hydrolysis problem could be avoided if a better solvent could be found. To this end, diethoxymethane proved to be the solution. GC analysis showed complete conversion 1 h after the periodate addition was completed. Even more encouraging was the fact that a rough cost calculation showed this method to be less expensive than the pyr•SO$_3$ method, but this may relate to DSM being a sodium periodate producer. It may also be possible to recycle the sodium iodate by-product, but this was never investigated. The amount of ruthenium not only affects the reaction rate, but if too little is present then the reaction can stall and be difficult or impossible to restart. The experimental procedures reflect our conservative concentrations to ensure that oxidation of **13** occurred and no problems with product purity were encountered. In addition to the amount of metal, the phase transfer catalyst can be used at low concentration. In the initial experiments *N*-benzyl-*N*,*N*,*N*-triethylammonium chloride (BTEAC) was employed, but it was found that this could be replaced by the cheaper tetra-*n*-butylammonium bromide (TBAB) at 1 mol %.

After this work had been performed, a report on the synthesis of Shi's diacetate catalyst appeared.[14] The sequence goes through Epoxone and uses sulphuric acid in acetone to prepare the diacetonide **13**. The oxidation of **13** to **10** is performed with RuCl$_3$•H$_2$O using sodium periodate as the oxidant. The method uses chlorinated solvents that were avoided in all reactions during the course of our studies.

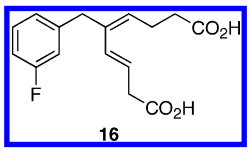
Synthesis of Alkene Substrate. The alkene **7** was prepared by a number of steps where the key carbon−carbon bond-forming reaction was a Suzuki coupling (Scheme 5). Due to the volatility of some of the intermediates and the necessity to neutralise metal ions, no isolations were performed during the sequence.

The first step in the process was deprotonation of 4-pentynoic acid (**9**) to give the lithium salt **15**. Commercial *n*-butyllithium was used to achieve this. This highly exothermic addition requires 4−6 h to complete. During the *n*-butyllithium charge, the lithium-4-pentynoate precipitates to afford a viscous, white slurry that thickens as the addition progresses. It was found that the agitation level was critical during this step. Effective mixing was necessary for starting material conversion and adequate heat transfer. Conversely, overly vigorous agitation led to the splattering of lithium-4-pentynoate solids onto the upper wall of the vessel. The solids strongly adhered to the vessel wall and could not be rinsed back into the batch. In the upcoming Suzuki coupling, lithium-4-pentynoate that remained above the liquid surface

(13) Mio, S.; Kumagawa, Y.; Soji, S. *Tetrahedron* **1991**, *47*, 2133.

(14) Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143.

was converted to the bis-acid impurity **16**. To address this dichotomy, the agitation rate was gradually increased as the *n*-butyllithium addition progressed. An identical agitation sequence was executed for all large-scale batches. Additionally, near-surface *n*-butyllithium addition was employed to reduce the potential for solids splattering. Visual inspection confirmed that salt splattering was effectively controlled in each batch.



16

There was no in-process monitoring performed at this stage. On the basis of the pK_a differential of the reactants and the 4% excess of *n*-butyllithium used, there was no reason to anticipate that the reaction would not go to completion.

The preparation of the disiamylborane (Sia_2BH) from BH_3·THF complex and isoamylene was performed under standard conditions.[15] The borane was used in 0.5 equiv excess compared to the amount of **15** to be reacted. Some problems were found with regard to the quality of the borane that were not completely established. If low-quality material was used, an increase in the amount of impurity **16** was observed. The disiamylborane solution was transferred to the lithium-4-pentynoate (**15**) slurry over approximately 30 min while maintaining the batch temperature below 0 °C. The resultant mixture was gradually heated to 35−40 °C to afford a homogeneous solution of the vinylborane **17**. Again, the instability of this vinylborane precluded in-process monitoring of this transformation.

After cooling, aqueous potassium hydroxide was added to the batch in preparation for the Suzuki coupling. Vigorous hydrogen evolution occurred during this addition and care was taken to ensure that the hydrogen concentration never built up to explosive limits. The coupling reaction was accomplished by treatment of the solution of **17** with 3-fluorobenzyl chloride (1.5 equiv.), triphenylphosphine (4 mol %), and palladium(II) acetate (1 mol %). The resultant mixture was heated under reflux for 6h, cooled to below 40 °C, and sampled to establish the reaction efficiency.

The only stable coupling component is 3-fluorobenzyl chloride. However, 3-fluorobenzyl chloride was used in 50% excess and undergoes a side reaction to give 3-fluorotoluene under the reaction conditions. Consequently, accurately tracking the reaction progress was not possible during the reaction. Instead, the alkenoic acid **7** content was established to gauge the success of the coupling. This is the first point in the process where the success of the first four chemical steps could be assessed.

Through the use of an external standard, the weight-percent of alkenoic acid in solution was determined by HPLC. This test proved to be a good indicator of the reaction efficiency, and provided a high degree of predictive ability with regard to the ultimate hydroxy-lactone yield. The yield predictions were based on a laboratory established empirical correlation between alkenoic acid **7** content and isolated hydroxylactone **5**. Following workup, the alkenoic acid was extracted into aqueous potassium hydroxide. The solution was analysed for alkenoic acid content and purity by HPLC. The levels of 4-pentenoic acid and bis-acid **16** were determined by NMR. The alkenoic acid purity ranged from 82 to 87%.

Epoxidation Step. The solution of **7** was pH adjusted to 10−11 with acid. It was already known that the optimal pH for the epoxidation step was 10 or above.[5,16] After the solution cooled, the Epoxone (**10**) was added as a solution in acetonitrile. A charge of about 30 mol % was used as the ketone is degraded by the competing Baeyer−Villiger reaction. Aqueous solutions of Oxone (potassium peroxymonosulphate) (at pH 2) and 20% aqueous potassium hydroxide were added simultaneously over approximately 4 h such that the reaction pH was maintained at 10−11 and the temperature at −5 to 5 °C. Upon completion of the Oxone charge, the resultant white slurry was warmed to 10−15 °C and held for 2 h. The reaction progress was monitored by HPLC (target of >97% conversion). If the target conversion had not been reached, additional **10**, Oxone, and base were added (vide infra). In the HPLC it was noted that an unknown impurity was formed. The lactone **5** is formed spontaneously under the reaction conditions after the epoxidation occurs.

To isolate the lactone **5**, the epoxidation reaction mixture was acidified to pH 2 with 25% sulphuric acid and extracted into toluene at 80−85 °C. The resultant toluene solution was filtered into the final isolation vessel. The toluene solution was concentrated under vacuum, cooled to 20−30 °C, and treated with heptane to crystallise the final product **5**. The overall yields were around 63%. The lactone had a chemical purity of 97% and an ee of 88%, sufficient to carry on for the subsequent reactions. The enantiomeric purity of each batch varied by only a few percent (±3%) unless problems were observed with the pH or temperature controls (vide infra). The ee of the product was then reduced. HPLC analysis of the reaction mixture and product showed that there was no change in ee during the isolation procedure.

As this was the first scale-up campaign for this reaction, a number of runs were performed at scale. Overall, in excess of 100 kg of the lactone **5** was produced. However, some problems were observed, although, to our satisfaction, the laboratory procedure was just used at a larger scale with no major changes. It should be noted that the above procedure is much simpler in terms of additives than the one given for the epoxidation of trans-β-methylstyrene and 1-phenylcyclohexene, as neither buffer, phase transfer catalyst, nor EDTA was used.[6,17,18]

The large-scale reactions were performed in a 500-gal reactor where pH monitoring had to be performed externally. This led to a time lag between the addition of the Oxone solution and a pH change. In one batch the temperature rose above the limit set and this led to degradation of the epoxidation catalyst and in this one case, additional reagents

(15) Zweifel, G., Brown, H. C. *Org. React.* **1963**, *13*, 1.

(16) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
(17) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.
(18) Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, F.; Shi, Y. *Org. Synth.* **2003**, *80*, 9.

had to be used to reach the target conversion. The asymmetric induction was reduced and the product **5** had an ee of 61%. This suggests that background epoxidation is a concern.

Although it may not be apparent from the description, the reaction had to be performed at a low concentration as Oxone is not very soluble in water as is the potassium sulphate by-product. This problem was also observed in other epoxidation reactions and led to the adoption of the use of hydrogen peroxide as the oxidant,[16,19] rather than Oxone, although this reagent was never used in this campaign nor to prepare the lactone **5**. In addition to the use of hydrogen peroxide as the oxidant, the ketone has been modified to circumvent the problems of the competing Baeyer−Villiger reaction.[16]

With the excepton of the batch where temperature control was an issue, the epoxidation reaxction was reproducible and provided consistent quality. The main problem in the sequence was associated with the formation of the borane intermediate that was traced to the quality of the borane.

Summary

The epoxidation of the *trans*-alkene **7** has been performed with good enantioselectivity and chemical yield by organocatalysis with the dioxirane derived from the ketone **10**. The campaign showed that the epoxidation is a viable reaction at scale although some small problems were encountered. Further research has addressed these problems at laboratory scale, and applications at larger scale are the topics of current work.

A cost-effective method was developed for the preparation of the ketone **10**. The overall synthesis of the lactone **5** was accomplished without the isolation of any intermediates.

Experimental Section

Gallon (gal) refers to a U.S. gallon. NMR spectra were obtained on a Bruker 300 in the solvent indicated. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates, 0.2 mm (Merck). Visualisation was achieved with an acidic anisaldehyde spray prepared by mixing anisaldehyde (2 mL) and sulphuric acid (2 mL) and diluting the resultant blue mass in 95% EtOH (36 mL) and a few drops of AcOH.

Gas chromatography (GC) was performed on a Shimadzu GC-14A with a Quadrex 007-225 column (25 m × 0.53 mm × 2 m). The carrier gas was helium at 5 mL/min. The initial column temperature was 150 °C for 2.5 min followed by a temperature ramp of 10 °C/min to 220 °C where it was held for 5 min. The acetonide **13** had a retention time of 9.7 min, and Epoxone (**10**), 8.6 min.

HPLC analyses were performed on a Hitachi L-7200 instrument. The alkene purity and epoxidation reaction were determined by HPLC on a Zorbax XDB Phenyl 25 cm × 4.6 mm × 5 mm column eluting with a 47:53 mixture of acetonitrile and 0.15% aqueous trifluoroacetic acid. Retention times were 4.1 min for 4-pentenoic acid, 5.8 min for the lactone **5**, and 10.6 min for the conjugate acid of **7**. This methodology was used to determine concentrations of solutions against external standards.

(19) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

Laboratory-Scale Experiments. *Preparation of Bisacetonide (**13**).* D-Fructose (**12**) (90.0 g, 0.5 mol) and 2,2-dimethoxypropane (116.5 g, 1.118 mol) were stirred in acetone (470 mL) and cooled to <50 °C. *p*-Toluenesulphonic acid (4.8 g, 0.025 mol, 5 mol %) was added and the reaction mixture held at 0−5 °C for 16−20 h. The pH was then adjusted to >7 with 50% aqueous NaOH, and the Me_2CO was removed under vacuum on a rotary evaporator. Toluene (100 mL) was added and removed on the rotary evaporator to aid in the removal of the remaining traces of acetone. The residue was then dissolved in toluene (400 mL) and washed with brine (125 mL) and then water (25 mL). Approximately half of the toluene was removed by vacuum distillation. Heptane (500 mL) was added slowly to the solution at room temperature. The resultant slurry was cooled to <50 °C and filtered. The crude product was washed with heptane (∼50 mL) and dried at 65 °C to give 55.2 g (42.5%) of **13** with a purity of 96% by GC.

*Preparation of Epoxone (**10**).* The alcohol **13** (40.0 g, 0.154 mol) was dissolved in diethoxymethane (DEM) (120 mL). To this solution, tetrabutylammonium bromide (TBAB) (48.8 mg, 1.5 mmol; 1 mol %), K_2CO_3 (4.9 g, 35.4 mmol, 23 mol %), and $RuCl_3 \cdot H_2O$ (1.0 g, 4.8 mmol, 3 mol %) were added. A solution of $NaIO_4$ (48.8 g, 0.228 mol) in water (340 mL) was prepared and added to the alcohol slowly, keeping the temperature below 40 °C by external cooling with an ice bath. After 1 h at room temperature, GC showed the reaction to be complete. IPA (10 mL) was added. The mixture was stirred for 30 min followed by filtration through Celite. The product was then extracted into EtOAc (120 mL followed by 3 × 40 mL). The combined organic extracts were washed with 10% Na_2SO_3 solution (40 mL) followed by 10% brine (40 mL). The EtOAc was removed by vacuum distillation and the residue dissolved in heptane (∼285 mL) at >45 °C. The solution was slowly cooled until a slurry formed. It was then cooled to <−5 °C, and the ketone **10** was isolated by filtration. The wetcake was washed with cold heptane (25−50 mL) and dried in a vacuum oven at 60 °C to yield 29.1 g (73.3%) of Epoxone.

Preparation of alkene (7). *Formation of Lithium-4-pentynoate (**15**).* A solution of 4-pentynoic acid (6.50 g, 0.066 mol) in THF (50 mL) was cooled to between −5° and 0 °C, then treated with 2.5 M *n*-butyllithium in hexanes (28.0 mL, 0.070 mol). The addition rate was adjusted such that the temperature was maintained below 5 °C. The resultant white slurry was stirred for 30 min at −5 to 5 °C. The mixture was used without any purification.

Preparation of Disiamylborane. In a flask separate from that used for the formation of **15**, 1 M $BH_3 \cdot$THF (100 mL, 0.100 mol) was cooled to between −10° and 0 °C, and then treated with isoamylene (21 mL, 0.198 mol) while maintaining the temperature below 10 °C. After stirring for 40 min at −5 to 5 °C, the disiamylborane solution was transferred to the lithium-4-pentynoate slurry as described below.

*Preparation of Vinylborane (**17**).* The solution of $(Sia)_2BH$ was added to that of the suspension of lithium 4-pentynoate (**15**), both prepared as described above, while maintaining the temperature between −10° and 0 °C. After stirring for

45 min, the mixture was gradually warmed to 35−40 °C and held for 1 h to afford the vinylborane intermediate **17**.

*Preparation of Alkene **7**.* The vinylborane solution from the previous step was cooled to 20−25 °C and 4 M aqueous KOH (33 mL, 0.132 mol) added slowly as hydrogen evolution occurred. The solution was then treated with 3-fluorobenzyl chloride (12 mL, 0.099 mol), Ph_3P (0.700 g, 2.67 mmol), and $Pd(OAc)_2$ (0.150 g, 0.667 mmol). The resultant olive-green mixture was heated to 65−70 °C for 1 h. After atmospherically stripping the THF and hexanes, MTBE (133 mL) and water (67 mL) were added. The layers were separated, and the aqueous layer was acidified with 25% H_2SO_4. The acidified aqueous layer was extracted with toluene (133 mL) at 50−55 °C. The toluene layer was extracted with KOH solution [from water (93 mL) and 45% KOH (7 mL)] to generate the aqueous potassium *trans*-alkenoate solution required for the epoxidation step. The concentration of the solution of **7** was determined by HPLC.

*Epoxidation of Alkene **7**.* The potassium *trans*-alkenoate solution from the Suzuki cross-coupling was adjusted to pH 10.5 with 25% aqueous H_2SO_4. The solution was cooled to between −5 to 5 °C and D-Epoxone (**10**) (4.3 g, 0.017 mol), as a solution in acetonitrile (20 mL) was added. While the mixture was stirred with vigorous agitation, Oxone (45.3 g, 0.074 mol) in water (160 mL) was added to the mixture. The temperature was maintained below 10 °C by control of the Oxone solution charge rate, and the pH was maintained at 10.0−11.0 by the addition of 20% KOH as necessary. After the addition was complete, the mixture was held at 10−15 °C for 1 h. The mixture was adjusted to pH 2 with 25% H_2SO_4. Toluene (233 mL) was added, the mixture was heated to 75−80 °C, and the layers were separated. The organic layer was filtered and concentrated until the pot volume was approximately 100 mL. The solution was cooled to 20−30 °C, and heptane (67 mL) was added over approximately 1 h to crystallise the product. The solids were filtered, washed with cold heptane (∼15 mL), and dried at 35−40 °C to afford a 55% yield of hydroxylactone **5** in 86% ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 1H), 6.98 (m, 3H), 4.43 (m, 1H), 4.11 (m, 1H), 2.83−2.17 (m, 7H).

Pilot-Plant Scale Experiments. *Preparation of Bis-acetonide (**13**).* D-Fructose (**12**) (500 lbs) and 2,2-dimethoxypropane (648 lbs) were stirred with acetone (314 gal), and the mixture was cooled to 0−5 °C. *p*-Toluenesulphonic acid (26 lbs) was added and the mixture held at 0−5 °C. for 24 h. When the reaction was complete (>65% **13** as indicated by GC), water (20 gal) and 50% NaOH solution (12 lbs) were added. The acetone and methanol were removed by vacuum distillation. Toluene (66 gal) was added. The mixture was distilled under vacuum to remove the last traces of acetone. Additional toluene (266 gal) was then added and the resultant solution washed with brine (70 lbs of NaCl in 84 gal of H_2O) and then water (16 gal). The volume was then reduced to approximately 120 gallons by vacuum distillation and the product crystallised by slow addition of heptane (334 gal) at 50−60 °C followed by slow cooling. The resultant slurry was cooled to <5°, isolated on the centrifuge, and washed with heptane (∼10 gal). After drying in a vacuum tumble drier at 40−50 °C, 379 lbs (52.5%) of the alcohol **13** was obtained.

*Preparation of Epoxone (**10**).* The alcohol **13** (220 lbs), TBAB (3 lbs), K_2CO_3 (27 lbs), and $RuCl_3 \cdot H_2O$ (5.5 lbs) were stirred in DEM (556 lbs) and H_2O (26 gal). A solution of $NaIO_4$ (268 lbs) in H_2O (224 gal) was mixed separately and added slowly to the alcohol intermediate at <40 °C. The reaction was then held for 1 h at 25−35 °C, at which point it was checked for completion by GC (<1% starting material). When complete, IPA (7 gal) and celite (2 lbs) were added, and the mixture was stirred for an additional 1 h. The solution was then filtered and the product extracted into EtOAc (598 lbs followed by 3 × 198 lbs). The combined extracts were washed with 10% Na_2SO_3 (22 lbs in 26 gal H_2O) followed by 10% brine (22 lbs NaCl in 26 gal H_2O) and then distilled under vacuum to a volume of approximately 86 gallons. Heptane (102 gal) was added and approximately the same volume of solvent removed by vacuum distillation. Additional heptane was then added to bring the pot volume up to 185 gallons, whereupon the temperature was adjusted to 50−60 °C. The batch was then filtered and slowly cooled to crystallise the product. When a slurry had formed, it was cooled to 0 °C and centrifuged. The crude product was then recrystallised from IPA (300 gal) by dissolution at 70−75 °C, filtering, and slowly cooling to 0 °C. The resultant slurry was centrifuged and the solid washed with IPA (10 gal). After drying in a vacuum tumble drier at 40−50 °C, 157 lbs (71.9%) of Epoxone (**10**) was obtained.

*Preparation of the Lithium-4-pentynoate Salt (**15**).* 4-Pentynoic acid (41 lb) was charged to a dry reactor, dissolved in THF (76 gal), cooled to −10 to 0 °C, and treated with 1.01 equiv of 24% *n*-butyllithium (113 lb). The resultant thick, white slurry was held at −10 to 0 °C until the disiamylborane reagent was prepared.

Preparation of Disiamylborane Reagent. In a precooled vessel, 1 M borane−THF was charged (557 lb), cooled to −5 to −15 °C, and treated with isoamylene (88 lb) while maintaining the temperature below 10 °C. The solution was maintained at −5 to 5 °C for approximately 30 min to ensure complete conversion to the disiamylborane reagent.

Preparation of the Vinylborane (17). The disiamylborane solution prepared above was transferred to the lithium-4-pentynoate slurry over approximately 30 min while maintaining the temperature below 0 °C. The mixture was gradually warmed to 35−40 °C to afford a homogeneous solution of the desired vinylborane.

Suzuki Coupling. The vinylborane (**17**) solution, prepared as described above, was treated with 4 M aqueous KOH (243 lb), and vigorous hydrogen evolution was observed. Next, 3-fluorobenzyl chloride (90 lb) was added, followed by triphenylphosphine (5 lb) and palladium (II) acetate (1 lb). The mixture was heated under reflux at approximately 60 °C for 3−6 h. THF was stripped from the mixture by atmospheric distillation, MTBE was added (621 lb), and the mixture was circulated through a bag filter. The phases were separated, and the product was contained in the aqueous layer, which was then acidified to pH 2 with 25% sulphuric

acid (197 lb). The product was then extracted into toluene (101 gal) at 50−55 °C. The layers were separated at 50−55 °C and the toluene layer was treated with aqueous KOH [from water (71 gal) and 45% KOH (65 lb)]. The resultant aqueous alkenoic acid salt **7** solution was used without further purification in the epoxidation reaction.

Asymmetric Epoxidation. In a 500-gal reactor, the pH of the alkenoic acid salt **7** solution was adjusted to 10−11 with 25% sulphuric acid and then cooled to −5 to 0 °C. In a separate vessel, an aqueous solution of Oxone (288 lb in 122 gal water) was prepared. This solution was not held for extended periods of time. Next, D-Epoxone (127 lb) in acetonitrile was added to the solution of **7** followed by the simultaneous additions of 20% KOH and Oxone solutions. The pH was maintained at 10−11, and the temperature was kept below 5 °C throughout the reaction. The pH was monitored by an in-line pH meter while the base solution was added by peristaltic pump. Once all of the Oxone had been added, the white slurry was warmed to 10−15 °C and held within this temperature range for 2 h while the reaction was checked for completion by HPLC (target of >97% conversion).

The epoxidation reaction mixture was then acidified to pH 2 with 25% sulphuric acid and extracted into toluene at 80−85 °C. The layers were separated, and the resultant solution was filtered into the final isolation vessel. The toluene was concentrated under vacuum and cooled to 20−30 °C; heptane was then added slowly to crystallise the hydroxylactone **5**, 59 lb (63% 97% chemical purity, 88% ee).

Received for review July 11, 2006.

OP060140E