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ARTICLE

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Design and Scale-Up of Diels−Alder Reactions for the Practical Synthesis of 5-Phenylbicyclo[2.2.2]oct-5-en-2-one

Jacques-Alexis Funel, Gunther Schmidt, and Stefan Abele*

Process Research Chemistry, Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, CH-4123 Allschwil, Switzerland

Supporting Information

ABSTRACT: Several synthetic pathways towards racemic 5-phenylbicyclo[2.2.2]oct-5-en-2-one **1** have been devised starting with a Diels−Alder reaction of (cyclohexa-1,5-dien-1-yloxy)trimethylsilane and α-acetoxyacrylonitrile, acrylonitrile, or α-chloroacrylonitrile. The first 'fit-for-purpose' route relied on α-acetoxyacrylonitrile as a dienophile and rapidly delivered kilogram amounts of **1**. Process safety data then triggered the development of a scalable Diels−Alder reaction using α-chloroacrylonitrile as the dienophile. This practical and volume-efficient route delivered **1** in a 44% yield in six chemical steps with two isolated intermediates. Notably, neither chromatography nor distillation was required for the multikilogram synthesis of **1**.

1. INTRODUCTION

For the synthesis of a preclinical candidate, multikilogram quantities of the intermediate 5-phenylbicyclo[2.2.2]oct-5-en-2-one **1** were urgently needed requiring the design and development of a scalable route. Reports on large-scale Diels−Alder reactions are scarce.[1,2] To our knowledge there is no literature precedence for the scale-up of a Diels−Alder reaction with trimethylsilyl (TMS) diene **2**[3] and α-acetoxyacrylonitrile **3**, acrylonitrile, or α-chloroacrylonitrile. The original medicinal chemistry protocol followed an approach with the C_2-symmetrical diketone **5** as an intermediate (Scheme 1).[4]

A neat Diels−Alder reaction of (cyclohexa-1,5-dien-1-yloxy)-trimethylsilane **2** with α-acetoxyacrylonitrile **3** afforded a diastereomeric mixture of the bicyclic α-acetoxycarbonitrile **4**.[5] The crude product was converted into diketone **5** by exhaustive hydrolysis with sodium methoxide in methanol. Grignard addition of phenylmagnesium bromide was accomplished either directly onto the diketone **5** (condition c) or onto the monoprotected ketal **10** (condition d).[6] The drawbacks that made this route unsuitable for delivering larger amounts were (i) the need for tedious chromatography on all stages, (ii) the low yields, (iii) the lack of solid intermediates, and (iv) the analytical difficulties posed by the lack of UV active moieties. Specifically, during liberation of diketone **5** we detected polymerization, water solubility and a cyanohydrin−ketone equilibrium, preventing a smooth scale-up. In addition, the Diels−Alder reagents posed a challenge due to their toxic nature (in essence the α-acetoxyacrylonitrile **3**, requiring NaCN for its preparation), their thermokinetic risks, and timely supply. While sourcing **2** and **3** it quickly became apparent that delivery times for the first kilograms would not be commensurate with a challenging preclinical schedule.[7] Attempts to selectively access the corresponding monoketal compound **10** (Scheme 3, vide infra) using a variety of diols[8] afforded at best a 12:1 ratio of mono-ketal versus bis-ketal at 80% conversion, using ethylene glycol. The route depicted in Scheme 1 did not deliver more than 50-g amounts and was not deemed suitable for scale-up.

2. ALTERNATIVE ROUTES

Several alternative syntheses of diketone **5** have been reported.[9] These approaches suffer either from very low yields, the use of toxic metals or from tedious chromatographic purification. We initially checked several alternative dienophiles for the Diels−Alder reaction with **2** (Figure 1): *tert*-butylacrylate, acryl amides (including *N*-acryl oxazolidinones), acrolein, a methylene Meldrum's acid surrogate,[10] phenyl acetylene,[11] ethyl propiolate,[12] and ethyl 3-phenylpropiolate.[13] The acetylene derivatives either gave no reaction or led to the predominant formation of Alder−Rickert products with a 1,4-substitution pattern. We also quickly tested alternative dienes as potential candidates for a Diels−Alder reaction using these dienophiles; however, none gave superior results.

Being cognizant of the problems to differentiate between the two carbonyl groups in **5** we speculated that an expedient route not involving this intermediate would be better suited to deliver the initial larger amounts of the ketone **1**. We presumed that the same dienophile **3** would engage in a Diels−Alder reaction with a diene already carrying the phenyl moiety, 3,4-dihydro-1,1′-biphenyl, see Scheme 2.[14] The latter was synthesized from enol triflate **6** by a CuI-mediated cross coupling with phenyl magnesium bromide.[15,16] Gratifyingly, this unprecedented Diels−Alder reaction produced **8** as a 1:1 mixture of endo/exo isomers in high regioselectivity with only <5−7% a/a of the undesired regioisomers. However, the diene **7** was not stable,[17] and the differential scanning calorimetry (DSC) of the reaction mixture suggested that exothermic decomposition started at the process temperature of 110 °C.[18] Considering these safety and stability caveats, this route was not further scaled up. Yet, it delivered valuable intermediate (331 g of **1**) for the early assessment of downstream steps. Attempts at performing the cycloaddition in the presence of Lewis acids such as $ZnCl_2$, $ZnBr_2$, ZnI_2, $TiCl_4$,

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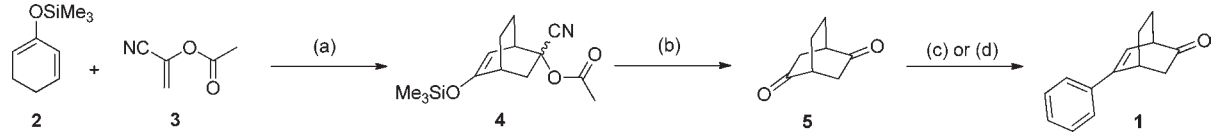
Scheme 1[a] Route used by Discovery Chemistry



[a] Reagents and conditions: (a) **2** (1.0 equiv), **3** (1.0 equiv), 150 °C (sealed); (b) NaOMe in MeOH (3 equiv), MeOH, 20 °C, 42% (two steps); (c) i) PhMgBr, 1 M in THF (1.05 equiv), Et_2O, 20 °C; ii) acetone, pTsOH·H_2O (1 equiv), 20 °C, 24 h, 18%. (d) i) Ethylene glycol (1.0 equiv), pTsOH·H_2O (0.05 equiv), reflux, **10** (Scheme 3 vide infra); ii) **10**, PhMgBr, 1 M in THF (1.4 equiv), THF, 0 °C; 15% aq HCl, THF, 20 °C, 35% two steps.

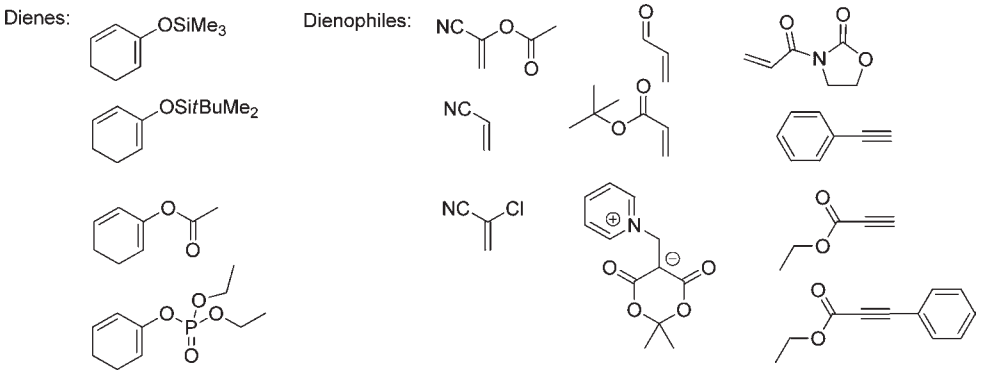
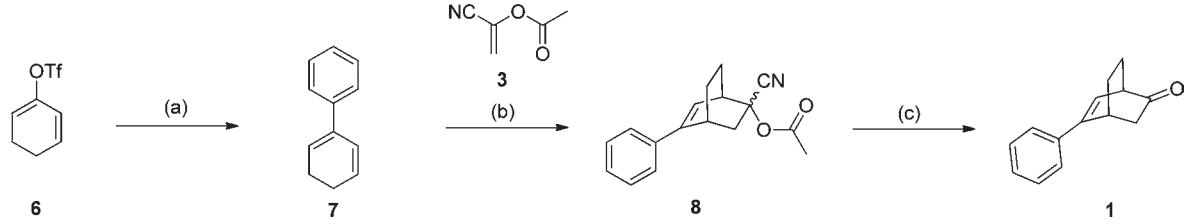


Figure 1. Dienes and dienophiles tested for the Diels–Alder reaction.

Scheme 2[a] Approach with diene **7** for the delivery of initial quantities of **1**



[a] Reagents and conditions: (a) PhMgBr, 1 M in THF (1.5 equiv), CuI, 2.5 mol %, THF 0 °C, 2 h, quant.; (b) **3** (1.1 equiv), 2,6-di-*tert*-butyl-4-methylphenol (BHT, 0.002 equiv), 110 °C (sealed), 15 h; (c) NaOMe in MeOH (1.3 equiv), formaldehyde[20] 36% in H_2O (4 equiv), 20 °C, SiO_2, 47% (two steps).

$EtAlCl_2$, $BF_3 \cdot OEt_2$, $LiClO_4 \cdot Et_2O$ showed either no reaction or decomposition.[19]

3. ROUTE DEVELOPMENT

α-Acetoxyacrylonitrile as Dienophile. To satisfy the immediate need for material, we then turned back to the initial route with the aim of profiting from the two differently protected carbonyl groups in **4**. Due to the lack of a rapid external supply,[7] both Diels–Alder reagents **2** and **3** were prepared in our laboratories on a kilogram scale to initiate work down the route to the active pharmaceutical ingredient (API).[21] This optimization work in combination with a risk assessment for the synthesis, distillation, stabilization, and storage of α-acetoxyacrylonitrile **3**,[22] enabled the expedient delivery of larger supplies by contractors. The first kilogram synthesis of ketone ketal **10** in our laboratories is described in Scheme 3.

The Diels–Alder reaction employing **2** and **3** at 140–150 °C delivered the bicyclic intermediate **4** in a yield of 66% after distillation.[23] Since the Diels–Alder reaction was exothermic, only one-third of the starting mixture was heated to 150 °C for 30 min followed by the dropwise addition of the remainder to the reaction mixture. We did not develop a semi-batch mode, i.e. dosing one Diels–Alder reagent to the other, due to the thermal instabilities of each single Diels–Alder reagent. Holding the mixture at 140 °C for 20 h resulted in a conversion of 95% (GC) to the products. The original report by Werstiuk et al.[5] on such Diels–Alder cycloadditions states that the desired product **4** was obtained as a 4:1 mixture of regioisomers.[24] Isolation of the major endo diastereoisomer **4a** after distillation and crystallization from heptane, followed by two-dimensional (2D) NMR and GC analyses allowed a better understanding of cycloadduct distribution (Scheme 4). Indeed, 15–20% of the undesired regioisomers (in a 1.5:1 ratio of endo/exo isomers) was obtained under these conditions, similar to the Diels–Alder reaction with diene **7**. Both endo and exo isomers **4a** and **4b** are productive precursors of the ketone function.

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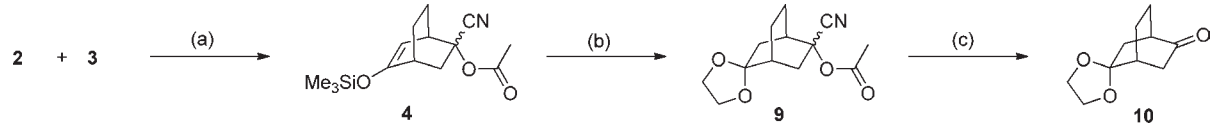
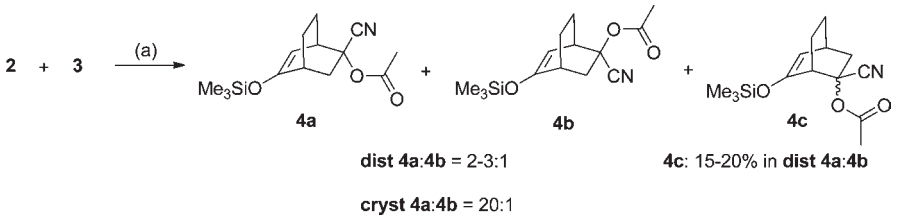
Scheme 3[a] First fit-for-purpose approach using α-acetoxyacrylonitrile **3** as dienophile



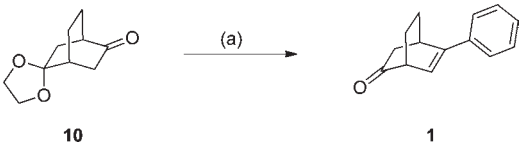
[a] Reagents and conditions: (a) 1-cyano vinyl acetate (1.0 equiv), 140 °C, distillation, 66%; (b) toluene, ethylene glycol (11 equiv), pTsOH·H_2O (0.05 equiv), 60 °C, 94%; (c) MeOH, NaOMe (2 equiv), 20 °C, 94%.

Scheme 4[a] Isomeric distribution of Diels–Alder reaction of **2** and **3**



[a] Reagents and conditions: **2** (1.0 equiv), **3** (1.0 equiv), BHT (0.002 equiv), 110 °C, sealed tube, 15 h, distillation, 70%. **dist 4a:4b** refers to the ratio of isomer **4a** vs isomer **4b** after distillation (0.1 bar, 115–120 °C). **cryst 4a:4b** refers to the ratio of isomer **4a** vs isomer **4b** after crystallization from heptane for analytical purposes.

Scheme 5[a] Grignard addition–elimination–ketal removal sequence to **1**



[a] Reagents and conditions: (a) i) 2.8 M PhMgBr in 2-methyl-THF (1.1 equiv), 2-methyl-THF, 5–20 °C; ii) toluene, 25% aq HCl, 30 °C, 98%.

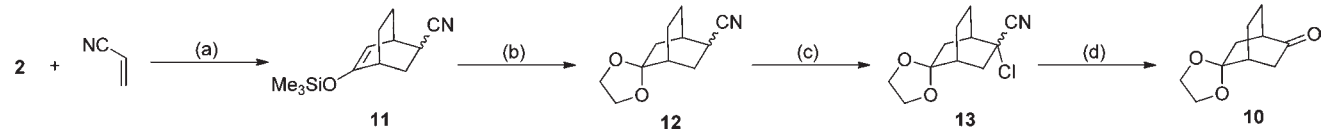
The ketalization (Scheme 3, vide supra) with excess ethylene glycol under catalytic acidic conditions was straightforward (94% yield). Double-protected diketone **9** was isolated after aqueous workup in a crude yield of 94% as an oil. One ketone function was liberated by treatment with sodium methoxide in methanol. The product **10** was isolated after aqueous workup in a yield of 94% and a purity of 92% a/a (GC) and was used without further purification in the ensuing Grignard reaction.

The crude mono-protected diketone **10** was treated with phenylmagnesium bromide in 2-methyl-THF[25] to produce a mixture of tertiary alcohols in a 3:2 ratio (Scheme 5). The reaction mixture was added to 25% aq HCl. Under these conditions, dehydration and deketalization took place concomitantly to generate the final product. The racemic phenyl ketone **1** was isolated as a crude oil in a yield of 98% and an assay of 88% w/w.[26] This quality was acceptable for downstream chemistry. Further purity enhancement could be achieved by short path distillation.[27] The overall yield starting from (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **2** was 57%. It took three months starting with route finding until the delivery of **1** (2 × 1 kg batch) following the synthesis as depicted in Schemes 3 and 5. This material ensured the rapid start and execution of the downstream chemistry towards the API.

To reduce the process temperature of the Diels–Alder reaction, several Lewis acids were tested for activation of the dienophile: TMSCl, SiO_2, $Eu(fod)_3$,[28] or $Ti(OiPr)_4$ produced no conversion; only $Yb(OTf)_3$[29] led to some conversion with decomposition. Ionic liquids (imidazolium salts) led to the decomposition of one or both Diels–Alder reagents. Safety studies of this Diels–Alder reaction resulted in a maximum temperature of the synthetic reaction (MTSR)[30] of 250 °C, at which temperature the decomposition would set in immediately, and the reaction mass would reach 429 °C.[31] Despite being straightforward, this neat Diels–Alder reaction was not judged feasible for more than a few kilograms.[32]

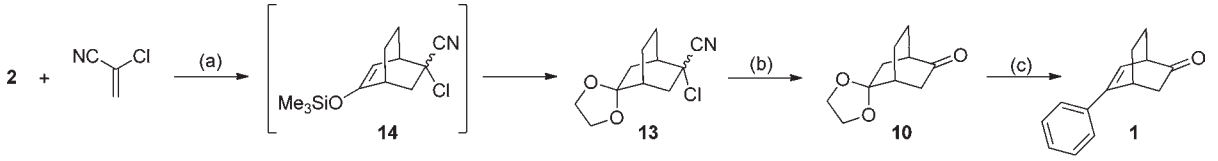
Acrylonitrile as Dienophile. The readily available acrylonitrile seemed to be an attractive alternative as a ketene equivalent[33] that does not require handling cyanide salts on scale. The Diels–Alder reaction with **2**[34] was plagued by the competitive polymerization of acrylonitrile. The bimolecular Diels–Alder reaction of acrylonitrile with **2** competes with the polymerization of the dienophile and the diene.[35] We checked the influence of stabilizers or antioxidants[36] on the stability of the reaction mixture: 2,6-di-*tert*-butyl-4-methylphenol (BHT),[9c] pyridine,[37] hydroquinone, and 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO).[38] Usually, hydroquinone or hydroquinone monomethyl ether are used as radical scavengers for acrylic monomers.[39] Except for the reactions stabilized by TEMPO, the reactions led to polymerization in the presence of these inhibitors. The reactions were carried out with excess acrylonitrile without solvent.[40] It seems that the diene influences inhibitor efficiency since the acrylonitrile monomer did not polymerize when heated with the scavengers alone. In practice (Scheme 6), the Diels–Alder reaction with 3 equiv of acrylonitrile[41] and catalytic amounts of TEMPO gave the desired product **11** after distillation in a yield of 84%.[42] The enol ether was transformed into ketal **12** in 79% yield. The chlorination of the nitrile to **13** succeeded with phosphorus pentachloride in chloroform and pyridine in 79% yield.[43] As ~50% deketalization took place, the ketal was reconstituted. Trials to replace the solvent by an environmentally more benign solvent such as methyl isobutylketone, α,α,α-trifluoromethylbenzene, chlorobenzene,

Scheme 6[a] Use of acrylonitrile in the Diels–Alder reaction



[a] Reagents and conditions: (a) **2** (1 equiv), TEMPO (0.011 equiv), acrylonitrile (3 equiv), 83 °C, 24 h, distillation, 84%; (b) ethylene glycol (11 equiv), pTsOH·H_2O (0.1 equiv), toluene, 65 °C, 79%; (c) i) PCl_5 (1.5 equiv), chloroform, pyridine (2 equiv), 75 °C, 18 h, toluene, ii) ethylene glycol, pTsOH·H_2O (0.1 equiv), 79%; (d) ethylene glycol, KOH (2.42 equiv), H_2O, 100 °C, 5 h, 51%.

Scheme 7[a] Route for scale-up using α-chloroacrylonitrile in the Diels–Alder reaction



[a] Reagents and conditions: (a) i) **2** (1 equiv), TEMPO (0.013 equiv), α-chloroacrylonitrile (1.24 equiv), $NaHCO_3$ (0.31 equiv), toluene, 100 °C, 24 h, water extraction, ii) ethylene glycol, pTsOH·H_2O (0.1 equiv), 67 °C, 2.5 h, 88%; (b) ethylene glycol, KOH (2.42 equiv), H_2O, 100 °C, 5 h, 51%. (c) see Scheme 5.

or pyridine failed. Only dichloromethane (DCM) proved a good alternative when the reaction was carried out at 75 °C in an autoclave. Under these conditions, the crude yield of double protected diketone **13** was 98% after an optimized workup that had the additional benefit of keeping the ketal intact. The liberation of the ketone in ethylene glycol with potassium hydroxide delivered the substrate for the Grignard addition **10** in a yield of 51%.[44] The difficulties of adding the α-chloronitrile prompted us to look for another Diels–Alder dienophile for larger-scale quantities. To cope with the restrictions imposed by the exothermic neat full-batch mode, flow reactor technology was developed to run the Diels–Alder reactions with **3** and acrylonitrile as a contingency.[45]

α-Chloroacrylonitrile as Dienophile. With this positive result in hand, the fully functionalized and readily available ketene equivalent, α-chloroacrylonitrile, was tested for the Diels–Alder reaction with **2**.[46] At the outset of the campaign the use of α-chloroacrylonitrile led to extensive polymerization, even when we added the reported stabilizers like BHT or hydroquinone. Only later in the campaign did we discover that TEMPO effectively prevented polymerization of the reaction mixture containing **2** and α-chloroacrylonitrile. Hence, both starting materials were mixed in a 1.5:1 ratio in favor of the dienophile and heated in the presence of catalytic amounts of TEMPO. A 90% conversion was achieved at 50 °C within 24 h, and after 2 h at 90 °C. Since the α-chloroacrylonitrile was contaminated with traces of HCl, solid $NaHCO_3$ was added to the reaction mixture. Using only 1.1 equiv of dienophile, the conversion was 87% after 20 h at a reaction temperature of 65 °C. After distillation, the product **14** was isolated in a yield of 55% and a purity of 93% a/a (GC–MS). Like acrylonitrile, this dienophile allows for the use of solvents,[47] which is essential to mitigate risks associated with exothermic full-batch mode. In practice (Scheme 7), the reaction was carried out in toluene at 100 °C, using 1.2 equiv of α-chloroacrylonitrile[48] and 4 vol. of toluene, and the conversion was 94% after 24 h. The product **14** was isolated in a yield of 74% after distillation. In order to facilitate scale-up the reaction mixture was telescoped to the next step without purification. The transformation of the TMS-protected enol ether **14** to the ketal **13** was performed in ethylene glycol using catalytic amounts of pTsOH·H_2O. The reaction was scaled up to 700 g of diene **2**. The ketal **13** was isolated in a yield of 88% and was further processed to ketone **10** under basic conditions in a yield of 51%.[49] Ketal **13** was not purified and thus contained byproduct (mainly regioisomers of the Diels–Alder reaction) that were the main reason for the moderate yield. The regioselectivity was not optimized in view of the tight schedule for material delivery. Furthermore, the nitrile was to some extent hydrolyzed to the unproductive acid.[50,51] Transformation to the target intermediate **1** was performed as depicted in Scheme 5.

A MTSR of 132 °C was derived from safety studies of this Diels–Alder reaction. At this temperature the reaction mixture is thermally uncritical: toluene starts to boil at 112 °C and acts as a thermal barrier.[52] The process was scaled to two 90-kg batches with an external partner, volumes, yields, and purities were consistent with the ones described in the Experimental Section.

■ CONCLUSION

A new practical synthesis of 5-phenylbicyclo[2.2.2]oct-5-en-2-one **1** was found and developed starting with a Diels–Alder reaction of readily available α-chloroacrylonitrile with (cyclohexa-1,5-dien-1-yloxy)trimethylsilane. Keys to this success were the choice of stabilizing TEMPO for the Diels–Alder reaction and the differentiation of the two masked ketone functions in the adduct **14**. The process comprises six chemical transformations with two isolated intermediates and delivered **1** in 44% overall yield. All products were obtained as oils in acceptable quality for downstream chemistry without any purification by chromatography or distillation.

■ EXPERIMENTAL SECTION

General. One vol or 1 wt means 1 L of solvent or 1 kg of reagent with respect to 1 kg of the reference starting material.

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Compounds are characterized by ^{1}H NMR (400 MHz, Bruker) or ^{13}C NMR (100 MHz, Bruker), internal standard for quantitative NMR was 1,4-dimethoxybenzene. Details for the GC- and LC methods are listed in the Supporting Information. Unless stated otherwise, yields are given as is. All compounds are oils that have been isolated by removal of the solvent under reduced pressure. Even though this was reproduced to deliver 180 kg of **1**, it is anticipated that this operation will be replaced by a solvent exchange or related operation on larger scales.

3,4-Dihydro-1,1′-biphenyl (7). This material was prepared in an analogous fashion to ref 15. Copper iodide (8.5 g, 0.025 equiv) was added to a solution of cyclohexa-1,5-dien-1-yl trifluoromethanesulfonate **6** (683 g, ∼60% w/w by ^{1}H NMR assay, contaminated with phenyltriflimide and silicon-containing impurities) in THF (2 L) at −5 °C. Vacuum was applied followed by nitrogen purge (3×). A 1 M solution of PhMgBr in THF (2.7 L, 1.5 equiv) was added over 2 h at <5 °C. The resulting turbid solution was stirred at 0 °C for 1 h. It was quenched by the addition of sat. aq NH_4Cl solution (0.75 L). Water (1 L) was added. Hexane was added (2.5 L) and the layers were separated. The aqueous layer was back-extracted with hexane (0.6 L). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated at 40 °C and 200 mbar to yield 474 g of crude **7**. This material was purified by quick filtration through a plug of silica gel eluting with hexane to yield **7** as a colourless oil. Yield of **7**: 301 g (108%, wrong estimation of assay content of **6**). This material tends to aromatize to biphenyl. Purity (LC−MS method 1): 90% a/a (10% a/a biphenyl), R_t 1.95 min, no mass detected; ^{1}H NMR ($CDCl_3$): δ 2.16−2.25 (m, 2H), 2.29−2.38 (m, 2H), 5.99−6.10 (m, 2H), 6.34 (dq, J = 9.9, 1.8 Hz, 1H), 7.22−7.42 (m, 5H).

2-Cyano-5-phenylbicyclo[2.2.2]oct-5-en-2-yl Acetate (8, endo/exo mixture). A mixture of **7** (301 g), **3** (235 g, 1.1 equiv) and BHT (1.0 g, 0.002 equiv) was heated to 110 °C in a sealed vessel for 15 h. It was cooled down to rt, and **8** was used as such in the next step. Purity (LC−MS, method 1): 60% a/a (1:1 mixture of endo/exo isomers of the major regioisomer, 5−7% a/a of undesired regioisomers), R_t 1.86 min, no mass detected; TLC: R_f = 0.35 (heptane/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$): δ 1.47−1.54 (m, 2H), 1.73−1.80 (m, 1H), 1.85−1.88 (m, 1H), 1.90−1.93 (m, 1H), 2.04 (s, 1.5H), 2.25 (s, 1.5H), 2.56−2.57 (m, 0.5H), 2.60−2.61 (m, 0.5H), 3.27−3.30 (m, 1H), 3.41−3.44 (m, 1H), 6.38 (d, J = 1.8 Hz, 0.5H), 6.40 (d, J = 1.8 Hz, 0.5H), 7.29−7.40 (m, 5H).

2-Cyano-5-((trimethylsilyl)oxy)bicyclo[2.2.2]oct-5-en-2-yl Acetate (4, endo/exo mixture). A mixture of **2**[3] (1.0 kg, 1.0 equiv) and **3**[21b] (0.66 kg, 1.0 equiv) was prepared. A third of this mixture was heated to 150 °C for 30 min. The rest of the starting materials were added to the reaction mixture over 2 h at 150 °C. The mixture was heated at 140 °C for 20 h. The reaction mixture was distilled under vacuum: The bath temperature was set to 85 °C and the pressure at 6 mbar to remove undesired fractions at a head temperature of 45 °C. The bath temperature was raised to 165 °C, and the product was distilled under oil pump vacuum (∼0.1 mbar) at head temperature 135 °C to yield **4** as a colourless oil. Yield: 1.105 kg (66%). Purity (GC): 88.9% a/a (73:27 endo/exo mixture), R_t 3.60, 3.64 min; ^{1}H NMR ($CDCl_3$): δ 0.23 (s, 9 H), 1.52 (m, 3 H), 1.94 (m, 1H), 2.01 (m, 1 H), 2.06 (s, 3H), 2.42 (m, 2 H), 3.26 (m, 1 H), 4.92 (dd, J = 7.1 Hz, 1H).

5-Cyanospiro[bicyclo[2.2.2]octane-2,2′-[1,3]dioxolan]-5-yl Acetate (9, endo/exo mixture). A solution of **4** (2.0 kg, 1 equiv), toluene (15 L), ethylene glycol (4.4 L, 11 equiv) and pTsOH·H_2O (62.7 g, 0.047 equiv) was heated to 60 °C for 30 min. The mixture was cooled to 40 °C. The bottom layer was separated and discarded. Triethylamine (45 mL, 0.047 equiv) was added to the mixture. The organic layer was washed with water (2 × 8 L) at 30 °C and then concentrated at 60 °C external temperature and 100−25 mbar to obtain **9** as a yellow liquid. Yield: 1.693 kg (94%). Purity (GC): 94.4% a/a (70:30 endo/exo mixture), R_t 3.87 min, 3.94; ^{1}H NMR ($CDCl_3$): δ 1.4−2.7 (m, 10H), 2.13 (s, 3H), 3.92 (m, 4H).

5-((Trimethylsilyl)oxy)bicyclo[2.2.2]oct-5-ene-2-carbonitrile (11, endo/exo mixture).[34]. A 500 mL flask was charged with **2** (50 g, 1 equiv), 2,2,6,6-tetramethyl piperidine-1-oxyl (0.5 g, 0.011 equiv) and acrylonitrile (47.3 g, 3 equiv). The mixture was heated to 83 °C for 24 h. The mixture was cooled to 20 °C. The reaction mixture was purified by distillation (bath temperature 130 °C, head temperature 87−89 °C, pressure ∼0.1 mbar) to yield **11** as a colourless liquid. Yield: 55 g (84%). Purity (GC): 88.5% a/a (68:32 endo/exo mixture), R_t 3.10, 3.12 min; ^{1}H NMR ($CDCl_3$): δ 0.21 (s, 9H (65%), 0.26 (s, 9H, (35%)), 1.3−2.95 (m, 9H), 5.07 (dd, J = 7.3, 2.3 Hz, 1H (65%)), 5.15 (dd, J = 7.0, 2.0 Hz, 1H (35%)).

Spiro[bicyclo[2.2.2]octane-2,2′-[1,3]dioxolane]-5-carbonitrile (12, endo/exo mixture). Nitrile **11** (100 g, 1 equiv), ethylene glycol (308 g, 11 equiv), pTsOH·H_2O (8.7 g, 0.1 equiv) and toluene (800 mL) were heated to 65 °C for 4 h. The mixture was cooled to 20 °C. The bottom layer was separated and discarded. Triethylamine (4.57 g, 0.1 equiv) and water (500 mL) were added to the upper layer. After separation of the aqueous layer, the organic layer was washed with water (250 mL) and concentrated at 50 °C and 700−25 mbar to obtain **12** as a yellow liquid. Yield: 80.9 g (79%). Purity (GC−MS): 96.7% a/a (70:30 endo/exo mixture), R_t 2.67 min, $[M + 1]^+$ = 194; 2.72, $[M + 1]^+$ = 194; ^{1}H NMR ($CDCl_3$): δ 1.35−2.78 (m, 11H), 3.84−4.05 (m, 4H).

5-Chlorospiro[bicyclo[2.2.2]octane-2,2′-[1,3]dioxolane]-5-carbonitrile (13, endo/exo mixture); from 12, in Chloroform (Scheme 6). PCl_5 (80.8 g, 1.5 equiv) was suspended in $CHCl_3$ (250 mL, *limited evidence of a carcinogenic effect*). Pyridine (41.6 mL, 2 equiv) was added to the suspension over 10 min, keeping the temperature < 25 °C. A solution of **12** (50 g, 1.0 equiv) in $CHCl_3$ (250 mL) was added. The suspension was heated to 75 °C and stirred for 18 h. The reaction mixture was cooled to 20 °C. Water (250 mL) was added. After phase separation, the organic layer was washed with sat. aq $NaHCO_3$ solution (250 mL) and with water (250 mL). The organic layer was dried with MgSO4 and evaporated to dryness to yield crude product (46.4 g). This crude material was dissolved in toluene (400 mL). Ethylene glycol (155 mL) and pTsOH·H_2O (4.85 g) were added. The solution was heated to 65 °C for 5 h and then cooled to 20 °C. The lower layer was separated. Triethylamine (3.5 mL) and water (250 mL) were added to the upper layer. After phase separation, the (upper) organic layer was washed with water (250 mL) and evaporated to dryness at 50 °C and 700−25 mbar to yield **13** as a yellow oil. Yield: 46.1 g (79%). Purity (GC): 100% a/a (38:62 endo/exo mixture), R_t 3.49, 3.54 min.

From 12, in DCM. A plastic-coated Pyrex flask was charged with PCl_5 (3.23 g, 1.5 equiv), DCM (15 mL), and pyridine (1.67 mL, 2 equiv). A solution of **12** (2 g, 1.0 equiv) in DCM (5 mL) was added. The Pyrex flask was closed and placed in an oil bath. The solution was stirred at 75 °C for 15 h. The reaction

mixture was cooled to 20 °C and then added to 32% aq NaOH solution (2 g, 5 equiv) and water (10 mL). After phase separation, the organic layer was washed with water (10 mL), dried with MgSO4, and concentrated at 50 °C and 700−25 mbar to yield **13** as a yellow liquid. Yield: 2.3 g (98%). Purity (GC−MS): 80.8% a/a (42:58 endo/exo mixture), R_t 2.79, 2.83 min, $[M + 1]^+ = 228$.

From Diels−Alder Reaction of 2 and α-Chloroacrylonitrile (Scheme 7). A 4-L double-jacketed reactor, equipped with a reflux condenser and mechanical stirrer, was charged with $NaHCO_3$ (137 g, 0.31 equiv), 2,2,6,6-tetramethyl-piperidine-1-oxyl (2.13 g, 0.013 equiv), diene **2**[3] (0.7 kg, 1 equiv), α-chloroacrylonitrile (0.453 kg, 1.24 equiv, TCI, > 99% a/a GC, stab. with hydroquinone), and toluene (2.8 L). The reaction mixture was stirred at 100 °C for 19 h. The mixture was cooled to 20 °C and washed with water (1.5 L). Ethylene glycol (2 L, 11 equiv) and $pTsOH \cdot H_2O$ (80 g, 0.1 equiv) were added to the organic layer. The mixture was stirred at 67 °C for 2.5 h. After the mixture was cooled to 20 °C, the lower ethylene glycol layer was separated. The ethylene glycol layer was back-extracted with toluene (2.8 L). The combined toluene extracts were washed with water (1.4 L) and concentrated at 60 °C and 100−40 mbar to obtain **13** as yellowish oil. Yield: 0.836 kg (88%). Purity (GC−MS): 84.0% a/a (8.5% a/a toluene), R_t 2.63 min, $[M + 1 - HCl]^+ = 192$, 2.75, $[M + 1]^+ = 228$; ^1H NMR ($CDCl_3$): δ 1.4−1.6 (m, 1H), 1.75−2.15 (m, 6H), 2.25−2.65 (m, 3H), 3.82−4.10 (m, 4H).

Spiro[bicyclo[2.2.2]octane-2,2′-[1,3]dioxolan]-5-one (10); From 9 (Scheme 3). To a mixture of **9** (1.7 kg, 1 equiv) in MeOH (8.5 L) was added 5.4 M NaOMe in MeOH (2.5 L, 2 equiv) at 5 °C. The mixture was stirred for 1 h at 20 °C. Water (13.5 L) was cooled to 1 °C in a Büchi reactor CR15-K. The reaction mixture was added to the water over 15 min. The mixture was transferred to a 50-L stirring tank and extracted with DCM (13.5 L). The organic layer was separated, washed with water (6.8 L), and concentrated at 50 °C with a pressure of 10 mbar at the end to yield **10** as a yellow oil. Yield: 1.158 kg (94%). Purity (GC): 92.5% a/a, R_t 3.11 min.

From 13 (Scheme 7). A 4-L double-jacketed flask, equipped with a reflux condenser, scrubber, and mechanical stirrer, was charged with **13**, (0.5 kg, 1 equiv). Ethylene glycol (2 L) and a solution of KOH (300 g, 2.42 equiv) in water (1 L) were added. The reaction mixture was heated at 100 °C for 4.5 h. In a parallel experiment, a 2.5-L flask, equipped with a reflux condenser, scrubber, and mechanical stirrer was charged with **13**, (270 g, 1 equiv). Ethylene glycol (1.1 L, 4 vol.) and aq KOH solution (162 g, 2.42 equiv) in water (650 mL) were added. The mixture was stirred at 100 °C for 5 h. The mixtures in the 4- and 2.5-L flasks were cooled to 20 °C, combined, and transferred to Büchi reactor CR15-K. MIBK (8 L) was added, and the solution was extracted with water (4 L). The aqueous layer was back-extracted with MIBK (4 L) at 45 °C. The combined organic layers were washed with water (2 × 4 L) at 40 °C. The organic layer was filtered via a Polycap HD 25, 10 μm (Whatman) into a 20-L Rotavap and concentrated at 55 °C and a final pressure of 40 mbar to yield **10** as a brown oil. Yield: 0.314 kg (51%). Purity (GC−MS): 95.3% a/a, R_t 2.38 min, $[M + 1]^+ = 183$; ^1H NMR ($CDCl_3$): δ 1.2−2.65 (m, 10H), 3.85−4.05 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 20.4, 22.0, 36.4, 38.7, 40.3, 44.3, 64.1, 64.4, 109.2, 215.4. Corresponds to literature.[53]

5-Phenylbicyclo[2.2.2]oct-5-en-2-one (1); From 8 (Scheme 2). Formalin (36% solution in water, 120 mL, 4 equiv) was added at rt to a solution of crude **8** (100 g) in THF (0.5 L). A 5.4 M solution of NaOMe in MeOH (90 mL, 1.3 equiv) was added dropwise so that the temperature did not exceed 20 °C. The resulting dark-brown mixture was stirred at rt for 1.5 h. Water (500 mL) was added followed by EtOAc (500 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 500 mL). The combined organic extracts were dried over Na_2SO_4, filtered off, and concentrated at 45 °C and a pressure of 100 mbar. The residue was purified by flash chromatography over silica gel (800 g SiO_2) eluting with heptane/EtOAc, 6:1, to yield **1** as a yellow oil. Yield: 34.6 g (47%). Purity (LC−MS method 1): 97.1% a/a, R_t 1.60 min, no mass detected. Further analytical data corresponding to batches of **1** synthesized from **10**.

From 10 (Scheme 5). PhMgBr (2.8 M) in 2-methyl-THF (2.136 L, 1.1 equiv) was diluted with 2-methyl-THF (1 L) and cooled to 5 °C. A solution of **10** (0.99 kg, 1 equiv) in 2-methyl-THF (1 L) was added to the Grignard reagent at 5 °C over a period of 20 min, keeping the temperature below 20 °C (*Caution: exothermic!*). Toluene (6 L) was added to the reaction mixture at 20 °C. The mixture was cooled to 10 °C, and aq 25% HCl (4 L) was added over a period of 10 min. The reaction mixture was stirred at 30 °C for 30 min. After phase separation, the organic layer was washed with water (2 × 4 L) and concentrated at 60 °C and 70−25 mbar to yield **1** as a brown oil. Yield: 1.058 kg (98%). Purity (GC−MS): 95.9% a/a, R_t 3.14 min, $[M + 1]^+ = 199$; assay by ^1H NMR ($CDCl_3$) with 1,4-dimethoxybenzene as internal standard: 88% w/w. Crude **1** (2 g) was purified by flash chromatography on silica gel (40 g) eluting with EtOAc/heptane, 1:3, to obtain 1.3 g (67%) of a yellow oil. Purity (GC−MS): 98.0% a/a, GC−MS: R_t 3.14 min, $[M + 1]^+ = 199$; purity (LC−MS method 2): 100% a/a, R_t 1.52 min, $[M + 1]^+ = 199$; single spot on TLC: $R_f = 0.4$ (EtOAc/heptane, 1:3); ^1H NMR ($CDCl_3$): δ 7.38 (m, 5H), 6.46 (m, 1H), 3.56 (d, $J = 2.4$ Hz, 1H), 3.33 (m, 1H), 2.21 (m, 2H), 2.01 (m, 1H), 1.90 (m, 1H), 1.72 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 212.4, 148.0, 137.6, 128.7, 127.8, 124.9, 122.1, 49.3, 40.4, 35.5, 24.5, 23.2. Corresponds to literature.[53]

■ ASSOCIATED CONTENT

Supporting Information. Synthesis and characterization data of **4** and **15**, and HPLC, GC, and ^1H and ^{13}C NMR data of **1**, **7**, **9**, **10**, **11**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-Mail: stefan.abele@actelion.com. Telephone: +41 61 565 67 59.

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(41) Acrylonitrile (bp 77 °C) as purchased from Aldrich, stabilized with 35–45 ppm of hydroquinone monomethyl ether.

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