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Baeyer–Villiger Oxidation of 5-*endo*-(Biphenyl-4-ylmethoxy)-7-*anti*-piperidinobicyclo[2.2.1]heptan-2-one: Process Development and Scale-Up

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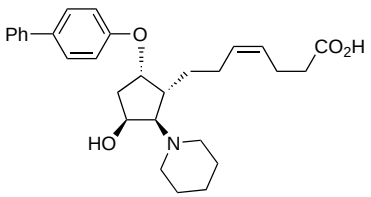
Abstract:

The Baeyer–Villiger oxidation of 7-*anti*-piperidino, 5-*endo*-biphenyl-4-ylmethoxy substituted norbornan-2-one was developed to provide a robust, reproducible process for manufacture of the regioisomeric lactone which results from migration of the bridgehead carbon atom. Yields of 60–63% theory were obtained in a 2250 L plant.

Introduction

The Baeyer–Villiger reaction is particularly useful when applied to oxidation of bicyclic ketones such as **2** to afford lactones, which on hydrolysis yield cyclopentyl derivatives with the four centres of defined regiochemistry required for conversion into compounds such as structure **1** which has been shown to possess thromboxane A2 antagonist activity potentially of value in the treatment of occlusive vascular disease.[1] This paper will discuss the process research, development, and scale-up of the oxidation of **2a** to afford lactone **9a**; performance on a 2250 L, 160 kg input scale will be presented.



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Discussion

The peracid oxidation of [2.2.1] bicyclic systems is well documented;[2] the ratio of lactones resulting from methylene and methine carbon migration is determined by several interdependent electronic and stereochemical factors. Recently a series of 5,7-substituted analogues, including 7-*anti*-piperidino-5-*endo*-biphenyl-4-ylmethoxy, have been oxidised with *m*-chloroperbenzoic acid in dichloromethane and the product ratios determined under strictly comparable conditions;[3] the lactones **5a** and **9a** were obtained in a ratio of 40:60 (Scheme 1). The cost and lack of commercial multikilogram quantities of this peracid, when we began process development, led us to use the readily available equilibrium peracetic acid (nominally a w/w mixture of 38% peracetic acid, ca. 3% hydrogen peroxide, 1% water, and 0.7% sulphuric acid in acetic acid). Our first substrate was the racemic analogue of **2b**, and the initial oxidation method employed addition of the 38% peracetic acid (4 molar equiv) to a solution of the ketone in a mixture of sodium acetate (4 molar equiv) and 33% aqueous acetic acid (12 volumes with respect to the substrate) at ca. 20 °C. Under these hydrolytic conditions the lactone *N*-oxide **4b** formed via migration of the adjacent methylene group is hydrolysed at a comparable rate to the rearrangement, whereas the lactone *N*-oxide **6b** resulting from migration of the adjacent methine group remains stable; this difference in hydrolytic susceptibility has been ascribed to relief of strain in a tetrahedral intermediate.[2] In practice the acid **7b**, resulting from methylene migration and hydrolysis, is not isolated, as the *N*-oxide undergoes immediate Cope elimination[4] to afford the unsaturated acid **10**. As a result of this hydrolysis the ratio of lactone *N-oxides* (**4**:**6**), formed as a reflection of migratory preference, have to be determined either via a material balance or by extrapolation*;* reaction mixtures were worked up via reduction with excess sodium metabisulphite, which converts the *N*-oxides **4** and **6** into the parent lactones **5** and **9.** Analytical methods which allowed quantification of total lactone (**5** + **9**, HPLC), ratio of lactones (**5**:**9**, GC or HPLC), and residual ketone (**2**, HPLC) in the reaction mixture permitted a reasonable estimate of migratory preference on the assumption that oxidation, rearrangement, and *N*-oxide reduction are quantitative.

The reaction conditions developed for scale-up evolved over several years, during which time several different 5,7-substituted norbornanones were examined. A comparison of the major changes in methodology is illustrated in Figure 1 for the 7-morpholino analogue **2b**; assuming no decomposition of the lactone *N*-oxide **6b** (vide infra), and correcting for residual norbornanone *N*-oxide **3b**, the estimated ratio **4b**:**6b** (determined as lactones **5b**:**9b)** ranged between ca. 44:56 and 75:25. The measured ratio will be influenced by the relative proportions of protonated and nonprotonated species, their intrinsic reactivity, migratory preference, and distribution in the biphasic system.

The yield of the required lactone **9** was also dependent on the stability of lactone *N*-oxide **6** to further rearrangement (vide infra). The significant results and observations that contributed to our understanding of the critical variables which control the scalable process will now be discussed.

(1) Lumley, P.; Finch, H.; Collington, E. W. C.; Humphrey, P. P. A. *Drugs Future* **1990**, *15*, 1087.
(2) Krow, G. R. *Tetrahedron* **1981**, *37*, 2697.
(3) Hamley, P.; Holmes, A. B.; Marshall, D. R.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1793.
(4) Cope, A. C.; Trumball, E. R. *Org. React. (N.Y.)* **1960**, *11*, 317.

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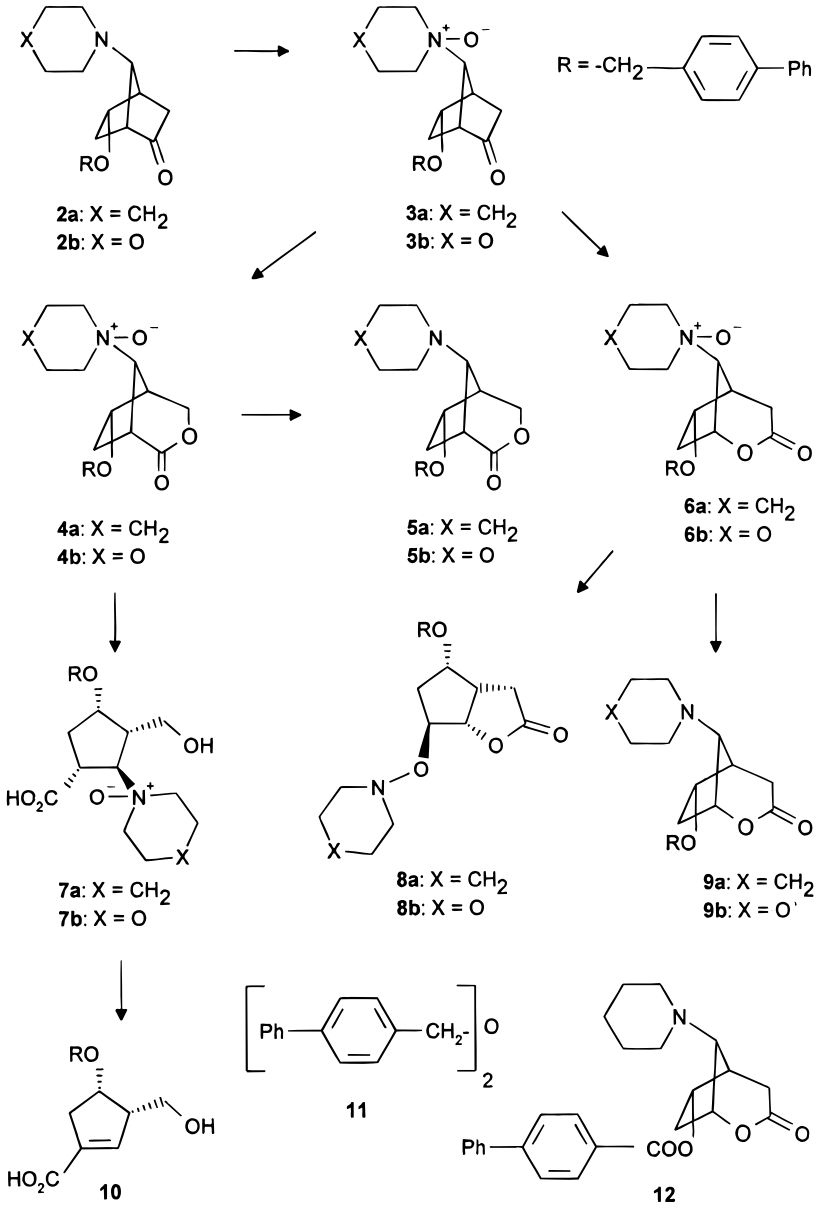
Scheme 1



Conversion of the norbornanone **2** into the *N*-oxide **3** occurs rapidly under neutral or basic conditions; mineral acid retards N-oxidation, and when it was present in excess of 2 molar equiv, the ratio of lactones, **9b**:**5b**, became less favourable, changing from ca. 74:26 with 2 equiv of acid to approximately 55:45 with 6 equiv. This change in selectivity may reflect oxidative rearrangement of the protonated amino ketone. This inference is supported by oxidation of **2a** in the presence of aqueous (10 volumes) sulphuric acid (2 molar equiv); in contrast to conditions in which dichloromethane was present, lactone **9a** was obtained in poor yield at a reduced reaction rate and the *N*-oxide **3a** was not detected (Figure 2).

An essential component of our strategy for achieving a scalable process, from a reaction that inherently produces a mixture of isomeric lactones, was that selective hydrolysis of the undesired lactone (the result of methylene migration) should occur in situ and be removable via basic extraction. Consequently we omitted sodium acetate and added dichloromethane with or without water (Figure 1). The rate of oxidation was increased although the hydrolysis rate of the lactone *N*-oxide **4b** remained comparable; surprisingly we achieved a greatly improved yield of lactone **9b**. Alternative aqueous solvent mixtures, chloroform, toluene, ethyl acetate (homogeneous reaction mixture), gave similar results and offered no advantage. Later the relative performance of these solvents was also determined in the presence of sulphuric acid (1 molar equiv) for norbornanone **2b**; dichloromethane afforded significantly higher yields of lactone **9b** (ca. 70% th in solution after 48 h at 20 °C as compared to ca. 40% th for ethyl acetate under similar conditions; "% th" designates percent of theoretical yield). The then current reaction conditions (peracetic acid, 5 molar equiv, dichloromethane, 5 volumes) were scaled up for the morpholino analogue **2b** with inputs of ca. 5 kg in a 110 L stainless steel reactor; isolated yields of **9b** were ca. 52% of theory with impurities totalling ca. 1% w/w. Details of the process development and optimisation will be illustrated for the piperidino analogue **2a** as it became the preferred intermediate in our process development programme.

The conditions described above for **2b** were confidently applied to norbornanone **2a**; however, it became immediately

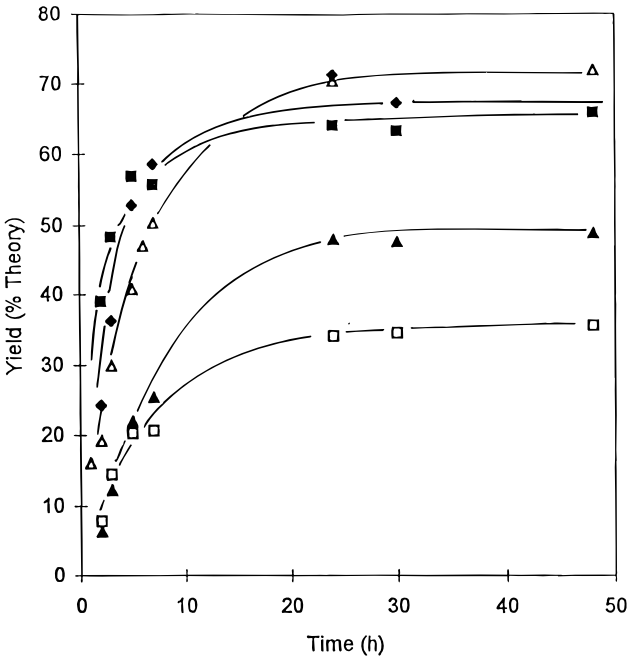


Figure 1. **Yield of 9b from oxidation of 2b: comparison of reaction conditions. △: PA (peracetic acid) (5 equiv), DCM (5 volumes), water (4 volumes), sulfuric acid (1 equiv). ◆: PA (5 equiv), DCM (5 volumes), water (4 volumes). ■: PA (5 equiv), DCM (5 volumes). ▲: PA (5 equiv), AcOH (8.5 volumes), water (4.25 volumes), NaOAc (8 equiv). □: PA (6 equiv), DCM (5 volumes), water (4 volumes), $KHCO_3$ (18.5 equiv) (with phase transfer catalyst (Aliquat 336, 0.05 volume)).**

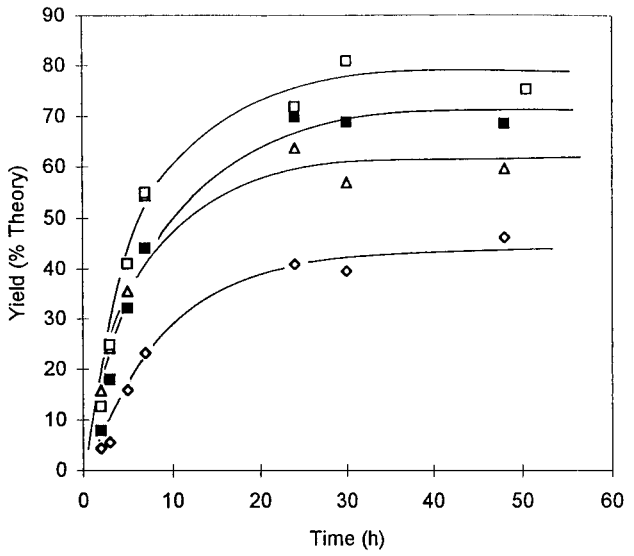


Figure 2. **Yield of 9a from oxidation of 2a as a function of added sulphuric acid. Reaction conditions: Peracetic acid (5 equiv), DCM (5 volumes), water (4 volumes), unless indicated. ◇: sulphuric acid (2 equiv), water (10 volumes), DCM omitted. ■: sulphuric acid (2 equiv). △: sulphuric acid (0.1 equiv). □: sulphuric acid (1 equiv).**

apparent that the performance was different from that of **2b**; the undesired lactone *N*-oxide **4a** hydrolysed more slowly than the morpholino analogue; after the typical 24 h reaction time it constituted ca. 10% of the total lactone content, and workup afforded an unacceptably contaminated product. Extended reaction times and addition of further peracetic acid resulted in decreased yield (40% th); scale-up to 0.7 kg input in 10 L glassware merely resulted in a further fall in yield to ca. 30% th. Analysis for norbornanone **2a** and lactone *N*-oxides (reduced and determined as lactones) **4a** and **6a** revealed that the maximum yield of **6a** was ca. 55% th (cf. **6b** at ca. 65%). More importantly, the stability of **6a** was dependent on both temperature and concentration. Under the reaction conditions the concentration of lactone *N*-oxide **6a** decreased via rearrangement to lactone **8a** at ca. 0.5% th/h, compared to that of the morpholino analogue, which decreased by less than 2% th over 24 h. Crystallisation of crude *N*-oxide **6a**, obtained by direct oxidation of lactone **9a**, from isopropyl acetate gave the rearranged lactone **8a**; *N*-oxide **6a** was converted into **8a** after being heated for ca. 18 h at reflux in dichloromethane. The lactone *N*-oxide **6a** may be stabilised by dilution (dichloromethane increased to 30 volumes) and lower reaction temperature (0 °C). The thermally induced Cope elimination of amine oxides[4] requires a planar five-membered transition state; this transformation will be disfavoured for **6** due to the inflexible structure and potential development of the double bond at the bridgehead; the opening of the γ-lactone and reclosure to the more stable δ-lactone **8** provides an alternative pathway for elimination of the quaternary amino function with generation of an alkylated hydroxylamine.

It was clear that, in order to achieve greater yields, the hydrolysis of the undesired lactone **4a** had to be increased substantially to allow workup before losses of lactone *N*-oxide **6a** became significant; to this end water (4 volumes) was added after 5 h at 20 °C. We were surprised to find that this stabilised the lactone *N*-oxide **6a**, but hydrolysis of **4a** remained impracticably slow (48−72 h reaction time). Nonetheless, yields of **9a** in ca. 55% th from 1.3 kg input **2a** and good analytical quality (<1% **5a**) were attained. The hydrolysis rate was not improved by addition of a phase transfer catalyst and basification with sodium carbonate. Addition of 1 molar equiv of sulphuric acid increased the rate of hydrolysis and improved the selectivity; however, at 2 molar equival both selectivity and rate of oxidation begin to fall (Figure 2).

The main features of the reaction process, namely, peracetic acid, 5 molar equiv; sulphuric acid, 1 molar equiv; dichloromethane, 5 volumes; and water, 4 volumes; had now been reached. An improved yield of ca. 65% th was achieved for our first batch (1.3 kg of **2a**) in 20 L glassware. Process development and scale-up issues are addressed below.

Substrate Quality. Norbornanone **2a** could only be obtained in reproducible quality by isolation as an oxalate; this process removed a significant impurity of synthesis, ether **11**. Although a suspension of the crystalline oxalate in dichloromethane could be used directly in the oxidation (lactone **9a** could be obtained in ca. 63% th yield assaying at 98% w/w on a 20 L glass scale), there was significant concurrent decomposition (ca. 1.7 equiv measured by oxygen evolution) of peracetic acid. Decomposition was reliably limited to ca. 0.25 equiv of oxidant by neutralising the oxalate and extracting the base into dichloromethane; the solution was used directly in the oxidation.

Optimisation. A simplex optimisation[5] technique, based on six reaction variables and a response in terms of yield (% theory of lactone **9b**) was applied to the morpholino analogue **2b.**) The first simplex, derived from seven sets of

(5) Nelder, J. A.; Mead, R. *Comput. J.* **1965**, *7*, 308.

experimental conditions, covered the following ranges for each variable: dichloromethane 7−14 volumes, water 7−13 volumes, sulphuric acid 3.5−6.6 molar equiv, peracid 8−14 molar equiv, time 23−41 h, and temperature 15−26 °C. Eleven simplexes (26 experiments) revealed that the major determinant of selectivity and yield of lactone **9b** was sulphuric acid stoichiometry, whereas the rate of reaction was largely controlled by both temperature and excess oxidant. Oxidation at 30 °C required ca. 20 h with 5 equiv and ca. 42 h with 4 equiv and failed to reach completion (ca. 5% norbornanone remained after 42 h) with 3 equiv of peracid. The optimum yield (73% th in solution), reached at the fifth simplex, was obtained at half our standard (dichloromethane and water, 5 and 4 volumes, respectively) concentration using peracid (11 molar equiv), 22 °C, and sulphuric acid (2 molar equiv); however, these conditions were not pursued due to the severely limited throughput. A total of 420 kg of lactone **9a** was prepared in a 340 L plant using 5 equiv of peracid at 20 °C/72 h; however, verification that oxidation of the piperidino analogue could be completed at 30 °C in 20 h mandated these latter conditions for the manufacturing plant.

Process Safety. Scale-up of a process involving peracid always requires careful assessment of the process conditions with respect to uncontrolled decomposition and concentration of the peracid and peroxidic byproducts. Although solutions of peracetic acid are preferably handled in glassware, we considered that for pilot plant scale the risk of potential metal ion catalysed decomposition, occasioned by a defect in a glass-lined mild steel vessel, was significant; use of stainless 316 steel vessels under controlled conditions was preferred. Oxidation of norbornanone **2a** in the presence of a stainless 316 steel billet afforded both a typical yield of lactone **9a** and no additional loss of oxidant. Nonetheless, scrupulous preparative cleaning of the steel vessels in contact with peracid was performed. Typically the reactor was charged to capacity with aqueous detergent (Decon 90) and aged for ca. 18 h at ambient temperature before discharge and washout with deionised water. Finally, filtered dichloromethane (ca. 80 L/340 L reactor) was heated to reflux for ca. 2 h, cooled, diluted with peracetic acid (ca. 1% by volume with respect to dichloromethane), and aged at ambient temperature for ca. 18 h before discharge. Glass vessels were treated with aqueous 5% w/v nitric acid at 20 °C for 18 h before washout with deionised water.

A thermal profile obtained by reaction calorimetry indicated that under adiabatic conditions the reaction mixture would self-heat to reflux during peracid addition; however, modest control is only required during the first hour of reaction when the *N*-oxide is formed (total heat evolved was ca. 465 kJ/mol of **2a**); reduction of the lactone *N*-oxide **6a** *and* excess peracid by sodium metabisulphite is rapid (ca. 365 kJ/mol of **2a)** and must be controlled. Gas evolution was measured via headspace displacement and compared to that obtained by heating the solvent mixture in the absence of substrate and peracid; the total volume of oxygen, most of which was evolved as the reaction mixture was heated from 20 to 30 °C, was 0.25 molar equiv with respect to substrate. Although mixtures of dichloromethane in air at ambient temperature are nonflammable, enrichment with oxygen produces flammable mixtures (20% dichloromethane and <60% nitrogen).[6] On a production scale the maximum oxygen concentration in the headspace was limited to 6% v/v by a nitrogen purge to provide a safety margin.

Workup. Reaction mixtures were basified to pH 3−4 to liberate the product as a free base in dichloromethane. Decomposition of excess peracid remaining in the organic extract was achieved by addition of aqueous sodium metabisulphite; this mode of addition is contrary to that recommended in the literature[7] where the presence of excess peracid with respect to metabisulphite resulted in formation of diacyl peroxides. However, in production, addition of the metabisulphite was technically more simple and in practice no diacetyl peroxide was detected by infrared spectroscopy (strong absorption at 1820 and 1796 cm^{-1}). Finally, the organic phase was extracted with aqueous 1.75 M sodium hydroxide, to remove acidic products, followed by aqueous sodium chloride (15% w/v). Each aqueous extract was back extracted with dichloromethane; although this significantly increased processing times, between 0.5 and 2% theory yield of lactone **9a** was recovered (total ca. 6%) from each extract. The combined organic extracts were washed with 15% w/v sodium chloride to minimise formation of emulsions and the attendant long separation times; the final aqueous phase was required to have a pH of ca. 7 to ensure neutrality of the organic phase before concentration at atmospheric pressure and concurrent solvent exchange with 2-propanol (4 volumes). Distillates containing dichloromethane were used for extraction in subsequent batches. The crystalline lactone was isolated by filtration, washed by displacement with 2-propanol (1 volume), and dried in vacuo at ca. 40 °C. Oven heating tests and differential scanning calorimetry on samples of lactone **9a** and on the residues from concentration of the final organic extract, respectively, indicated thermal stability under the processing conditions.

Quality Control. This was established through a combination of process control and specifications for both norbornanone **2a** and the product, and an in-process check for complete reaction. The norbornanone could only be obtained in satisfactory quality (vide supra) via isolation as a crystalline oxalate (1:1); total impurities (HPLC by area) of 2% and principal impurity <1% were typical. The in-process check is required to ensure both complete oxidative rearrangement of the norbornanone *N*-oxide **3a** and complete hydrolysis of the minor isomeric lactone **4a**; the former was determined by TLC and the latter by HPLC. The product **9a** routinely contained <2% (HPLC by area) total impurities; in addition to the norbornanone **2a** and the isomeric lactone **5a** present at <0.3%, a further major impurity, typically present at up to 0.5%, was identified as the biphenyl ester **12.** This is presumably an oxidation byproduct as the biphenylmethanol used to prepare norbornanone **2a,** via alkylation of the 5-*endo*-hydroxy analogue, did not contain detectable biphenylcarboxylic acid.

The process (see Experimental Section for details) was operated in a 2250 L plant on inputs of 348 mol (162 kg of norbornanone **2a** as oxalate); yields (six batches) were in

(6) Jones, G. W.; Kennedy, R. E.; Scott, F. E. *U.S. Bur. Mines Rep.* **1943**, *3727*.
(7) Manley, T. D. *Chem. Br.* **1982**, *18*, 341.

the range 60−63% of theory. Quality was typical with impurities <2% (HPLC by area).

Some minor changes to the processing were introduced from experience at the largest scale of operation. Originally the free base **2a** was liberated by stirring a mixture of the oxalate and potassium carbonate in aqueous dichloromethane at ca. 22 °C; however, prolonged age times were required to achieve solution; separation of the phases was seriously impeded by formation of an emulsion. Processing was made more effective by dissolution of the carbonate before addition of the oxalate and dichloromethane; the mixture was heated to 30 °C, which resulted in more rapid dissolution and good phase separation; a further extraction with dichloromethane was introduced to ensure good recovery of norbornanone free base.

Good control of the reactor headspace oxygen content was achieved during addition of peracid at 10 °C; however, increasing the reaction temperature from 20 to 30 °C over 1 h raised the oxygen level (alarm set at 6% v/v) to 7−8% v/v despite a nitrogen purge; control was reestablished by reducing the temperature ramp to 10 °C over 2.5 h; after 2 h at 30 °C a nitrogen flow of <14 L/min was adequate.

The in-process checks were initially performed at 2 h intervals; after 10 h the proportion of isomeric lactone **5a** had decreased to 1%; however, the proportion subsequently appeared to increase slightly; this was attributed to some loss of the required lactone *N*-oxide **6a** via rearrangment to **8a** (vide supra).

Good phase separation was generally achieved within 1−2 h; a third brine wash of the combined organic extracts was required to achieve a pH of 7−9.

Crystallisation was not well controlled despite seeding; physical form was heterogeneous, and filtration times were unexpectedly slow, but adequate, compared to laboratory operation.

In conclusion, the process, despite intrinsic weaknesses of poor regioselectivity and long plant turnaround time, proved robust and reproducible in the manufacturing plant.

Experimental Section

Note: The *N*-oxides **3a, 4a, 6a** were prepared as reference samples by oxidation of the parent amine with *m*-chloroperbenzoic acid in dichloromethane; the compounds were characterised by H^1 NMR, TLC performance, and reduction with sodium metabisulphite to the parent amine.

[1*R*-(*endo,anti*)]-(−)-6-[(1,1′-Biphenyl-4-yl)methoxy]-8-(1-piperidinyl)-2-oxabicyclo[3.2.1]octan-3-one (9a). General Method for All Scales. The oxalate of norbornanone[8] **2a** was added to a stirred mixture of dichloromethane (DCM, 2.5 volumes with respect to weight of substrate **2a**) and aqueous (deionised water, 3.33 volumes) potassium carbonate (1 equiv); after ca. 0.5 h at ambient temperature, the aqueous phase was separated and extracted with DCM (0.83 volume). The combined organic solution of the norbornanone, as its free base, was diluted with aqueous sulphuric acid (1.04 equiv, 3.24 volumes), the temperature being maintained between 5 and 10 °C before the addition of peracetic acid (36−40% w/w, 5.0 equiv) while the reaction mixture was maintained at ca. 15 °C. The temperature of the mixture was raised to 30 °C over ca. 2.5 h (rate of temperature rise defined by maintenance of headspace oxygen content at <6% v/v with nitrogen purge). After ca. 20 h and a satisfactory in-process check (see below for analytical conditions), the mixture was adjusted to pH 3−4 by the addition (temperature maintained at <20 °C) of aqueous 5 M sodium hydroxide (0.6 volume). The aqueous phase was further extracted with DCM (0.66 volume) before the combined organic extracts were washed successively with aqueous sodium metabisulphite (17% w/v, 4.8 volumes), aqueous sodium hydroxide (1.75 M, 5.2 volumes and 0.47 M, 2.1 volumes), and aqueous sodium chloride (15% w/v, 2 × 3.2 volumes). Each aqueous phase was extracted with DCM (0.67 volume); finally the combined organic extracts were washed with aqueous sodium chloride (15% w/v, ca. 3 volumes) until the wash had a pH of 7−9. The solution of lactone in DCM was concentrated at reduced pressure to ca. 1.5 volume; distillation was continued concurrent with the addition of propan-2-ol until a residue temperature of 70−75 °C was reached. The solution was cooled to ca. 60 °C and seeded, and when crystallisation was well established, the suspension was aged at ca. 5 °C for 45 min before filtration; the product was washed by displacement with propan-2-ol (1 volume) before being dried in vacuo at ca. 45 °C to constant weight.

In-process checks: samples from the vigorously stirred reaction mixture were worked up as above; the relative concentrations of the norbornanone **2a** and lactones **5a** + **9a** were determined (R_f values of 0.93 and 0.81, respectively) by TLC (silica gel eluted with diethyl ether and detected by UV light and iodine vapour); the relative concentrations of the required lactone **9a** and the regioisomer **5a** were determined by HPLC (Hypersil BDS eluted with acetonitrile−0.05 M $NH_4H_2PO_4$ (55:45); flow rate, 1.5 mL/min; detection at 270 nm; relative retention time, **9a/5a**, was 0.64).

(3a*R*,4*R*,6*R*,6a*R*)-Hexahydro-4-[(1,1′-biphenyl-4-yl)-methoxy]-6-(1-piperidinyloxy)-2*H*-cyclopenta[*b*]furan-2-one (8a). *m*-Chloroperbenzoic acid (ca. 50% w/w water, 19.03 g, ca. 61 mmol) was added to a solution of the lactone **9a** (25 g, 65 mmol) in dichloromethane at ca. 5 °C; the mixture was aged at 20−25 °C for 2 h; further portions of the lactone were added (total 2.6 g, 6.6 mmol) until the oxidant was consumed as indicated by a trace of starting material **9a** remaining. The reaction mixture was concentrated in vacuo before trituration with aqueous 8% w/v $NaHCO_3$ (1.5 L) and diethyl ether (1.5 L). A solid which precipitated from the aqueous phase was removed by filtration before further extraction with dichloromethane (2 × 1 L); the solid was dissolved in the organic extracts, which were washed with water (100 mL) and dried ($MgSO_4$) before concentration to dryness; the crude product (cream solid, 40.2 g) was recrystallised (2×) from isopropyl acetate to give the title compound (16.0 g, 61.5% theory). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.7; H, 7.2; N, 3.4. Found: C, 73.4; H, 7.3; N, 3.6. ^{1}H NMR ($CDCl_3$): δ 1.0−1.8 (6H), 1.9, 2.0 (2H, 5-H), 2.35 (2H, CH_{ax}−N), 2.5, 2.92 (2H, 3-CH_2), 3.1−3.3 (3H, 3a-H and CH_{eq}−N), 4.22, 4.26 (2H, 4-H and 6-H), 4.47, 4.58 (2H, CH_2O), 4.89 (1H, 6a-H), 7.3−7.6 (9H, aromatic). IR (Nujol): 1767 (C═O) cm^{-1}.

(8) Hallett, P.; Collington, E. W. C.; Hayes, N. F.; Wallis, C. J.; Wadsworth, A. UK Pat. Appl. GB2097397A.

[1*R*-(*endo,anti*)]-(+)-5-[(1,1′-Biphenyl-4-yl)methoxy]-7-(1-piperidinyl)bicyclo[2.2.1]heptan-2-one Ethanedioate (1:1) (2a Oxalate). A solution of the free base (**2a**, 100 g, 266 mmol) in dichloromethane (1 L) was added with rapid stirring to a solution of oxalic acid dihydrate (37 g, 290 mmol) in acetone (250 mL) at reflux; after ca. 0.5 h at reflux the suspension was cooled to ca. 5 °C before filtration; the filter cake was washed by displacement with acetone (2 × 100 mL) and dried in vacuo at 50 °C to afford 118.9 g (96% of theory) of the title salt. Typical sample had the following analysis. ^{1}H NMR (DMSO-d_6): δ 1.26 (1H, 6-*endo*-H), 1.4−1.6 (6H), 2.10 (1H, 3-*exo*-H), 2.4−2.6 (6H), 2.72 (1H, 1-H), 2.84 (1H, 7-H), 3.08 (1H, 4-H), 4.40 (1H, 5-H), 4.50 (2H, CH_2O), 7.3−7.8 (9H, aromatic). IR (Nujol): 2678, 2560 (N^+H), 1762 (C═O), 1595 (COO^-), 764, 703 (Phenyl) cm^{-1}. Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.7; H, 6.7; N, 3.0. Found: C, 69.3; H, 6.8; N, 3.0.

***cis*-3-(Hydroxymethyl)-4-[(1,1′-biphenyl-4-yl)methoxy]-1-cyclopentenecarboxylic Acid (10b).** Peracetic acid (ca. 38% w/w, 128 mL) was added to a stirred mixture of norbornanone **2b** (racemic, 59 g, 156 mmol) and sodium acetate (64 g) in water (250 mL) and acetic acid (500 mL), the temperature being maintained below 30 °C; after 48 h at ambient temperature excess peracid was decomposed by addition of aqueous saturated sodium sulphite. The mixture remaining, after removal of acetic acid in vacuo, was diluted further with water (500 mL), made alkaline with 2 N sodium carbonate, and extracted with ethyl acetate (5 × 400 mL). The aqueous phase was adjusted to pH 6 and extracted with dichloromethane (3 × 400 mL); the organic extract was dried ($MgSO_4$) and evaporated to dryness to afford a dark red semisolid (28 g); a sample (3 g) was purified by chromatography (silica gel eluted with ethyl acetate) to give **10b** (racemic), 1.24 g (23% of theory), mp 132−134 °C. ^{1}H NMR (DMSO-d_6): δ 2.6−2.8 (2H, 5-CH_2), 3.03 (1H, 3-H), 3.58−3.80 (2H, 3-CH_2OH), 4.32 (1H, 4-H), 4.51, 4.58 (2H, CH_2O), 6.69 (1H, 2-H), 7.3−7.7 (9H, aromatic). IR (Nujol): 1695 (C═O), 1630 (C═C) cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2. Found: C, 73.75; H, 6.2.

Acknowledgment

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