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Routes for the Synthesis of (2*S*)-2-Methyltetrahydropyran-4-one from Simple Optically Pure Building Blocks

Kevin R. Anderson,[†] Stéphanie L. G. Atkinson,[†] Takahiro Fujiwara,[‡] Melvyn E. Giles,[†] Takaji Matsumoto,[‡] Eric Merifield,*[,†] John T. Singleton,[†] Takao Saito,[‡] Tsukasa Sotoguchi,[‡] James A. Tornos,[†,§] and Edward L. Way[†]

AstraZeneca R&D Charnwood, Process Research and Development, Bakewell Road, Loughborough, Leicestershire LE11 5RH, United Kingdom, and Takasago International Corporation, Corporate Research and Development Division, 4-11, 1-Chome, Nishi-Yawata, Hiratsuka City, Kanagawa, Japan

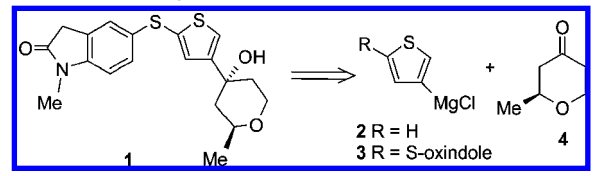
Abstract:

Routes to (2*S*)-2-methyltetrahydropyran-4-one of high optical purity starting from readily available chiral pool precursors and suitable for large-scale manufacture are described. In one approach, the key step is cyclisation of (*S*)-5-hydroxyhex-1-en-3-one, derived either from an alkyl (*S*)-3-hydroxybutyrate or (*S*)-propylene oxide. Formation of the tetrahydropyran ring directly via an intramolecular oxy-Michael reaction under acid-catalysed conditions resulted in loss of optical purity, whereas proceeding through the intermediate (2*S*)-2-methyl-2,3-dihydropyran-4-one, via an oxidative Pd-catalysed ring closure, followed by hydrogenation of the alkenyl bond, preserved the optical purity. An alternative approach to (2*S*)-2-methyl-2,3-dihydropyran-4-one is also reported, again starting from an alkyl (*S*)-3-hydroxybutyrate by elaboration to a carbonyl-protected (6*S*)-6-methyl-5,6-dihydropyran-2,4-dione derivative, followed by partial reduction and dehydration. Alternatively, the carbonyl group can be reduced out completely in one step to furnish (2*S*)-2-methyltetrahydropyran-4-one directly after deprotection.

Introduction

Leukotrienes are a family of important biological molecules which display powerful spasmogenic action in vascular and bronchial tissue. 5-Lipoxygenase is the first enzyme in the biosynthesis of these leukotrienes from arachidonic acid. Drugs which block this biosynthetic pathway by inhibition of 5-lipoxygenase may have therapeutic potential in a variety of inflammatory conditions including inflammatory bowel disease, asthma, chronic obstructive pulmonary disease (COPD), and psoriasis. A compound which displays such activity is AZD4407 (**1**),[1] which possesses three distinct moieties, an *N*-methyloxindole bridged by a thioether linkage to a 2,4-disubstituted thiophene and a chiral 2-methyltetrahydropyran-4-ol. Disconnection of **1** conveniently gives rise to the thienyl Grignard reagents **2** or **3** and (2*S*)-2-methyltetrahydropyran-4-one **4** (Scheme 1).[2] To support the development of AZD4407 we needed an efficient, robust, low-cost synthesis of pyranone **4** of high optical purity (>99%). This paper describes the identification, development, and scale-up of some routes to this intermediate, starting from small chiral molecules.

Scheme 1. **Retrosynthesis of AZD4407**



The initial discovery synthesis of pyranone **4** has been published;[3] however, this was not envisaged as a potential route for production of kilogram quantities due to its length, starting material availability, and use of some undesirable reagents for large-scale manufacture. Synthesis of pyranone **4** has also previously been reported *via* reductive resolution of the racemic mixture by a horse liver alcohol dehydrogenase;[4] however, the yield was low and the enantiomeric excess only 85%. In view of the requirement of a scaleable synthesis to supply pyranone **4** with an optical purity in excess of 99% as the (*S*)-enantiomer, an alternative resolution approach was devised, Scheme 2.[5] It was found that a racemic mixture, containing predominantly pyranols **6a** and **6c**, generated from a Prins reaction between acetaldehyde and 3-buten-1-ol **5**,[6] could be resolved by selective esterification of the unwanted (2*R*,4*S*)-isomer using Novozyme 435 and vinyl butyrate. Separation of compounds **6a** and **8** by an aqueous/organic partition was facilitated by the greater aqueous solubility of the pyranol. The desired enantiomer **6a** was then oxidised under Jones conditions to provide pyranone **4**. This route was used to manufacture around 100 kg of this intermediate to supply the initial needs of the project, and whilst this strategy was very attractive for a large-scale manufacturing route, it had some drawbacks. The undesired *trans*-pyranol isomers **6b** and **6d** formed in small amounts in the Prins reaction, which are left unreacted in the enzymatic resolution step, and would progress downstream with the major product **6a**, thus approximately doubling in level. One of these [the (2*R*,4*R*)-isomer] oxidised to (2*R*)-2-methyltetrahydropyran-4-

* Author to whom correspondence may be sent. E-mail: eric.merifield@astrazeneca.com.

[†] AstraZeneca.

[‡] Takasago.

[§] Current address: Pfizer Global R&D, Ramsgate Road, Sandwich, UK, CT13 9NJ.

(1) Bird, T. G. C.; Ple, P.; Crawley, G. C.; Large, M. S. Preparation of 4-aryl-4-hydroxy-tetrahydropyrans and 3-aryl-3-hydroxy-tetrahydrofurans as 5-lipoxygenase inhibitors. EP 623614 A1, 1994.

(2) Alcaraz, M.-L.; et al. *Org. Process Res. Dev.* **2005**, *9*, 555.

(3) Crawley, G. C.; Briggs, M. T.; Dowell, R. I.; Edwards, P. N.; Hamilton, P. M.; Kingston, J. F.; Oldham, K.; Waterson, D.; Whalley, D. P. *J. Med. Chem.* **1993**, *36*, 295. Crawley, G. C.; Briggs, M. T. *J. Org. Chem* **1995**, *60*, 4264.

(4) Haslegrave, J. A.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4666.

(5) Holt, R. A.; Rigby, S. R.; Waterson, D. Production of optically active 2-substituted tetrahydropyran-4-ones. WO 9719185 A1, 1997.

(6) Hanschke, E. *Chem. Ber.* **1955**, *88*, 1053.

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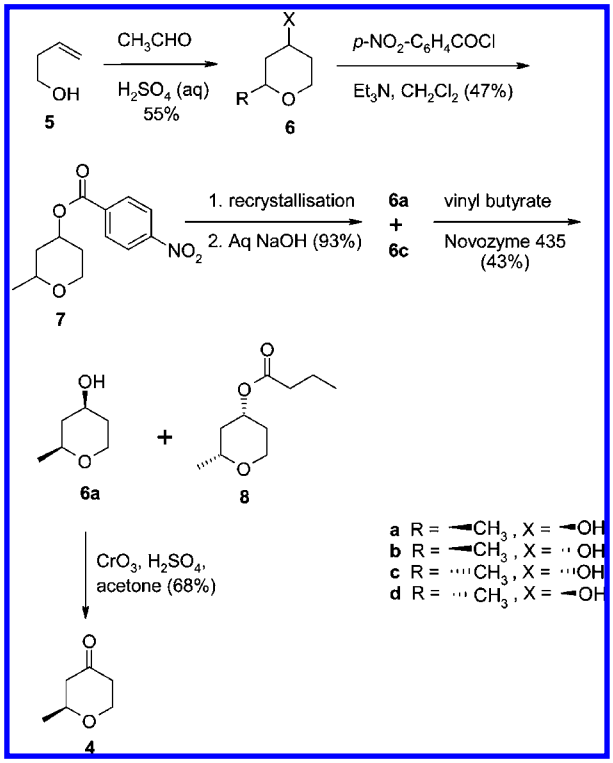
10.1021/op900163a

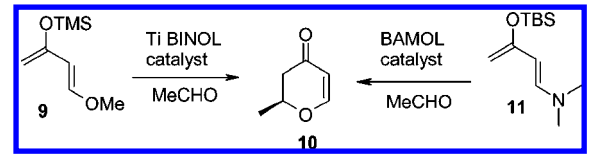
Scheme 2. **Synthesis of pyranone 4 *via* enzymatic resolution**



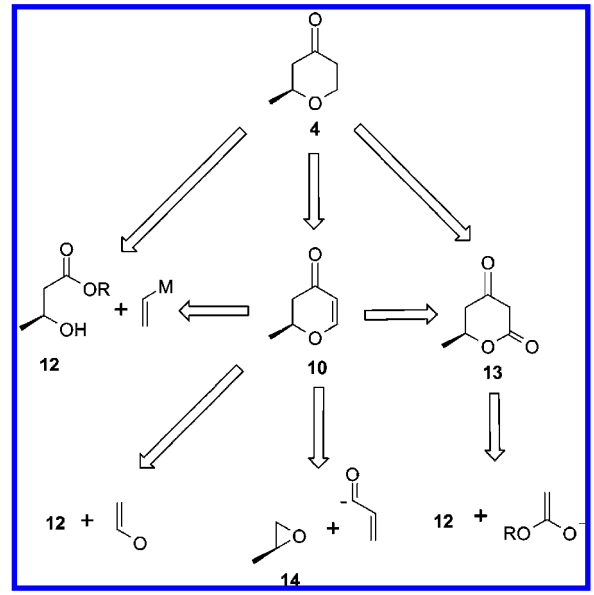
one, with a consequent reduction of the optical purity of pyranone **4**. To overcome this and minimise another troublesome impurity,[7] the crude pyranol mixture **6a**−**d** was converted to the crystalline *p*-nitrobenzoate ester **7**, which underwent several recrystallisations, after which the mixture of pyranols **6a** and **6c** was regenerated by hydrolysis with much higher purity. As well as increasing the number of steps, this additional processing regime led to an overall yield of less than 10% for this approach. A Jones oxidation was also found to be the most efficient oxidation method (at the time this work was carried out), and this was deemed unacceptable on environmental grounds for future production campaigns. These factors prompted us to focus our efforts on finding an alternative, more efficient synthesis, which would ultimately become a manufacturing route for this intermediate, in preference to development and optimisation of the chemistry shown in Scheme 2.

One alternative approach to a precursor **10**, namely the hetero Diels−Alder reaction between Danishefsky's diene **9** and acetaldehyde using a chiral titanium BINOL catalyst, has been published (Scheme 3).[8] This approach afforded dihydropyranone **10** in up to 80% yield and with an enantiomeric excess of up to 93%. A more recent publication[9] has reported the low-temperature hetero Diels−Alder reaction between a 1-amino-3-silyloxybutadiene **11** and acetaldehyde using a BAMOL catalyst system to provide dihydropyranone **10** in 75% yield

Scheme 3. **Hetero Diels−Alder approach to a pyranone precursor**



Scheme 4. **Strategies for the synthesis of pyranone 4 from small chiral molecules**



and 97% enantiomeric excess, Scheme 3. Although the absolute stereochemistry of the product was not determined, in principle either enantiomer of the dihydropyranone can be obtained by selection of the appropriate enantiomer of the catalyst. The utility of the hetero Diels−Alder reaction in general for the synthesis of the dihydropyranone ring has been amply demonstrated over recent years by the optimisation of various catalyst systems and application to the synthesis of many related products.[10]

To satisfy ongoing and future demand for this project, there was a clear need for a short route to pyranone **4** with good stereocontrol so that material of high optical purity could be obtained without recourse to time-consuming purification protocols. Consequently, strategies involving resolution, enantioselective synthesis, and synthesis from readily available chiral pool building blocks were all considered during the course of this research programme. This paper describes the results of our endeavours starting from two types of readily available small chiral molecules incorporating the desired stereocentre and having suitable functionality for further elaboration to pyranone **4**, namely esters of (*S*)-3-hydroxybutyric acid **12** and (*S*)-propylene oxide **14**, Scheme 4. These chiral pool building blocks gave us a variety of options for building up pyranone **4**

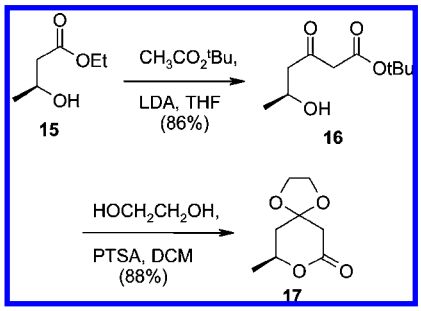
(7) The synthesis of pyranol **6** by an intramolecular Prins cyclisation between 3-buten-1-ol and acetaldehyde is reversible and can go back either to the same starting materials or to formaldehyde and 4-penten-2-ol. The latter will undergo a Prins reaction with acetaldehyde to generate 2,6-dimethylpyran-4-ol which remains essentially unreacted in the resolution step.

(8) Mitsuda, M.; Hasegawa, J. Stereoselective preparation of 2-hydrocarbyl-2,3-dihydro-4*H*-pyran-4-ones. GB 2304339 A1, 1997.

(9) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

(10) See for example: Chaladaj, W.; Kwiatkowski, P.; Jurczak, J. *Tetrahedron Lett.* **2008**, *49*, 6810. Du, H.; Zhang, X.; Wang, Z.; Bao, H.; You, T; Ding, K. *Eur. J. Org. Chem.* **2008**, 2248. Wang, Y.; Wolf, J.; Zavalij, P.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1439. Seki, K.; Ueno, M.; Kobayashi, S. *Org. Biomol. Chem.* **2007**, *5*, 1347. Berkessel, A.; Vogl, N. *Eur. J. Org. Chem.* **2006**, 5029. Du, H.; Zhang, X.; Wang, Z.; Ding, K. *Tetrahedron* **2005**, *61*, 9465. Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665.

Scheme 5. **Small-scale synthesis of lactone 17**



by incorporation of a C_2 or C_3 unit by simple functional group manipulation.

Results and Discussion

Lactone Reduction Route. Esters of (*S*)-hydroxybutyric acid are readily available materials which can be prepared by hydrogenation of the corresponding acetoacetates in good yield and high optical purity using transition metal catalysts with chiral ligands.[11] One strategy utilising such a chiral molecule as the starting point for synthesis of pyranone **4** was to install the required additional two-carbon unit by incorporation of an acetate equivalent, Scheme 5. The resulting β-keto ester **16** would then undergo cyclisation together with selective protection of the more electrophilic ketonic carbonyl group to form the protected pyran-2,4-dione **17**, which would then be subject to reduction and deprotection steps to generate the desired pyranone **4**. Whilst methods of preparing the unprotected lactone **13** (Scheme 4) are known in the literature, either by enantioselective hydrogenation[12] or *via* biotransformations[13] we chose to evaluate the chemistry given in Scheme 5 due to requirements for high optical purity and high throughput. On a small lab scale,[14] a short route to the reduction substrate was demonstrated *via* a low-temperature Claisen condensation between *tert*-butyl acetate and ethyl (*S*)-3-hydroxybutyrate **15** according to the reported conditions[15,16] to furnish β-keto ester **16** in 86% yield. Cyclisation to the lactone[16] with concomitant ketalisation was achieved in good yield, utilising ethylene glycol with TsOH as catalyst to generate lactone **17**. Despite the requirement for cryogenic reaction conditions, this provided the basis of an efficient route to the key reduction substrate.

(11) A Ru-BINAP catalyst can be used for the preparation of methyl (*S*)-hydroxybutyrate **36** from methyl acetoacetate; see: Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Organic Syntheses*; Wiley & Sons: New York, 1998; Collect. Vol. 9, p 589. SEGPHOS, however, was used as ligand in place of BINAP since it gives better results for reduction of β-keto esters: Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(12) Huck, W.-R.; Burgi, T.; Mallat, T.; Baiker, A. *J. Catal.* **2001**, *200*, 171. Fehr, M. J.; Consiglio, G.; Scalone, M.; Schmid, R. *J. Org. Chem.* **1999**, *64*, 5768.

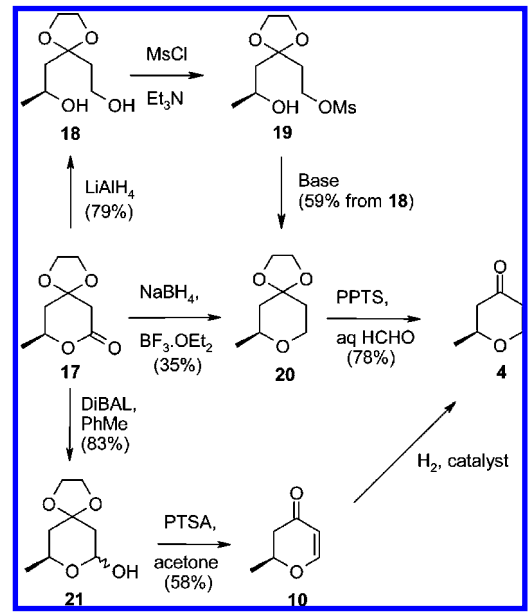
(13) Sato, M.; Sakaki, J.; Sugita, Y.; Nakano, T.; Kaneko, C. *Tetrahedron Lett.* **1990**, *31*, 7463. Tamarez, M. M.; Franck, R. W.; Geer, A. *Tetrahedron* **2003**, *59*, 4249.

(14) On a kilogram scale, lactone **17** was prepared from methyl-(*S*)-hydroxybutyrate by conversion to methyl-(*S*)-3-oxo-5-(tetrahydropyran-2-yloxy)hexanoate using methods developed from a published synthesis. Liu, L.; Tanke, R. S.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 5332. followed by acid-catalysed cyclisation to (*S*)-6-methyl-5,6-dihydropyran-2,4-dione and subsequent carbonyl protection.

(15) Deschenaux, P.-F.; Kallimpoulos, T.; Stoeckli-Evans, H.; Jacot-Guillarmod, A. *Helv. Chim. Acta* **1989**, *72*, 731.

(16) Drochner, D.; Müller, M. *Eur. J. Org. Chem.* **2001**, 211.

Scheme 6. **Options for reduction of lactone 17**

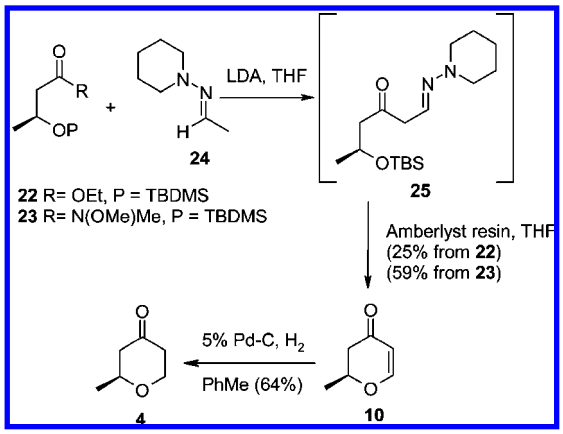


The various options for reduction of lactone **17** are given in Scheme 6. Use of lithium aluminium hydride unfortunately led to over-reduction yielding diol **18** in 79% yield. Whilst this could be converted to pyran **20** in 59% overall yield, by a selective monomesylation followed by treatment with base, the optical purity of the product dropped slightly to 98%. This was attributed to some mesylation at the secondary hydroxyl centre with resultant inversion of stereochemistry upon S_N2 ring closure. Similarly, reduction using sodium borohydride in THF under reflux gave mainly diol **18**.

Clearly, reduction of the lactone carbonyl group without ring-opening was highly desirable to maintain the chiral integrity. Reduction using one equivalent of DIBALH at low temperature afforded lactol **21** as a mixture of epimers at the newly formed hydroxyl centre. Without purification, this underwent acid-catalysed deprotection to regenerate the carbonyl group, with concomitant dehydration to furnish dihydropyranone **10**, having an identical optical purity to that of the starting material **15**. Conversion of this intermediate through to pyranone **4** by hydrogenation was demonstrated on the same substrate prepared *via* an alternative route and with no loss in optical purity (*vide infra*).

In order to shorten the route, direct reduction of lactone **17** to pyran **20** was sought. Many reagent systems have been identified for achieving such transformations in pyran and furan synthesis and we opted for sodium borohydride in the presence of acid. In the presence of sulphuric acid, deketalisation occurred resulting in low selectivity for the lactone carbonyl group, whereas boron trifluoride etherate allowed much better selectivity, giving no deprotection of the ketal, although the yield of isolated purified pyran **20** was low (20% following distillation or 35% if purified by chromatography on a 120 g scale). Deketalisation of **20** was then carried out under mild conditions due to the sensitivity of pyranone **4** to acid (*vide infra*), for which PPTS proved most amenable. In the presence of acetone a slow conversion at elevated temperature was observed; however, replacing acetone by formaldehyde allowed much faster reaction, albeit still at elevated temperature. Pyranone **4**

Scheme 7. **Hydrazone route to pyranone 4**

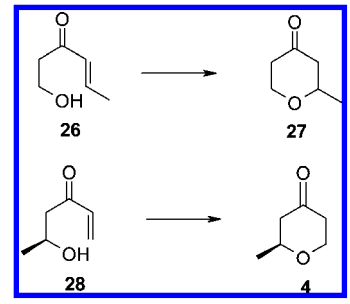


was thus obtained in 78% yield and with an optical purity of 99.5% on a 76-g scale. The difficulties encountered with this step (and indeed a consideration with all approaches to this molecule) were due to the significant volatility and water solubility of the product **4**, requiring multiple extractions during work-up and care during concentration and distillation. Nevertheless, this approach was used for manufacture of 250 g of pyranone **4**, providing material with 99.5% optical purity and 98% chemical purity, a reflection of the mild conditions used for the final step, under which the product was shown to be stable. Overall, this route appeared very attractive, offering a four-step synthesis of pyranone **4** with high optical purity from readily available materials. Nevertheless, this approach would have required development and refinement to improve yields, particularly for the reduction step, and to move away from the use of chromatography and cryogenic reaction conditions associated with the efficient route to the reduction substrate **17**.

Cyclisation onto Aldehyde Equivalents. It has recently been reported that 4-substituted 2-oxetanones (β-lactones) can be used as precursors for the preparation of 2,3-dihydropyranones.[17] Rather than look at this approach starting from β-butyrolactone, we chose to focus on a variation by attempting this chemistry on acyclic substrates derived from the much more readily available ethyl 3-(*S*)-hydroxybutyrate, Scheme 7. Hydrazone **24** derived from acetaldehyde and 1-aminopiperidine[18] was lithiated and then reacted with the protected ethyl (*S*)-hydroxybutyrate **22** to furnish β-keto hydrazone **25**. Subsequent acid mediated hydrolysis gave the desired dihydropyranone **10**, though in only 25% yield. It was determined by isolation of the intermediate β-keto hydrazone **25** that the low yield was due to the poor reaction of ester **22** with the lithiated hydrazone. Therefore, we envisaged the possibility of using Weinreb amide **23** as the substrate. The first step proceeded cleanly to give β-keto hydrazone **25** as the major product, which was treated with Amberlyst 15 resin in THF to give dihydropyranone **10** in 59% yield after purification by chromatography and with 98.5% optical purity, unchanged from the starting material. Hydrogenation over a Pd/C catalyst afforded the desired pyranone **4**, again with an unchanged optical purity of 98.5%. Although this route was not particularly atom efficient, it

(17) Zipp, G. G.; Hilfiker, M. A.; Nelson, S. G. *Org. Lett.* **2002**, *4*, 1823.
(18) Marques-Lopex, E.; Herrera, R. P.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2008**, 3457.

Scheme 8. **Synthesis of pyranones by an oxy-Michael reaction**



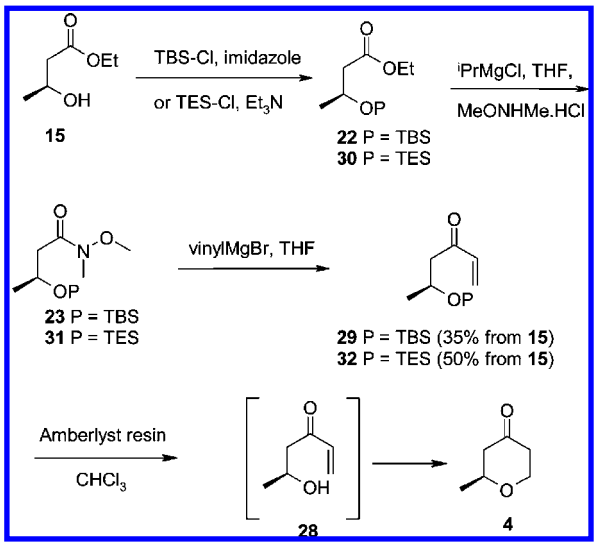
constituted a short synthesis of pyranone **4** of high optical purity and once again demonstrated the utility of dihydropyranone **10** as a stable intermediate, which could be converted to the target pyranone **4** under mild conditions without loss of optical purity.

Intramolecular Oxy-Michael Approach. It is known[19] that α,β-unsaturated ketone **26** can be cyclised to 2-methyltetrahydropyran-4-one **27** by treatment with Amberlyst 15 resin in chloroform. In a similar manner, we expected that the α,β-unsaturated ketone **28**, incorporating the required stereocentre, would provide a route to the optically pure product **4**, Scheme 8. A detailed study[20] of reagents capable of effecting such a transformation on related, more substituted substrates has appeared after this work was carried out. Furthermore, a paper[21] has also recently been published describing an antibody-mediated kinetic resolution of hydroxyenones and cyclisation of the enantioenriched products to the tetrahydropyranones in the presence of TMSOTf and Hünig's base with no loss in optical purity.

It was envisaged that the enone functionality would be constructed by addition of a vinyl Grignard reagent into a suitable amide derived from an ester of (*S*)-hydroxybutyric acid, necessitating hydroxyl protection. With appropriate choice of protecting group, deprotection could then either be accomplished *in situ* under the anticipated acidic cyclisation conditions or as a separate step if necessary.The chemistry used for conversion of ethyl (*S*)-hydroxybutyrate **15** through to oxy-Michael precursor **29** is shown in Scheme 9.[22] Initially, we chose to carry out TBS protection of starting material, which was achieved in quantitative yield under standard conditions, and followed this by Weinreb amide[23] formation, to ensure control during the enone formation. Preliminary studies demonstrated that Weinreb amide formation on TBDMS-protected ethyl (*S*)-hydroxybutyate using carbonyl diimidazole (CDI) as a coupling agent was inefficient, whilst addition of vinyl magnesium bromide directly to ester **15** was also unsuccessful. Therefore, we turned to a published protocol for direct conversion of esters to Weinreb amides using isopropylmagnesium chloride[24] rather than using

(19) Prandi, C.; Venturello, P. *J. Org. Chem.* **1994**, *59*, 3494.
(20) Reiter, M.; Turner, H.; Gouverneur, V. *Chem.—Eur. J.* **2006**, *12*, 7190.
(21) Baker-Glenn, C.; Hodnett, N.; Reitner, M.; Ropp, S.; Ancliff, R.; Gouverneur, V. *J. Am. Chem. Soc.* **2005**, *127*, 1481.
(22) Atkinson, S.; Tornos, J. Preparation of Optically Active Pyranone Derivatives. WO 2003051862 A1, 2003.
(23) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.
(24) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461. Colle, S.; Taillefumier, C.; Chapleur, Y; Liebl, R.; Schmidt, A. *Bioorg. Med. Chem.* **1999**, *7*, 1049.

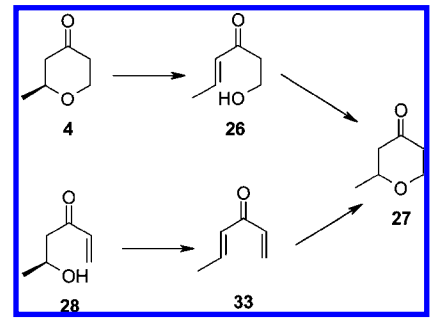
Scheme 9. **Oxy-Michael route to pyranone 4**



trimethylaluminium.[25] Thus, TBS ether **22** was treated with *N,O*-dimethylhydroxylamine hydrochloride in the presence of isopropylmagnesium chloride to afford amide **23** in 76% yield and with good purity. Interestingly, a recent paper has reported conversion of unprotected methyl hydroxybutyrate to the Weinreb amide in good yield under similar conditions at low temperature;[26] however, subsequent reaction with vinyl magnesium bromide proceeded better if the hydroxyl group was protected. Reaction of **23** with vinyl magnesium bromide then afforded enone **29** in 42% yield[27] which was subjected to an *in situ* silyl ether cleavage and ring-closure process by treatment with Amberlyst 15 resin in chloroform. This provided pyranone **4** in 40% yield, which disappointingly had an optical purity of only 82%. Interestingly, deprotected enone **28** was not detected by GC during the course of the reaction, suggesting a facile ring closure. In a control experiment to assess product stability, pyranone **4** was subjected to the acidic cyclisation conditions and after 24 h was recovered with unchanged chemical purity as judged by ^{1}H NMR spectroscopy and analysis by GC. However, the optical purity had decreased from 99% to 59%, suggesting that a ring-opening/ring-closure reaction was taking place, *via* primary alcohol **26** (Scheme 10), despite no acyclic intermediates being observed by GC.

Attempts to facilitate the ring closure within alternative acidic media (TsOH, camphor sulphonic acid, PPTS, sulphuric acid in THF or dichloromethane) led to either poor conversion, unwanted reactions, or in the case of PTSA in dichloromethane, pyranone formation but with complete racemisation. Isolation of dienone **33** from this reaction provided evidence for an alternative racemisation pathway (Scheme 10), which was confirmed by submitting a sample of this compound to the

Scheme 10. **Pathways for loss of optical purity**

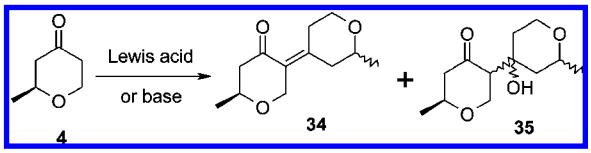


cyclisation conditions and observing complete consumption and formation of racemic pyranone **27**. Cyclisation of TBS ether **29** took up to 24 h for complete reaction, and therefore the pyranone formed was exposed to the acidic conditions for a significant period of time, causing the loss in optical purity. In an attempt to speed up the cyclisation reaction and thus minimise racemisation, use of the more labile triethylsilyl (TES) protecting group was evaluated. Ethyl (*S*)-3-hydroxybutyrate **15** was converted to TES ether **30** then through to vinyl ketone **32** in an analogous manner to the TBDMS series in 50% overall yield, Scheme 9. This substrate was then subjected to the *in situ* silyl deprotection/ring-closure reaction under the same conditions, which reached completion much more rapidly within 2 h. Isolated pyranone **4** was found to have an optical purity of 94% as the (*S*)-enantiomer, a significant improvement over cyclisation of TBS-protected substrate **29**, but still well below our requirement. An investigation into alternative solvents for this reaction showed that chloroform could be replaced by toluene, although product **4** was obtained with slightly lower optical purity, whereas use of alcoholic solvents led to complications due to Michael addition of the solvent into the enone. Elevating the reaction temperature to 40 °C in order to increase the rate of reaction led to a more dramatic lowering of the product optical purity, whereas cyclisation at a lower temperature (0 °C) in chloroform gave a product with 97% optical purity over an 8 h reaction time.

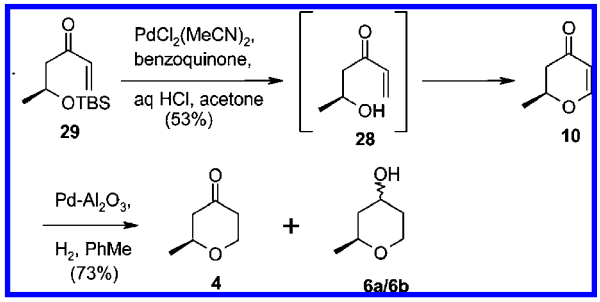
Attempts at acid-mediated oxy-Michael ring closure on an isolated, purified sample of hydroxyenone **28** were also undertaken. This substrate was prepared by deprotection of **29** using methanesulphonic acid in 85% yield and was purified by chromatography rather than by distillation to avoid thermal decomposition (*vide infra*). However, under conditions where good conversion to pyranone **4** was achieved (MsOH in a range of solvents at low temperature), a reduction in optical purity of the product resulted. We then turned to Lewis acid mediated oxy-Michael ring-closure, whereby catalysts such as $FeCl_3$, $Pd(OAc)_2$, $Fe(acac)_3$ and $Cu(OTf)_2$ gave poor conversion or significant loss in optical purity. However, a breakthrough came during screening of some palladium catalysts where certain species were found to promote the desired cyclisation reaction. $PdCl_2(MeCN)_2$ in THF was found to be most active, providing pyranone **4** with very good optical purity (99.2%) although the reactions were slow (13 h at 40 °C and 24 h at rt). Moreover, these transformations required a high catalyst loading (10 wt %) to achieve a good conversion, which would have had a significant impact on cost. On the other hand, attempts to cyclise either hydroxyenone **28** under basic conditions (KO^{t}Bu) or

(25) Hodgetts, K. J. *Tetrahedron Lett.* **2001**, *42*, 3763.
(26) Gebauer, J.; Rost, D.; Blechert, S. *Heterocycles* **2006**, *68*, 2129.
(27) Prior studies on the racemic version of **23** demonstrated that the yield was compromised by formation of the product of *aza*-Michael addition of *N*-methoxymethylamine to the newly formed enone system **29**. Investigation into the formation of this impurity demonstrated that it was formed during work-up, and by careful control of temperature and addition rate of the reaction quench this impurity could be minimised to less than 5%. Use of more acidic quench conditions was expected to suppress the formation of the impurity but led to some deprotection.

Scheme 11. **Impurities derived from pyranone 4**



Scheme 12. **Pd-catalysed oxidative cyclisation route**



TBDMS ether **29** by treatment with tetrabutylammonium fluoride were unsuccessful. It was also later demonstrated that pyranone **4** was susceptible to Lewis acid and base mediated aldol reactions to generate impurities **34** and **35** (Scheme 11). Given the susceptibility of the product towards racemisation in the presence of acid (hexadiene **33** was observed in most of the acid catalysed processes) and the high catalyst loading required for the only process which provided a product with an acceptable optical purity, we shifted focus to study formation of dihydropyranone **10** in the ring-closure step, which would allow conversion to pyranone **4** under mild, neutral conditions to avoid degradation in the final step.

Oxidative Pd-Catalysed Ring Closure. Formation of the dihydropyranone skeleton from hydroxyenone **28** via an oxidative cyclisation (intramolecular Wacker-type reaction), Scheme 12, was appealing as an alternative means of synthesising the previously prepared dihydropyranone **10**. Following earlier studies (Schemes 6 and 7), it was expected that dihydropyranone **10** would be relatively stable towards loss of optical purity since it is believed that a higher pK_a of the C_3 methylene protons and reduced electrophilicity would infer greater stability compared with tetrahydropyranone **4**. It was noted during studies into the Lewis-acid mediated oxy-Michael cyclisations of this substrate described above that a small amount of dihydropyranone **10** generally accompanied formation of the major product **4** when Pd catalysis was used. This was rationalised by a Pd-mediated cyclisation of the hydroxyl group onto the enone system[28] followed by β-hydride elimination to generate dihydropyranone **10** together with a reduced Pd (0) species. By inclusion of a stoichiometric oxidant in the reaction, a more complete conversion was anticipated by regeneration of the Pd (II) catalyst, in agreement with recent publications reporting similar oxidative Pd-catalysed cyclisations for construction of tetrahydropyran ring systems.[20,28] A subsequent selective hydrogenation of the alkene bond would transform the product into the target tetrahydropyranone **4** under mild, neutral conditions, Scheme 12.

Initial studies into the oxidative ring-closure were carried out on isolated, purified hydroxyenone **28**, and a simple screen of a few palladium complexes and either $CuCl_2$ under air or with benzoquinone as stoichiometric co-oxidant was carried out, Table 1.

From this screening, $PdCl_2(MeCN)_2$ or $PdCl_2(PhCN)_2$ were almost equally effective in allowing low catalyst loading and giving the cleanest reaction profile with an excess of benzoquinone as the stoichiometric oxidant, of which the former was selected for further development. An extensive solvent screen was not carried out; however, THF as solvent gave a far better conversion and product purity profile compared with ethyl acetate at 1 mol % catalyst loading. Under such conditions, with 1.2 equiv of benzoquinone in THF, dihydropyranone **10** was formed cleanly together with only 1% of the reduced tetrahydropyranone **4** within 1 h at elevated temperature. The direct cyclisation *via* a Pd-assisted oxy-Michael reaction to form tetrahydropyranone **4** required controlling since it was shown subsequently that, when formed in this manner, this product could have reduced optical purity and would therefore contribute partially to an overall depletion of optical purity on progression into the reduction step.

Because of the observed instability of hydroxyenone **28** in the deprotection step and the requirement for purification by chromatography due to decomposition encountered during distillation, avoiding its isolation through a one-pot deprotection/oxidative ring-closure was sought. Aqueous hydrochloric acid was found suitable for the deprotection reaction and aqueous acetone an ideal solvent for both steps. However, it was found that the effect of water was opposed in that the rate of deprotection was better with a low concentration of water, whereas the oxidative cyclisation reaction proceeded best with a higher concentration of water present. Thus, the process was established with initially one volume of water in acetone for deprotection and then additional water added part way through to facilitate ring-closure. Formation of hydroxyenone **28** was almost complete within 1 h under these conditions and cyclisation proceeded over 4.5 h total reaction time. The appreciable solubility of dihydropyranone **10** in water was a feature of the work-up, where removal of the silyl protecting group residues was achieved by washing an aqueous solution of the product with heptane. Following extraction into toluene, the mixture was separated by distillation to afford the pure dihydropyranone **10** in 53% yield on an 800 g (input scale), with a chemical purity of 94.6 area % and an optical purity of 99.5%, very close to that of the starting material. Although the isolated yield from this process was typically only 50%, a small amount of material did remain in the aqueous layer, and it is believed that polymerisation may account for some of the mass balance. Stability studies conducted on the reaction solution containing dihydropyranone **10** after pH adjustment demonstrated no loss in optical purity at pH 5−8 on heating to 80 °C for 9 h. This compound was also stable towards racemisation at pH 2 at rt, whereas after 9 h at 80 °C, a drop in optical purity of 5% was observed, indicating that high temperatures had to be avoided during this step.

To achieve the final transformation to tetrahydropyranone **4**, a selective reduction of dihydropyranone **10** was required. To ensure a high yield and to minimise over-reduction to pyranols **6a/6b**, extensive screening of catalysts and conditions

(28) Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91. Reiter, M.; Turner, H.; Mills-Webb, R.; Gouverneur, V. *J. Org. Chem.* **2005**, *70*, 8478.

Table 1. **Conditions screened for oxidative cyclisation of 28**

entry[a]	reagent system	solvent	*t* (h)	conversion (%)	**10** (area %)	**4** (area %)
1	$PdCl_2$ (6 mol %), air	H_2O	24	13	10	3
2	$PdCl_2$ (10 mol %), $CuCl_2$ (10 mol %), air	H_2O	3	99	95	5
3	$PdCl_2(MeCN)_2$ (2 mol %), BQ[b] (1 equiv)	THF	1	99	99	1
4	$PdCl_2(MeCN)_2$ (1 mol %), BQ[b] (1.5 equiv)	EtOAc	1	75	63	12
5	5% Pd/C (10% *w*/*w*), $PdCl_2(MeCN)_2$ (2 mol %)[c] BQ[b] (1.2 equiv)	EtOAc	3 + 1	>99	99	1
6	$PdCl_2(MeCN)_2$ (1 mol %), BQ[b] (1.2 equiv)	THF	1	>99	99	1
7	$PdCl_2(PhCN)_2$ (1 mol %), BQ[b] (1.2 equiv)	THF	0.5	>99	99	1

[a] All reactions run at 60 °C except entry 1 (rt). [b] BQ = benzoquinone. [c] 3 h with Pd−C catalyst (<1% conversion), then 1 h with $PdCl_2(MeCN)_2$.

Table 2. **Screening of catalyst for reduction of dihydropyranone 10**

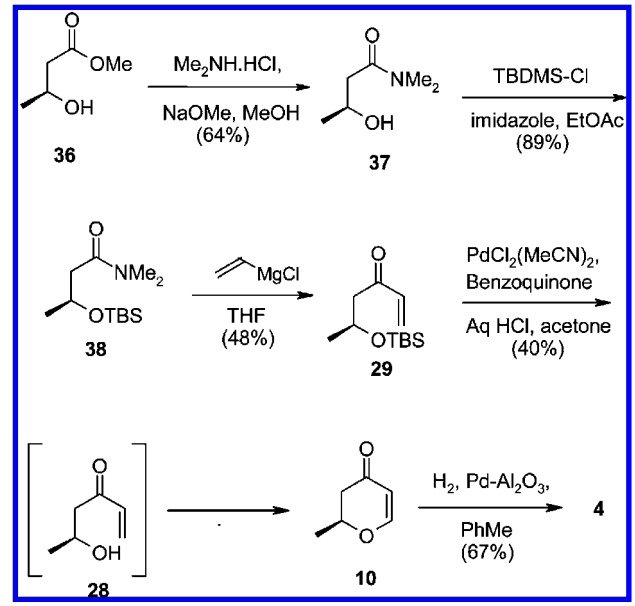
entry	catalyst[a]	solvent	H_2 (Mpa)	*T* (°C)	*t* (h)	**10**[b]	**4**[b]	**6a/6b**[b]
1	3% Pd−Al_2O_3	PhMe	3	50	3	−	89.8	5.4
2	5% Pd−1.5% S-Al_2O_3	PhMe	3	50	3	−	93.3	2.1
3	3% Pd−1.5% S-MgO-Al_2O_3	PhMe	3	50	12	−	93.1	0.9
4	3% Pd−Al_2O_3	PhMe	3	50	6	0.3	89.7	7.2
5	3% Pd−Al_2O_3	AcOMe	3	50	5	−	81.3	14.2
6	3% Pd−Al_2O_3	THF	3	50	3	0.11	86.5	9.0
7	3% Pd−Al_2O_3	Me_2CO	3	50	3	−	85.9	9.5
8	3% Pd−Al_2O_3	PhMe	1	50	2	−	87.5	3.5
9	3% Pd−Al_2O_3	PhMe	3	50	2	−	92.1	1.9
10	3% Pd−Al_2O_3	PhMe	1	27	3	22.0	69.6	2.6
11	3% Pd−Al_2O_3	PhMe	1	60	2	45.8	45.8	2.0
12[c]	3% Pd−Al_2O_3	PhMe	1	60	17	11.4	82.9	1.7

[a] 5 wt % except entries 11 (3 wt %) and 12 (1 wt %). [b] GC area % [c] Prior reaction at 27 °C for 6 h.

was required, and some results are presented in Table 2. Of the catalysts investigated, 3% Pd on alumina was selected, affording a 94:6 ratio of **4**:**6a**/**6b** based on analysis by GC (entry 1). Although not the most selective catalyst under the conditions screened,[29] it was readily available in quantities required for the planned large-scale production. Choice of solvent had only a slight effect on the level of pyranol produced (entries 4−7), and so toluene was selected; more significant effects were seen with catalyst loading, hydrogen pressure, and reaction temperature (entries 8−12). From this series of experiments, the conditions given for entry 9 were clearly the best, and a scale-up reaction (180 g input) under these conditions afforded pyranone **4** in 73% yield with 99.8% chemical purity and 99.4% optical purity after isolation by distillation.

Large-Scale Synthesis of Pyranone 4. During the course of studies into the oxy-Michael ring closure and Pd-mediated oxidative cyclisation, the synthesis of enone **29** was evolving. Together with the cyclisation and hydrogenation steps, these were being developed into a route suitable for manufacture of initially a 10 kg batch of optically pure pyranone **4** and subsequently a 100 kg batch (Scheme 13). The starting material used was methyl (*S*)-hydroxybutyrate **36**, a commercially available compound which can be readily prepared in good yield and very high optical purity by asymmetric hydrogenation of methyl acetoacetate.[11] The dimethylamide was the preferred electrophilic moiety for introduction of the vinyl group[30] rather than the Weinreb amide on cost grounds and was put in place prior to the protection step. Thus, methyl (*S*)-hydroxybutyrate

Scheme 13. **Large-scale synthesis of pyranone 4**



36 (optical purity 99.7%) was converted to dimethylamide **37** by reaction with dimethylamine hydrochloride and sodium methoxide in methanol in 64% yield on a 300 kg scale. The sodium methoxide stoichiometry was set so as to achieve maximum conversion to product while minimising byproduct formation from dehydration (methyl crotonate and its amide). The high water solubility of amide **37** limited the range of efficient extraction solvents, but *n*-butanol was found to be ideal for this purpose, from which the pure product was isolated by distillation. Direct vinylation of amide **37** proceeded in only 30% yield; therefore, TBDMS protection was retained and was accomplished under standard conditions in 89% yield. This was

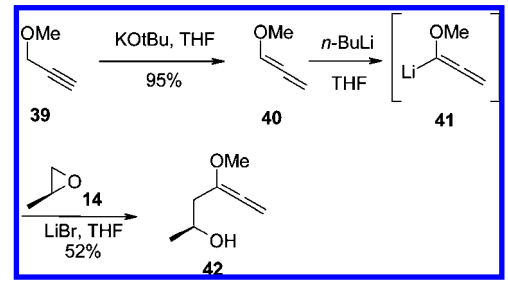
(29) Use of the alternative catalyst 3% Pd−0.3% S on MgO/Al_2O_3 was found to give slightly better selectivity for pyranone **4** over pyranols **6a/6b**, but the rate of reaction was slower.
(30) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *Synthesis* **1984**, 228.

slightly lower than expected due to some decomposition of the product during work-up whilst destroying excess TBDMS-Cl by hydrolysis. For conversion to enone **29**, amide **38** was slowly added to a solution of excess vinyl magnesium chloride in THF, allowing good control of the exotherm. The aqueous acidic work-up was carefully controlled to avoid loss of the silyl protecting group whilst breaking down the hemiaminal intermediate to the desired product, which was achieved by quenching with dilute sulphuric acid then extracting into toluene. Pure enone **29** was isolated by distillation, carried out in the presence of a small amount of hydroquinone to suppress degradation. Smaller-scale reactions proceeded well with yields of up to 85% at end of reaction and 75% after isolation. Unfortunately, during scale-up to 320 kg, the yield at end of reaction was 76%; however, this dropped to 60% after concentration to remove THF and further still to 48% after distillation of the product **29**. The reasons for this were thought to be a consequence of longer exposure to the acidic work-up on scale leading to decomposition or polymerisation of the enone, coupled with some degree of decomposition during distillation, although it was deemed preferable in the short term to have a purification sequence in place at this stage at the expense of yield. Indeed, stability studies carried out on batches of neat enone **29** indicated rapid decomposition at 50 °C (75% loss over 5 h) to polymeric materials. Subsequent one-pot deprotection and cyclisation of **29** were accomplished under the conditions identified (described above) and afforded dihydropyranone **10** in 31% yield on a 100 kg (input) scale, after work-up and distillation. Further material was obtained from re-extraction of the aqueous layer, bringing the total up to 40% yield, which was still lower than anticipated, but with an optical purity of 99.7%. The final hydrogenation step, using 3% Pd on alumina in toluene at 45−55 °C, was only scaled up to 10−20 L due to some variability encountered in the rate of reaction. However, complete conversion within 4.5 h was achievable on a 2.5 kg (input) scale under these conditions, with a selectivity of 98% for pyranone **4** over pyranols **6a/6b** and an averaged yield of 94% for formation of the crude product. Combination of multiple batches of crude pyranone **4** and purification by distillation provided a 10 kg batch of product having very high optical and chemical purities by GC (99.7 area % and 99.6 area %, respectively) in an average 67% yield from dihydropyranone **10**.

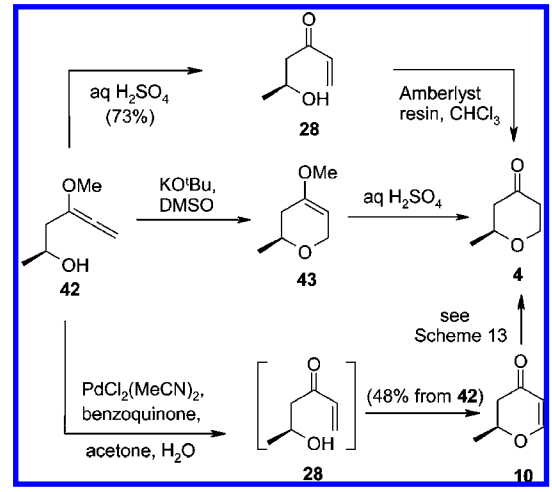
Whilst this chemistry did provide the first multikilogram batch of pyranone **4** using a new route, some problems were encountered during scale-up and these would have been addressed had the project continued. Additionally, it would have been highly desirable to shorten the route by dispensing with the protection step during the enone synthesis or using an alternative, cheaper protecting group, e.g., TMS or THP. Dispensing with protection altogether, by addition of a vinyl Grignard reagent into dimethylamide **37** as demonstrated recently for Weinreb amides,[31] would be particularly appealing due to the water-solubility of hydroxyenone **28**, potentially allowing its progression without isolation and purification into the oxidative cyclisation.

(31) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2594.

Scheme 14. **Route to allene alcohol 42**



Scheme 15. **Ring-closure pathways for allene 42**



Routes from (*S*)-Propylene Oxide. An alternative short route to pyranone **4** *via* dihydropyranone **10** starting from (*S*)-propylene oxide was envisaged in which a suitably functionalised C_3 nucleophile would be incorporated to build up the pyranone ring. It has been reported that methoxyallene can be lithiated to generate 3-lithio-3-methoxy allene and that this reacts readily with a variety of electrophiles.[32,33] Thus, incorporating the successful cyclisation methodology already developed, we postulated that reaction of 3-lithio-3-methoxyallene **41** with (*S*)-propylene oxide **14** followed by ring closure would construct the 6-carbon framework of the target pyranone with the required stereocentre installed, Scheme 14. Essentially, allene ether **42** is a latent enone and thus offered many possibilities for cyclisation, Scheme 15. (*S*)-Propylene oxide **14** can be produced with very high optical purity (typically >99.5%) and is available in large-scale quantities, thus making it a convenient chiral building block. Methoxyallene **40** was not commercially available at the time this work was carried out but is reportedly generated in a straightforward manner in high yield from methyl propargyl ether **39** by heating under reflux with catalytic potassium *tert*-butoxide followed by isolation of the product by distillation (bp 53 °C).[32,34] However, it was immediately apparent that this synthesis would require modification for scale-up for reasons of safety. Acetylenes (especially metalloacetyl-

(32) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916.
(33) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1179. Tius, M. A. 1-Methoxyallenyllithium. In *e-EROS: Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 2001.
(34) See for example: Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308. Perez, M.; Canoa, P.; Gomez, G.; Teijeira, M.; Fall, Y. *Synthesis* **2005**, 411. Chengebroyen, J.; Linke, M.; Robitzer, M.; Sirlin, C; Pfeffer, M. *J. Organomet. Chem.* **2003**, *687*, 313.

enes) can be thermally unstable and with low-molecular weight structures, decomposition is inevitably highly energetic and potentially explosive (the heat of decomposition of methyl propargyl ether **39** was determined by DSC to be ~1600 J/g). These problems were confounded in the literature synthesis by the absence of solvent (to provide dilution and a heat sink) and the "all-in" nature of the reaction in which there is no control of the heat of the primary (desired) chemical reaction by reagent addition. These initial concerns were duly confirmed by running the reaction in a PHI-TEC II adiabatic calorimeter. In this test, self-heating was detected immediately on mixing the potassium *tert*-butoxide and methyl propargyl ether **39** (at ambient temperature) that led to an extremely violent reaction resulting in the complete destruction of the internals of the calorimeter less than eight minutes later. Thus, a modification of the process was developed to overcome the all-in nature of many of the reported syntheses,[32,34] by adding a solution of methyl propargyl ether in THF in a controlled manner over 1 h to a solution of potassium *tert*-butoxide in THF maintained at 50 °C. Under these conditions, the reaction is addition-rate controlled, and less than 6% methyl propargyl ether remained immediately upon completion of the addition. Methoxyallene **40** was then isolated in 95% yield as a solution in THF, ready for use directly in the downstream chemistry as a telescope, following distillation of the solution under vacuum (bp 15 °C at 70 mmHg). Chemically, such solutions showed no significant degradation after storage at rt over a period of 6 weeks. The thermal stability of the THF solution of methoxyallene **40** was assessed by DSC and by running an adiabatic PHI-TEC test which showed that the reaction could probably be operated safely at scale with the provision of suitable control measures. Having a significantly higher onset temperature meant that this modified process was deemed acceptable to run at up to 2 L scale within our laboratories. Whilst efficient conversion of methyl propargyl ether **39** to methoxyallene **40** could be achieved using the alternative system of potassium hydroxide in DMSO at ambient temperature,[35] this method was not adopted due to the difficulty of isolating the product from such a reaction mixture.

Lithiation of methoxyallene was carried out in THF solution at 0 °C, and the resulting anion **41** was reacted with (*S*)-propylene oxide **14** at the same temperature. A regioselective reaction followed, and under these conditions, the yield of allene alcohol **42** was typically 41% after isolation by distillation. Forming the lithio species at −30 °C and reacting with benzaldehyde gave a quantitative yield of the addition product, indicating that lithiation was complete under these conditions and that the problem was the reactivity of the epoxide. The reaction profiles of lithio anions formed and quenched with (*S*)-propylene oxide at −30 and 0 °C were comparable, demonstrating cryogenic temperatures were not critical to the success of the reaction. The propensity of allene alcohol **42** towards degradation (over a few days at 4 °C, faster at rt) was also a key consideration and meant that a fast low-temperature reaction was imperative. Several Lewis acids were evaluated in this process and presence of lithium bromide in a reaction carried out at 0 °C to rt was found to improve the yield significantly to 52% after isolation, and most importantly, analysis by GC demonstrated no loss in optical purity. Of the other Lewis acids investigated it is noteworthy that BF_3OEt_2 caused violent polymerisation of methoxyallene. Due to termination of the project prior to running all but small-scale reactions, no in-depth safety evaluation of this stage was undertaken. It could be expected, however, that allene alcohol **42** may also present safety issues for scale-up.

The versatile allene alcohol **42** offered various options for conditions under which to attempt ring-closure; basic, acidic, Lewis acidic, or transition-metal-mediated, Scheme 15. We found that acid-mediated cyclisation of allene alcohol **42** by protic or Lewis acids to generate pyranone **4**, as expected, proceeded through the intermediate enone **28**. However, as before, under the most successful conditions, loss of optical purity was evident accompanied by formation of a variety of side products. A base-mediated cyclisation was also investigated,[36] using a catalytic amount of potassium *tert*-butoxide, anticipating formation of methyl enol ether **43**, and this did provide the desired product together with another unidentified compound. Subsequent acid-mediated hydrolysis generated pyranone **4** as the major component of a mixture; however, this was not developed further due to the high level of byproduct formation and drop in optical purity of pyranone **4** to 90%.

Following the successful use of Wacker-type conditions for cyclisation of enone **28** to generate dihydropyranone **10** (Scheme 13), we envisaged subjecting allene alcohol **42** to these conditions to generate this intermediate (Scheme 15). Initially, we found that 10 mol % palladium chloride and copper(II) chloride in the presence of benzoquinone gave the best conversion in a mixture of acetone and water. Typically, enone **28** was observed almost immediately after addition of the palladium and copper species, indicating that the first transformation was hydrolysis of the enol ether moiety. However, formation of tars indicated polymerisation was a significant side reaction. Whilst reducing the palladium to 5 mol % still gave product **10**, reducing the palladium amount below this led to formation of pyranone **4** directly, presumably from competing oxy-Michael cyclisation promoted by HCl generated *in situ* during the reaction. It was essential that direct pyranone formation in this step was minimised due to its propensity for racemisation and potential for decomposition (*vide supra*). The conditions found to be successful earlier were then applied to allene alcohol **42** in an attempt to improve selectivity. Thus, $PdCl_2(MeCN)_2$ (0.5 mol %) and benzoquinone (1 equiv) were added to the allene alcohol in aqueous acetone, generating dihydropyranone **10** cleanly in 48% yield, again following rapid formation of the intermediate enone **28**. The drawback of using these conditions was separation of the product from large amounts of benzoquinone and hydroquinone during work-up

(35) Eroshchenko, S. V.; Sinegovskaya, L. M.; Tarasova, O. A.; Frolov, Y. L.; Trofimov, B. A.; Ignatyev, I. S. *Spectrochim. Acta, Part A* **1990**, *46A*, 1505.

(36) Previous work in this area has focused on the base-mediated cyclisations of the products from lithio-methoxyallene additions to carbonyls. These have been shown to cyclise to generate furan species; see: Reissig, H.-U.; Hormuth, S.; Schade, W.; Amombo, M. O.; Toshiko, W.; Pulz, R.; Hausherr, A.; Zimmer, R. *J. Heterocycl. Chem.* **2000**, *37*, 597, and references therein. It was our suspicion that the same type of transformation to form pyran ring systems may occur from allene alcohols derived from epoxide ring opening. This was in contrast, however, to a literature publication which reported formation of furans: Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609.

for which use of toluene as an extraction solvent was found to minimise progression of these materials downstream. Dihydropyranone **10** prepared in this way was then hydrogenated to afford pyranone **4**, which was shown have an optical purity greater than 99% as the (*S*)-enantiomer. Typically in this cyclisation, conversion of allene **42** to enone **28** is observed almost immediately on adding the palladium and copper species to the reaction mixture. A comparison study in which allene alcohol **42** and enone **28** were subjected to the same conditions demonstrated no difference in reactivity. This approach has demonstrated on a small lab scale the utility of methoxyallene for generation of a C_3 anion containing latent enone functionality and coupling with (*S*)-propylene oxide as an alternative approach to the cyclisation precursor **28**. In addition, subsequent *in situ* hydrolysis releases the enone moiety ready for the oxidative Pd-catalysed ring closure under mild conditions. Although defining a safe mode of operation with such energetically unstable intermediates on scale would need addressing, perhaps through continuous manufacture, this approach demonstrates in principle an alternative highly efficient four-step synthesis of pyranone **4** from simple starting materials.

Conclusions

(*S*)-2-Methyltetrahydropyran-4-one has proved a challenging molecule to synthesise due to its sensitivity to acidic, basic, and Lewis acidic reaction media giving rise to decomposition, condensation products, and loss of optical purity. Despite this inherent instability, the basis for short, efficient routes to this target of high optical purity from readily available small chiral building blocks has been established and demonstrated successfully on multigram to multikilogram scale. Synthesis of an appropriately functionalised δ-lactone followed by reduction and deprotection steps afforded the target compound in four steps in 21% overall yield, although some of the reaction conditions used in their present form are undesirable for large-scale manufacture and would have required further development. Identification of dihydropyranone **10** as a robust intermediate allowed conversion to the target pyranone **4** under mild, neutral conditions with preservation of optical purity. A straightforward synthesis of this intermediate *via* an intramolecular Pd-mediated oxidative cyclisation of a hydroxyl group onto an enone provided an efficient five-step synthesis of the target pyranone in 19% overall yield on 100s-g scale, although the overall yield was lower for multikilogram manufacture, reflecting difficulties of handling and isolation of the hydroxyenone intermediates. Furthermore, if the highly energetic intermediates in the methoxyallene route can be safely handled at scale, the number of steps is reduced, affording an alternative highly efficient four-step synthesis that was demonstrated in an overall yield of 19% on a small laboratory scale. Clearly, much of this chemistry would have required further development to improve yields and gain a better understanding of key parameters to improve performance on multikilogram scale; however, termination of the project left many of these aspects incomplete.

Experimental Section

General. All experiments were carried out under a nitrogen atmosphere unless otherwise stated. Commercially available starting materials and dry solvents were used as received without further purification. Small-scale chromatography was carried out on Biotage KP-Sil silica gel cartridges (40−63 μm), and product-containing fractions were concentrated to dryness under vacuum. ^{1}H NMR spectra were recorded at a probe temperature of 25 °C, and chemical shifts are reported in ppm downfield relative to TMS as an internal standard in $CDCl_3$ unless otherwise stated. Assays were performed against purified, characterised reference materials. MS data were obtained on an HP6890 series GC and HP5973 Mass Selective Detector (MSD) using electron impact ionisation at 70 eV. HRMS were performed on an LC-MS-IT-TOF spectrometer (Shimadzu corporation) using positive electrospray ionisation (ESI) at 4.5 keV. GC method used for determination of the chemical purity of **4**: DB-FFAP column, 30 m × 0.25 mm id, 0.25 μm, oven temp 60 °C/10 min then to 200 at 5 °C/min, He carrier gas at 0.5 mL/min, injector 180 °C, detection by FID at 230 °C. GC method used for determination of the optical purity of **4** and **10**: Chiraldex G-TA column, 50 m × 0.25 mm id, 0.125 μm, oven temp 100 °C, He carrier gas at 2.2 mL/min, injector 220 °C, detection by FID at 220 °C. HPLC method used for determination of the optical purity of **10**: Chiralcel OB column, 4.6 mm × 250 mm, at 40 °C, detector 220 nm, mobile phase 90:10 *n*-hexane/^{i}PrOH, flow rate 1.0 mL/min. GC method used for determination of the chemical purity of **29**, **37**, and **38**: Neutrabond 1 column, 30 m × 0.25 mm id, 0.25 μm, oven temp 120 °C/5 min then to 230 at 5 °C/min, He carrier gas at 0.5 mL/min, injector 180 °C, detector FID at 230 °C. For other intermediates, the following GC purity method can be used: J&W DB-5 column, 30 m × 0.32 mm id × 1 μm, oven temp 70 °C/5 min then to 220 at 15 °C/min, carrier gas hydrogen at 60 kPa, injector 250 °C, detection by FID at 300 °C.

(*S*)-9-Methyl-1,4,8-trioxaspiro[4.5]decan-7-one (17). To a stirred solution of **16**[15] (3.5 g, 17.1 mmol) in dichloromethane (15 mL) at rt was added ethylene glycol (3.55 mL, 63.7 mmol) followed by $TsOH\cdot H_2O$ (0.66 g, 3.5 mmol). The solution was heated under reflux with stirring for 6 h, then allowed to cool before saturated aqueous sodium bicarbonate (50 mL) was added. The layers were separated, the aqueous phase was extracted with dichloromethane (30 mL), the combined organic phases were washed with saturated aqueous sodium chloride (50 mL), dried (Na_2SO_4) and then concentrated under reduced pressure to give **17** as a yellow oil (2.6 g, 88%) which was used without further purification. Purity by GC 75.6 area %. Spectral data were obtained on a sample purified by chromatography, eluting with 30% ethyl acetate in isohexane. ^{1}H NMR (400 MHz) δ 4.58 (dqd, J = 11.9, 6.1, 2.9 Hz, 1H), 4.03−3.95 (m, 4H), 2.78 (dd, J = 17.2, 1.8 Hz, 1H), 2.70 (d, J = 17.4 Hz, 1H), 2.05 (dt, J = 13.9, 2.2 Hz, 1H), 1.83 (dd, J = 13.8, 11.8 Hz, 1H), 1.42 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz) δ 169.5, 105.6, 73.4, 64.8, 64.7, 40.9, 40.7, 21. $[\alpha]^{25}_D$ −19.5 (*c* 1.2, $CHCl_3$).

(*S*)-7-Methyl-1,4,8-trioxaspiro[4.5]decane (20). A solution **17** (118.1 g, 84.7% *w/w*, contained weight 100 g, 581 mmol) in THF (100 mL) was added dropwise over 1 h to a cooled (<0 °C) suspension of sodium borohydride (22.0 g 582 mmol) in THF (100 mL) with stirring (hydrogen evolution observed). $BF_3\cdot OEt_2$ (147.2 mL, 164.9 g, 1.16 mol) was then added

dropwise over 30 min, maintaining the reaction temperature below 0 °C (exothermic and continued gas evolution). On completion of the addition, the viscous reaction mixture was maintained at between 20 and 30 °C for 2 h with stirring (continued exotherm). The reaction was quenched by the dropwise addition of a mixture of ethyl acetate (500 mL) and aqueous $NaHCO_3$ (10% *w/w*, 500 mL). The organic layer was separated, washed with water (500 mL), and then evaporated to dryness under reduced pressure. The residue was purified by chromatography, eluting with a 2:1 mixture of hexane and ethyl acetate to afford **20** (32.3 g, 35.1%). ^{1}H NMR (400 MHz) δ 4.06−3.94 (m, 5H), 3.68−3.60 (m, 2H), 1.78 (dt, J = 12.9, 5.4 Hz, 1H), 1.69 (m, 1H), 1.61 (m, 1H), 1.50 (t, J = 16 Hz, 1H), 1.21 (d, J = 8 Hz, 1H). HRMS. Calcd for $C_8H_{15}O_3$ (MH^+) 159.1016. Found 159.1010.

(*S*)-2-Methyltetrahydropyran-4-one (4) via Deprotection of 20. A mixture of crude **20** (121.8 g, 76.46 g contained wt, 483 mmol), aqueous formaldehyde solution (37% *w/w*, 156.9 g, 1.93 mol), and PPTS (3.06 g, 12 mmol) was heated at 80 °C with stirring for 5 h. After cooling to rt, the reaction mixture was extracted with ethyl acetate (1 × 360 mL, 4 × 180 mL). The organic layers were combined and washed with aqueous $NaHCO_3$ (5% *w/w*, 60 mL) and water (60 mL). The solvent was removed under reduced pressure and the residue purified by distillation under reduced pressure to give **4** (43.12 g, 78%). Bp 57−58 °C/19 mmHg. Purity by GC 91.9 area %. Optical purity by GC 99.6%. ^{1}H NMR (400 MHz) δ 4.28 (ddd, J = 11.5, 7.4, 1.3 Hz, 1H), 3.78−3.70 (m, 1H), 3.68 (ddd, J = 12.3, 11.5, 2.8 Hz, 1H), 2.58 (dddd, J = 14.6, 12.3, 7.4, 1.0 Hz, 1H), 2.40 (dt, J = 14.6, 2.6 Hz, 1H), 2.35−2.25 (br m, 2H), 1.28 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz) δ 206.9, 74.3, 66.4, 49.9, 41.9, 22.0. MS (*m*/*z*) 114 [M^+].

(*S*)-2-Methyl-2,3-dihydropyran-4-one (10) via lactol 21. A stirred solution of **17** (2.5 g, 14.5 mmol) in toluene (40 mL) was cooled to −70 °C, and a solution of diisobutylaluminium hydride in toluene (1.0 M, 14.5 mL, 14.5 mmol) was added dropwise over 30 min. The solution was stirred at −70 °C for a further 2 h, and then saturated aqueous ammonium chloride (5 mL) was added dropwise. The solution was then allowed to warm to rt and stirred for 30 min. Sodium sulfate (5 g) was added followed by diethyl ether (200 mL) and stirring continued for 30 min. The solids were removed by filtration through Celite and washed with diethyl ether (100 mL), and the combined filtrates were concentrated under reduced pressure to give the intermediate lactol **21** as a yellow oil comprising a mixture of epimers at C-7 (2.1 g, 83%) which was used without purification and characterisation.

Lactol **21** (2.0 g, 11.5 mmol) was dissolved in a mixture of acetone (20 mL) and water (20 mL) at rt, and $TsOH \cdot H_2O$ (2.2 g, 11.5 mmol) was added. The solution was heated to 50 °C for 2 h and then allowed to cool to rt before a saturated aqueous solution of sodium bicarbonate (20 mL) was added. The solution was partially concentrated and extracted with ethyl acetate (3 × 40 mL); the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give a yellow oil which was purified by chromatography, eluting with 20% ethyl acetate in isohexane, to afford **10** as a pale-yellow oil (0.75 g, 58%). Purity by GC 97.3 area %. Optical purity by GC 98.6% as the (*S*)-enantiomer. $[\alpha]^{25}_D$ +199.5 (*c* 0.46, $CHCl_3$). ^{1}H NMR (400 MHz) δ 7.35 (d, J = 5.9 Hz, 1H), 5.41 (d, J = 6.2 Hz, 1H), 4.60−4.52 (m, 1H), 2.56−2.42 (m, 2H), 1.47 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz) δ 192.6, 163.2, 106.9, 76.0, 43.5, 20.3. MS (*m*/*z*) 112 [M^+].

(*S*)-2-Methyl-2,3-dihydropyran-4-one (10) via Hydrazone 25. To a solution of diisopropylamine (1.57 mL, 11.2 mmol) in tetrahydrofuran (45 mL) cooled to 0 °C was added dropwise a solution of *n*-butyllithium (2.5 M in hexanes, 4.2 mL, 10.5 mmol) over a period of 5 min. The resulting pale-yellow solution was stirred for 15 min at this temperature, and then hydrazone **24**[18] (1.32 g, 10.5 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for a further 1 h during which time a precipitate formed. The suspension was cooled to −78 °C, and then a solution of **23** (1.83 g, 7 mmol) in tetrahydrofuran (5 mL) was added dropwise. After stirring at −78 °C for 3 h the mixture was allowed to warm to rt and stirred overnight. Water (3.5 mL) and diethyl ether (140 mL) were added, the suspended solids were removed by filtration, the filtrate was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford intermediate **25** as a yellow oil (3.5 g) which was used without further purification. This material was dissolved in tetrahydrofuran (50 mL), and Amberlyst 15 ion-exchange resin (3.5 g) was added and the suspension heated under reflux for 2 h. After cooling to rt, the resin was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by chromatography, eluting with a 1:9 mixture of ethyl acetate and isohexane to afford **10** as a yellow oil (0.46 g, 59%). Optical purity by GC 98.8% as the (*S*)-enantiomer. Purity by GC 97.8 area %.

Ethyl (*S*)-3-(*tert*-Butyldimethylsilyloxy)butyrate (22). Ethyl (*S*)-3-hydroxybutyrate **15** (5 g, 37.8 mmol) was dissolved in dichloromethane (10 mL). After cooling to 10 °C, *tert*-butylchlorodimethylsilane (6.84 g, 45.3 mmol) was added and when most of the solid had dissolved this was followed by imidazole (5.15 g, 75.6 mmol) in one portion (exotherm to 30 °C). After stirring the thick suspension at rt for 16 h, water (25 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with water (25 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave crude **22** as a colourless oil (10 g, ≫100%). Purity by GC 95.0 area %. A sample was purified by chromatography, eluting with 5% ethyl acetate in isohexane, to afford a pure sample of the title compound as a colourless oil for characterization purposes. Purity by GC 100 area %. $[\alpha]^{25}_D$ +21.7 (*c* 1.05, $CHCl_3$).[37] ^{1}H- and ^{13}C NMR data in agreement with published data.[37] MS (*m*/*z*) 245 [$M - H]^+$.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methylbutyramide (23). Crude **22** (5 g, 20.3 mmol) was dissolved in tetrahydrofuran (50 mL) and *N*,*O*-dimethylhydroxylamine hydrochloride salt (3.07 g, 31.5 mmol) added. After cooling the slurry to −20 °C, a solution of isopropylmagnesium chloride in THF (2.0 M, 30 mL, 60 mmol) was added dropwise over 30 min, maintaining the reaction temperature at below −15 °C. After keeping at −20 °C for a further 2 h, the reaction was

(37) Wattanasereekul, S.; Maier, M. E. *Adv. Synth. Catal.* **2004**, *346*, 855.

quenched with a saturated aqueous solution of ammonium chloride (100 mL) and diluted with diethyl ether (40 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (100 mL), the combined organic layers were washed with water (100 mL) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to leave crude **23** as a pale-yellow oil (4.8 g, 90%). Purity by GC 88.7 area % (main impurity TBDMS-OH, 7.8 area %). A portion of the residue (1.3 g) was purified by chromatography, eluting with a 1:9 mixture of ethyl acetate and isohexane, to afford the title compound as a colourless oil (1.09 g, 84% recovery). Purity by GC 100 area %. $[\alpha]^{25}_D$ +18.1 (*c* 1.37, $CHCl_3$).[38] ^{1}H- and ^{13}C NMR data in agreement with published data.[38] MS (*m*/*z*) 260 $[M - H]^+$.

(*S*)-5-(*tert*-Butyldimethylsilyloxy)hex-1-en-3-one (29) from Amide 23. Crude **23** (3.5 g, 13.4 mmol) was dissolved in tetrahydrofuran (70 mL) at rt then cooled to 0 °C. A solution of vinylmagnesium bromide in THF (1.0 M, 20 mL, 20 mmol) was added dropwise over 30 min, maintaining the reaction temperature below 5 °C. After keeping for a further 1 h at between 0 and 5 °C, the solution was quenched into a stirred mixture of saturated aqueous ammonium chloride (70 mL) and diethyl ether (175 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (100 mL), the combined organic layers were washed with water (100 mL) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by chromatography, eluting with a 1:20 mixture of ethyl acetate and isohexane, to provide **29** as a colourless oil (1.27 g, 42%). Purity by GC 96.9 area %. $[\alpha]^{25}_D$ +30.9 (*c* 1.08, $CHCl_3$). ^{1}H NMR (400 MHz) δ 6.36 (dd, J = 17.7, 10.5 Hz, 1H), 6.22 (dd, J = 17.7, 1.3 Hz, 1H), 5.85 (dd, J = 10.5, 1.3 Hz, 1H), 4.37−4.33 (m, 1H), 2.85 (dd, J = 14.9, 7.2 Hz, 1H), 2.54 (dd, J = 14.9, 5.4 Hz, 1H), 1.20 (d, J = 6.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H), 0.02 (s, 6H). ^{13}C NMR (100 MHz) δ 199.8, 137.4, 128.5, 65.8, 49.1, 25.8, 25.7, 24.2, 18.0, −4.6, −5.0. MS (*m*/*z*) 227 $[M - H]^+$.

(*S*)-2-Methyltetrahydropyran-4-one (4) via Intramolecular Oxy-Michael Addition on 29. 29 (0.4 g, 1.75 mmol) was dissolved in chloroform (30 mL) at rt. Amberlyst 15 ion-exchange resin (0.15 g) was added in one portion, and then the reaction mixture was held at rt with stirring for 24 h. After removal of the resin by filtration, solvent was removed by evaporation under reduced pressure and the residue purified by chromatography, eluting with 20% ethyl acetate in petroleum ether, to afford the title compound as a pale-yellow oil (80 mg, 40%). Optical purity by GC 81.6% as the (*S*)-enantiomer.

Ethyl (*S*)-3-(Triethylsilyloxy)butyrate (30). Ethyl (*S*)-3-hydroxybutyrate **15** (5 g, 37.8 mmol) was dissolved in dichloromethane (20 mL), and then triethylamine (6.4 mL, 46 mmol) was added followed by chlorotriethylsilane (7.6 mL, 45 mmol) dropwise, resulting in precipitation of a white solid (exotherm to 35 °C over 30 min). After allowing to cool back to rt and stirring for 5 h, water (30 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (50 mL) followed by brine (50 mL), and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to leave crude **30** as a colourless oil (9.53 g, >100%). Purity by GC 97.9 area %. Spectral data were obtained on a sample purified by chromatography, eluting with 1% ethyl acetate in isohexane. Purity by GC 100 area %. $[\alpha]^{25}_D$ +18.2 (*c* 0.99, $CHCl_3$). ^{1}H NMR (400 MHz) δ 4.33−4.28 (m, 1H), 4.07−4.18 (m, 2H), 2.50 (dd, J = 14.6, 7.2 Hz, 1H), 2.36 (dd, J = 14.6, 5.6 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 6 Hz, 3H), 0.95 (t, J = 8 Hz, 9H), 0.56 (q, J = 8 Hz, 6H). ^{13}C NMR (100 MHz) δ 171.6, 65.6, 60.2, 44.9, 24.0,14.2, 6.7, 4.8. MS (*m*/*z*) 245 $[M - H]^+$.

(*S*)-3-(Triethylsilyloxy)-*N*-methoxy-*N*-methylbutyramide (31). This was prepared in a similar manner to that described above for compound **23**, starting from 13.3 g of crude **30**), with appropriate scaling of quantities, affording **31** as a colourless oil (12.6 g, 89%). $[\alpha]^{25}_D$ +6.4 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz) δ 4.39 4.32 (m, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 2.77 (dd, J = 14.6, 7.2 Hz, 1H), 2.40 (dd, J = 14.6, 5.9 Hz, 1H), 1.22 (d, J = 6 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H). ^{13}C NMR (100 MHz) δ 170.0, 65.7, 61.3, 41.8, 32.0, 24.2, 6.7, 4.7. MS (*m*/*z*) 260 $[M - H]^+$.

(*S*)-5-(Triethylsilyloxy)hex-1-en-3-one (32). This compound was prepared in a similar manner to that described above for compound **29**, starting from 10 g (38.2 mmol) of crude **31**, with appropriate scaling of quantities. After purification by chromatography, **32** was obtained as a colourless oil (4.9 g, 56%). Purity by GC 80.4 area %. $[\alpha]^{25}_D$ +20.7 (*c* 1.20, $CHCl_3$). ^{1}H NMR (400 MHz): δ 6.36 (dd, J = 17.7, 10.5 Hz, 1H), 6.22 (dd, J = 17.7, 0.9 Hz, 1H), 5.85 (dd, J = 10.5, 1.0 Hz, 1H), 4.38−4.31 (m, 1H), 2.86 (dd, J = 15.1, 6.7 Hz, 1H), 2.58 (dd, J = 15.1, 5.9 Hz, 1H), 1.21 (d, J = 6.2 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.54 (q, J = 7.9 Hz, 6H). ^{13}C NMR (100 MHz) δ 199.6, 137.4, 128.5, 65.4, 49.1, 24.2, 6.8, 4.7. MS (*m*/*z*) 227 $[M - H]^+$.

(*S*)-2-Methyltetrahydropyran-4-one (4) via Intramolecular Oxy-Michael Addition on 32. Crude **32 (**0.2 g, 0.88 mmol) was treated with Amberlyst 15 ion-exchange resin (0.1 g) in toluene (10 mL) at 0 °C for 8 h. Work-up and purification as described above afforded **4** as a pale-yellow oil (0.05 g, 50%). Purity by GC 97.6 area %. Optical purity by GC 94.6% as the (*S*)-enantiomer.

(*S*)-3-Hydroxy-*N*,*N*-dimethylbutyramide (37). Sodium methoxide in methanol (28% *w*/*w*, 930 kg, 4.82 kmol) was added over a period of 95 min to a stirred, cooled (4 °C) solution of dimethylamine hydrochloride (250 kg, 3.07 kmol) in methanol (640 kg). During the course of the addition, the reaction temperature increased to 12.8 °C and was brought back to 3.1 °C during a subsequent 2 h stir. Methyl (*S*)-3-hydroxybutyrate **36** (316 kg, 2.68 kmol) was added to the reaction mixture over a period of 85 min, and stirring continued for 18 h at between 2 and 4 °C. After cooling to 0 °C, aqueous sulphuric acid (10% *w*/*w*, 316 kg) was added over 57 min, which brought the pH to 8−9; then further aqueous sulphuric acid (20% *w*/*w*, 42.7 kg) was charged over 40 min, bringing the pH to 7. The reaction temperature was allowed to rise to a maximum of 14 °C during these exothermic additions. The inorganic byproduct was removed by centrifugation and the filtrate concentrated under vacuum (100 mmHg) at below 51 °C to remove methanol (1770 kg). The residue was extracted with *n*-butanol (3 × 316

(38) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3477.

kg), and the combined extracts were concentrated by distillation (50 mmHg/88 °C) to remove a mixture of *n*-butanol and water (1895 kg). Additional inorganic salts were removed by centrifugation and washed with *n*-butanol (316 kg). The combined filtrates were separated by distillation to afford **37** (223 kg, 63.5%). Bp 88−90 °C at 0.3 mmHg. Purity by GC 97.5 area % with 1.56 area % **36**. ^{1}H NMR (300 MHz) δ 4.27−4.12 (m, 1H), 4.07 (br s, 1H), 2.97 (s, 6H), 2.49 (ABX system, J = 15, 2.4 Hz, 1H), 2.30 (ABX system, J = 15, 9 Hz), 1.22 (d, J = 6.3 Hz, 3H). HRMS. Calcd for $C_6H_{13}NO_2Na$ ([M + Na]$^+$) 154.0839. Found 154.0834.

(*S*)-3-(*tert*-Butyldimethylsiloxy)-*N*,*N*-dimethylbutyramide (38). Imidazole (138.3 kg, 2.03 kmol) was added to a solution of **37** (222 kg, 1.69 kmol) in ethyl acetate (603 kg) with stirring. Once dissolution was complete, a solution of TBDMS chloride in ethyl acetate (50% *w/w*, 561 kg, 280.5 kg contained weight, 1.86 kmol) was added over a period of 125 min, during which the reaction temperature rose from 12.6 °C to a maximum of 17.2 °C. After stirring at 15−20 °C for 16 h, imidazole hydrochloride was removed by centrifugation, and the solids were washed with ethyl acetate (100 kg). The combined filtrates were concentrated under reduced pressure (80 mmHg/76 °C) until 909 kg solvent had been removed. Toluene (385 kg) was added to the residue, and the mixture was washed with water (3 × 222 kg) and then concentrated under vacuum (40 mmHg/86 °C) until 377 kg of solvent had been removed. The residue was separated by distillation to provide **38** (371 kg, 89.3%). Bp 80 °C at 0.3 mmHg. Purity by GC 96.8 area %. ^{1}H NMR (300 MHz) δ 4.40−4.28 (m, 1H), 3.05 (s, 3H), 2.94 (s, 3H), 2.65 (ABX system, J = 14, 7.5 Hz, 1H), 2.28 (ABX system, J = 14, 5 Hz), 1.21 (d, J = 6 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (2, 3H). HRMS found 268.1705 calcd for $C_{12}H_{27}NO_2SiNa$ ([M + Na]$^+$) 268.1703.

(*S*)-5-(*tert*-Butyldimethylsiloxy)hex-1-en-3-one (29) from Dimethylamide 38. 38 (320 kg, 1.30 kmol) was added to a cooled solution of vinyl magnesium chloride in THF (0.85 M/kg, 2783 kg, 2.37 kmol) over a period of 75 min (initial temperature 4.9 °C, final temperature 11.6 °C). On completion of the addition, the mixture was stirred for a further 110 min whilst it was cooled back to 6.8 °C. The reaction mixture was then added to a cooled solution of aqueous sulphuric acid (5% *w/w*, 3500 L) over a period of 105 min (initial temperature 1.1 °C, final temperature 6.9 °C, maximum temperature 8.1 °C) and stirred for a further 30 min. Toluene (510 kg) was added, the layers were separated, and the organic layer was washed sequentially with water (370 kg), aqueous sodium carbonate (5% *w/w*, 368 kg), and water (370 kg). Hydroquinone (370 g, 3.36 mol) was added to the toluene phase which was then concentrated under vacuum (70 mmHg/106 °C) until 2117 kg of solvent had been removed. The residue was purified by distillation under vacuum to afford **29** (142 kg, 47.7%). Bp 64 °C at 0.6 mmHg. Purity by GC 95.3 area %.

(*S*)-2-Methyl-2,3-dihydropyran-4-one (10) via Oxidative Cyclisation Route. Benzoquinone (56.1 kg, 519 mol), aqueous hydrochloric acid (37% *w/w*, 2.16 kg) and $PdCl_2(CH_3CN)_2$ (0.57 kg, 2.20 mol) were added to a solution of **29** (100 kg, 438 mol) in a mixture of acetone (237 kg) and water (100 kg) at 15 °C. The mixture was then heated to 35−40 °C and maintained at this temperature for 65 min. Further water (400 kg) was added, and the reaction mixture was held at 35−40 °C for another 255 min when analysis showed 97 area % conversion. The reaction mixture was brought to pH 5−6 by the addition of solid sodium bicarbonate in portions (total 8.9 kg, 106 mol added) and then concentrated under vacuum (350 mmHg, 67.5 °C) until 249 kg of solvent had been removed. After cooling, heptane (68.4 kg) was added to the residue, and the layers were allowed to separate. The organic phase was extracted with water (2 × 150 kg), and then the combined aqueous layers were extracted with toluene (4 × 340 kg). The combined toluene phases were concentrated under vacuum (70 mmHg/81.3 °C) until 1298 kg of solvent had been removed. PEG#400 (9.8 kg) was added to the residue which was then purified by distillation to afford **10** (17.28 kg, 15.22 kg corrected for assay, 31.0%). Bp 68−70 °C at 10 mmHg. Optical purity by HPLC 99.8 area %.

The aqueous layer remaining after toluene extraction was re-extracted with the recovered toluene (1298 kg) and the organic phase was concentrated under vacuum to leave 79 kg of residue to which PEG#400 (0.5 kg) was added. Following distillation, further dihydropyranone **10** was obtained (5.44 kg, 4.57 kg corrected for assay, 9.3%). Optical purity by HPLC 99.7%. Total yield 19.79 kg (40.3%).

(*S*)-2-Methyltetrahydropyran-4-one (4) from Dihydropyranone 10. A mixture of **10** (5.48 kg, weight corrected for assay 4.83 kg, 43.1 mol) and 3% Pd on alumina (0.28 kg) in toluene (8.66 kg) was hydrogenated at 45−55 °C/30 bar pressure until uptake of hydrogen had ceased (18.5 h) when analysis by GC demonstrated 100% conversion and 99.6 area % selectivity for pyranone **4**. After cooling to rt, the catalyst was removed by filtration and toluene was removed by distillation (temperature 44 °C/45 mmHg pressure) to leave a concentrated solution of pyranone **4** in toluene (8.16 kg. This was combined with the product concentrates from several other reactions carried out under similar conditions, starting from a total weight of 11.57 kg of **10** (10.19 kg corrected for assay, 103.2 mol) and the mixture was purified by distillation under reduced pressure to afford **4** as a colourless oil (10.2 kg, 67%). Bp 52−54 °C/20 mmHg. Chemical purity by GC 99.6 area %. Optical purity by GC 99.7% as the (*S*)-enantiomer.

Methoxyallene (40). A solution of methyl propargyl ether (90.6 g, 1.29 mol) in THF (109 mL) was added in 5 mL portions over a period of 1 h to a solution of potassium *tert*-butoxide (14.5 g, 0.129 mol) in THF (436 mL) at 55 °C. Once the addition was complete, the solution was allowed to cool to rt, and methoxyallene was isolated as a solution in THF by distillation under vacuum (486 g). Assay by ^{1}H NMR 17.8% *w/w*, therefore contained weight of methoxyallene 86.3 g (95%). Bp 15−20 °C at 70 mmHg. ^{1}H NMR (400 MHz) δ 6.77 (t, J = 6.1 Hz, 1H), 5.48 (d, J = 6.1, 2H), 3.41 (s, 3H). ^{13}C NMR (75 MHz) δ 201.1, 122.8, 91.2, 55.8. MS: 70 (M$^+$, 100%), 55 (M-15, 25%).

(*S*)-4-Methoxyhexa-4,5-dien-2-ol (42). A solution of methoxyallene (**40**) in THF solution (150 g, 17.8% *w/w*, containing methoxyallene 26.6 g, 0.379 mol) was cooled to −4 °C and heptane (27.8 mL) added as an internal GC standard. A solution of *n*-butyllithium in hexanes (2.5 M, 167 mL, 0.418 mol) was

then added over a period of 1 h, maintaining the reaction temperature between −2 °C and +2 °C. Once the addition was complete, the mixture was stirred at 0 °C for 0.5 h (complete lithiation was confirmed by ^{1}H NMR spectroscopy on a sample quenched into d_4-MeOH). The lithio-methoxyallene solution was then added to a mixture of LiBr (32.9 g, 0.379 mol) and (*S*)-propylene oxide (26.6 mL, 0.380 mol) in THF (100 mL) at 0 °C over a period of 30 min, maintaining the reaction temperature between 0 °C and +5 °C. The reaction mixture was then allowed to warm to rt (exotherm to 35 °C occurred, mixture allowed to cool back to rt) and stirred for 1 h. Water (350 mL) was slowly added (exothermic) and the product extracted into diethyl ether (2 × 250 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure (bath temperature 25 °C) to leave an orange oil, 35.2 g (72.5%). This was purified by distillation to afford **42** (28.1 g). Bp 45−50 °C at 1 mbar. Purity by GC 88.1 area %. Assay by GC 90% *w/w*., therefore yield corrected for assay 51.8%. ^{1}H NMR (400 MHz) δ 5.45 (s, 2H), 4.05 (m, 1H), 3.42 (s, 3H), 2.35 (m, 2H), 2.30 (br s, 1H), 1.25 (d, J = 6.4 Hz, 2H). ^{13}C NMR (75 MHz) 199.0, 132.3, 90.3, 66.2, 56. 2, 41.8, 22.6. MS 128 (M^+, 50%), 113 (M^+−15, 60%). Chiral purity by GC: 100% as the (*S*)-enantiomer.

(*S*)-2-Methyl-2,3-dihydropyran-4-one 10 (via Methoxyallene Route). Allene **42** (17.1 g, 0.13 mol) was dissolved in acetone (80 mL) and water (33 mL) added. Benzoquinone (14.4 g, 0.13 mol) was then added portion-wise, washed in with acetone (10 mL). Bis(acetonitrile)dichloropalladium(II) (0.173 g, 0.67 mmol) was then added, again washed in with acetone (10 mL) before the mixture was heated to 55 °C and held at this temperature for 2 h. The mixture was allowed to cool to rt then diluted with water (100 mL) and extracted with toluene (4 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated (bath temperature 35 °C, vacuum 60 mmHg) to give the crude product as an oil (14.2 g). This was purified by distillation to afford **10** as a colourless oil (7.2 g, 48%). Bp 59−61 °C at 6 mbar. Assay by GC 85% *w/w*. HRMS calcd for $C_8H_{12}NO_2$ ($MH^+ + CH_3CN$) 154.0868, found 154.0864. Optical purity by GC 100% as the (*S*)-enantiomer.

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