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Scalable Synthesis of 6,6-Dimethylbicyclo[3.1.0]hexan-3-one

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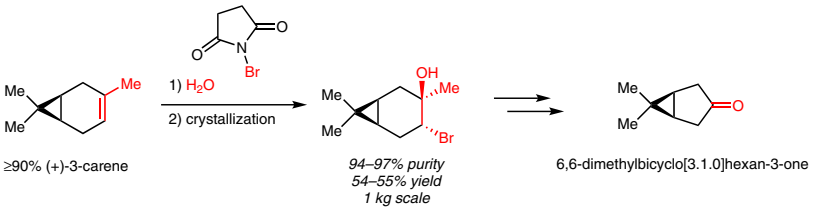

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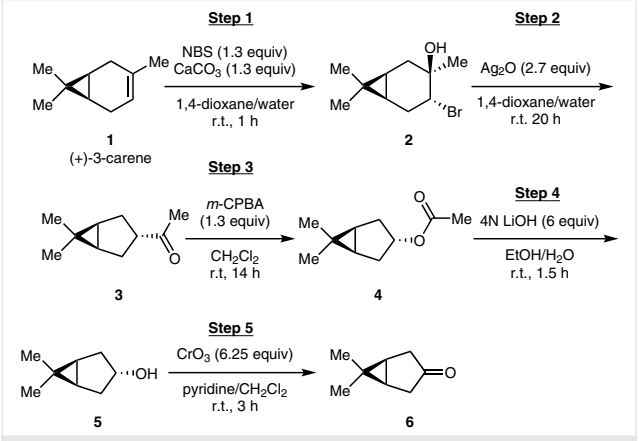
Abstract A simple five-step process for the conversion of technical grade (+)-3-carene into 6,6-dimethylbicyclo[3.1.0]hexan-3-one was developed. A robust process was required that delivered the 6,6-dimethylbicyclo[3.1.0]hexan-3-one, minimized chromatography, reduced the excess of silver salts, and avoided toxic chromium oxidants. A simple and scalable process that relies on crystallization and distillation was developed and demonstrated to produce hundreds of grams of 6,6-dimethylbicyclo[3.1.0]hexan-3-one.

Key words semipinacol, Dess–Martin, carene, bromohydrin, silver nitrate, Baeyer–Villiger

6,6-Dimethylbicyclo[3.1.0]hexan-3-one (**6**) is a compact bicyclic ketone whose ridged structure and *meso* stereochemistry make **6** an excellent component for the introduction of a nonflexible lipophilic *tert*-butyl isostere.[1] Several literature preparations of **6** have been published, however, **6** is not readily available beyond the gram quantities needed in medicinal chemistry. Installing the *gem*-dimethylcyclopropane is limited to only a handful of synthetic strategies which include conjugate addition of a sulfonium ylide,[2] cyclopropanation of allylic alcohols,[3] palladium-catalyzed cycloisomerization,[4] and conversion of a *gem*-dibromocyclopropane into the *gem*-dimethycyclopropane.[5] All of these synthetic strategies either do not allow access to the desired 6,6-dimethylbicyclo[3.1.0]hexan-3-one and/or could not be readily applied to multikilogram scale. Alternatively, (+)-3-carene and chrysanthemic acid are readily available natural products which contain *gem*-dimethylcyclopropane and could be converted into the desired 6,6-dimethylbicyclo[3.1.0]hexan-3-one.[6,7]

The synthesis of **6** has been previously published employing a synthetic sequence that was particularly attractive because it started from readily available (+)-3-carene (**1**, Scheme 1).[6] The synthetic sequence begins with the conversion of **1** into bromohydrin **2** which is isolated as a solid after silica gel chromatography. The bromohydrin **2** is then treated with excess Ag_2O and undergoes a semi-Pinacol rearrangement to give the ring-contracted product **3**. Baeyer–Villiger oxidation transforms ketone **3** to acetate **4**, and hydrolysis of acetate **4** with aqueous LiOH affords alcohol **5** which is subsequently oxidized with pyridine/CrO_3 to give the target compound **6**.



Scheme 1 Synthesis of **6** from (+)-3-carene

During route evaluation, several areas were identified that required development in order to allow for a practical route capable of a multikilogram delivery. Silica gel chromatography was required after step 1 to ensure that bromohydrin **2** was sufficiently pure for downstream processing and step 2 required a large excess of Ag_2O to perform the semi-Pinacol rearrangement. Chromatography significantly limited the throughput of the process, and Ag_2O resulted in partial plating the reaction vessel with silver. Besides the

challenges from a processing standpoint, Ag_2O was the largest cost driver of the synthesis. The final oxidation with chromium was not desired due to the toxicity of chromium and risk of contamination of **6** and multiproduct reactors with chromium. Lastly, all of the intermediates of the process are low-molecular-weight compounds which were prone to being removed during concentration or azeotropic distillation processes.

The challenges to prepare large quantities of **6** became apparent once our discovery team had identified a candidate compound which contained this specific pharmacophore and was a key bottleneck to further advancement. We identified several development requirements to ensure **6** could be readily available on multikilogram scale when necessary: use ≥90% (+)-3-carene due to cost and availability compared to 99% (+)-3-carene ($97/kg vs. $5,400/kg),[8] identify alternatives to Ag_2O and CrO_3 due to issues with cleaning silver and chromium toxicity, and develop processes capable of purification by crystallization or distillation. Additionally, our aim was to develop analytical methods to monitor the reaction and assess purity of intermediates and the final product as adequate methods were not available in the literature.[9]

Step 1: Conversion of (+)-3-carene into bromohydrin **2** is produced in quantitative yield by the reaction of (+)-3-carene with *N*-bromosuccinimide (NBS), $CaCO_3$ in dioxane/water. Isolation of **2** by extraction with diethyl ether followed by silica gel chromatography affords **2** in 47% yield with 78% GC purity (Table 1, entry 1). The low purity of **2** following silica gel chromatography is attributed to decomposition during concentration of the chromatography fractions and highlights the reactivity of the bromohydrin. The extent of decomposition would likely become even greater with the extended times required to concentrate material on large scale. To ensure a consistent product purity profile, our primary focus for improving the process was to develop the process to allow for isolation by crystallization.

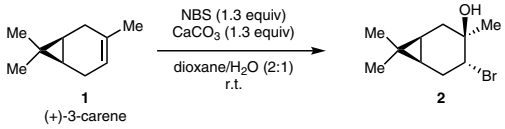
The extraction solvent was changed to petroleum ether (PE), which on concentration of the petroleum ether extract afforded crude **2** that was 89% pure (Table 1, entry 2). Although the crude material was significantly improved, the purity was not sufficient for the downstream process and required purification.[10] Recrystallization studies with pure isolated **2** indicated that polar solvent mixtures provided an amorphous solid that was viscid and not amendable to scale up (Table 1, entry 3); whereas cold *n*-hexane provided >98% purity of an off white crystalline solid (Table 1, entry 4), The low recovery at –20 °C could be improved by conducting the recrystallization at –40 °C (Table 1, entry 4). Execution of the full process using crude petroleum ether extract followed by *n*-hexane isolation was successfully executed three times on 1 kg scale to provide highly reproducible yield and purity (Table 1, entries 6–8).[11] The isolated yield of the process on kilogram scale was lower than the recrystallization of pure **2** (Table 1, entry 5) which is hypothesized to be the result of residual dioxane and/or succinimide in the crude reaction stream. Nevertheless, changing the process from chromatography to crystallization not only improve the cycle time, yield, and purity; the performance of isolated **2** in the downstream process was significantly improved.

Step 2: With a scalable process to synthesize and isolate bromohydrin **2** in hand, efforts were focused on improving the silver oxide mediated semi-Pinacol rearrangement. We found that less than 2.0 equivalents of Ag_2O led to incomplete conversion (Table 2). Such excess of Ag_2O was not unacceptable as a superstoichiometric reagent for scale-up because of the high cost of a silver salt that contains two atoms of silver. In addition to the high cost of excess Ag_2O, the insoluble salts in the reaction were both difficult to stir and resulted in partial plating of the reactor with silver. We sought to identify an alternative silver source that reduce the cost by using less silver and allowed for a simple process to execute.

Silver(I) nitrate is both readily available and contains only one molar equivalent of silver compared to the two equivalents in Ag_2O. Since silver is used as a stoichiometric reagent, reducing the total equivalents of silver has a positive impact on the viability of the process.[12] After an initial feasibility study we observed that $AgNO_3$could provide a process advantage of a mobile slurry amendable to scale-up, no observed silver platting of the reactor, and clean-up could be executed with HCl.

Harding and coworkers previously demonstrated the mechanistically related semi-Pinacol rearrangement of an

Table 1 Experimental Conditions for Step 1[a]



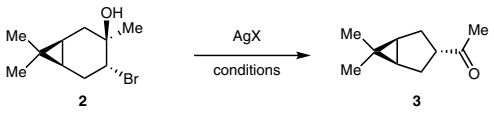
1
(+)-3-carene

2

Entry	Scale	Isolation solvent	Yield (%)	GCAP (%)[b]
1	10 g	chromatography	47	78
2	50 g	PE	76	89
3[c]	5 g	recryst. MeOH/H_2O	n/d	n/d
4[d]	5 g	recryst. *n*-hexane/–20 °C	30	98
5[d]	50 g	recryst. *n*-hexane/–40 °C	70	96
6	1.0 kg	*n*-hexane/–40 °C	55	97
7	1.0 kg	*n*-hexane/–40 °C	56	94
8	1.0 kg	*n*-hexane/–40 °C	54	94

[a] Unless otherwise noted: 1 equiv (+)-3-carene, 1,4-dioxane/water (2:1 v/v, 10 V), $CaCO_3$ (1.3 equiv), NBS (1.3 equiv); V = mL solvent/g solute.
[b] Area percent purity of isolated product measured by GC; GCAP = gas chromatography area percent.
[c] Run at 25 °C, material isolated as a viscid solid.
[d] The yield given is the recovery after recrystallization of pure isolated **2**.

Table 2 Step 2: Experimental Results[a]



2 3

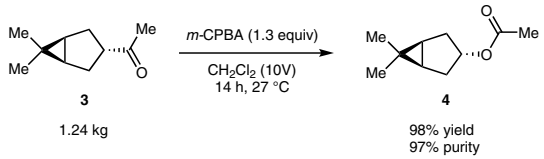
Entry	Scale	Base	AgX (equiv)	Conv. (%)[b]	GCAP (%)[c]
1	10 g	n/a	Ag_2O (2.0)	quant.	91
2	10 g	n/a	Ag_2O (1.5)	70%	n/a
3	5 g	Na_2CO_3	$AgNO_3$(2.0)	quant.	61
4	5 g	$NaHCO_3$	$AgNO_3$(2.0)	quant.	80
5	5 g	$NaHCO_3$	$AgNO_3$(1.5)	quant.	86
6	25 g	Et_3N	$AgNO_3$(1.5)	quant.	83
7[d]	250 g	Et_3N	$AgNO_3$(1.5)	>99	96
8[d]	2.2 kg	Et_3N	$AgNO_3$(1.5)	>99	91

[a] Unless otherwise noted, reactions were run at 25 °C.
[b] In-process conversion test for remaining **2** as measured by GC.
[c] Area percent purity of isolated product measured by GC; GCAP = gas chromatography area percent.
[d] Reaction temperature –5 °C to 0 °C.

α-chloroketone in alcoholic solution mediated by $AgNO_3$.[13,14] We hypothesized that we could extend this investigation and replace Ag_2O with $AgNO_3$ if an appropriate base was added to the reaction which avoided base-mediated epoxidation of the bromohydrin.[7c] Throughout the investigation a general observation that stronger bases lead to increased levels of impurities (Table 2).[15] Triethylamine was found to be best in terms of yield and purity of the product, with an optimal reaction temperature between –5 °C and 0 °C (Table 2, entry 6 vs. entry 7). Triethylamine was preferred over the insoluble base $NaHCO_3$ since AgBr precipitates throughout the reaction and could negatively impact mass transfer with an insoluble base. This new process was executed on 2.2 kg scale with only 1.5 equivalents of $AgNO_3$ and afforded results that were consistent with the smaller scale process (Table 2, entry 8).

Steps 3 and 4: Conversion of **3** into **5** was conducted in a two-step two-isolation sequence of a Baeyer–Villiger rearrangement followed by saponification of the resulting acetate. Baeyer–Villiger rearrangement performed as expected to afford **4** in 96–98% yield with 88–98% purity by GC. Extraction of the 3-chlorobenzoic acid byproduct and excess reagent after the reaction was changed from NaOH to $NaHCO_3$ to avoid unplanned saponification of the acetate.

Purification of crude **4** was investigated by distillation and was capable of improving the purity of **4** from 97% to 99%.[16] When both crude and distilled **4** were investigated in the downstream process, we found that both produced the same quality final product and therefore purification after step 3 was not justified. The Baeyer–Villiger process was executed on 1.24 kg scale affording 98% yield and 97% purity (Scheme 2).

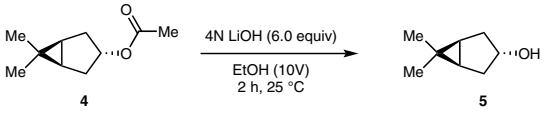


3 4
1.24 kg
98% yield
97% purity

Scheme 2 Baeyer–Villiger rearrangement of **3**

Acetate **4** is further processed to the alcohol by saponification using LiOH. To improve the volumetric efficiency we executed the process in 10 V of EtOH and six equivalents of 4 N LiOH to afford quantitative conversion into **5** (Table 3, entry 1). Lowering the amount of base to four equivalents of LiOH resulted in only 88% conversion to **5**, which could be driven to 99% conversion with the charge of an additional two equivalents of LiOH (Table 3, entry 2). The low conversion with four equivalents of LiOH is hypothesized to be a result of residual 3-chlorobenzoic acid carried through from step 3 which is observed in the crude ^{1}H NMR spectrum.

Table 3 Step 4: Experimental Results[a]



4 5

Entry	Scale	Conv. (%)[b]	Yield (%)[c]	GCAP (%)[d]
1	16 g	quant.	86	88
2	10 g	95 (quant.)[e]	84	99
3	34 g	quant.	86	98
4[f]	1.31 kg	quant.	52	99

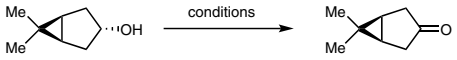
[a] Unless otherwise noted, reactions conditions were: 10 V of EtOH, 6.0 equiv 4 N LiOH, 25 °C for 2 h; V = mL solvent/g solute.
[b] In-process conversion test measured by GC.
[c] Unless purification conditions are noted, isolated yield based on crude weight.
[d] Area percent purity of isolated product measured by GC; GCAP = gas chromatography area percent.
[e] Reaction initially performed with 4.0 equiv LiOH, number in parenthesis are after additional LiOH (2.0 equiv) was added.
[f] Crude (850 g) was purified by silica gel chromatography.

The scale-up batch was executed in a similar fashion as the development batches, however, given the time pressure on the project we were unable to fully evaluate if crude material could be carried through to step 5. Chromatographic purification was performed on a kilogramm-scale batch to afford **4** with 99% purity and 60% yield for the purification and the overall yield of 52% (Table 3, entry 4). Purification of crude **5** by fractional distillation successfully removed the residual 3-chlorobenzoic acid, however, the purification did not significantly improve the product quality compared to the crude material.[17] Following the completion of the campaign, we successfully demonstrated that crude materi-

al from step 4 could be fully telescoped through step 5, thus avoiding the requirement for chromatography in step 4 for future deliveries.

Step 5: Oxidation of alcohol **5** has previously been executed with more than six equivalents of CrO_3 in >60 V of CH_2Cl_2 to prepare ketone **6** (Table 4, entry 1). The deployment of a chromium-based oxidation is undesirable due to the carcinogenicity of chromium which requires careful control of residual chromium in pharmaceutical products and intermediates down to ppm levels.[18] Additionally, the use of chromium would result in an arduous cleaning process to ensure there is no residual chromium in a multiuse reactor that could carry over to other processes.

Table 4 Step 5: Experimental Results



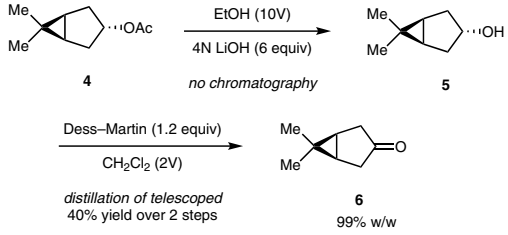
5 6

Entry	Scale	Oxidant (equiv)	Yield (%)[a]	Purity (%)[b]
1	5 g	CrO_3(6.25)	81	86
2	5 g	$(COCl)_2$ (1.5)	75	56
3	2 g	MnO_2 (1.2)	0	n/a
4	2 g	$KMnO_4$ (1.0)	0	n/a
5[c]	12 g	DMP (1.2)	85	97
6[c]	500 g	DMP (1.2)	99	96
7[c,d]	10 g	DMP (1.2)	95	97

[a] Isolated yield based on crude weight.
[b] Purity of isolated product measured by GC.
[c] Reaction conditions: Dess–Martin reagent (1.2 equiv)/CH_2Cl_2 (22 V), 0–20 °C, 3 h; V = mL solvent/g solute.
[d] Crude material from step 4 used.

Alternative oxidants which are readily available and amendable to kilogram scale were investigated in an effort to avoid CrO_3. Swern oxidation provided **6** in 75% yield (Table 4, entry 2), however, foul smell of the dimethylsulfide byproduct is not desired and the cryogenic reactor available to our team is made of stainless steel and is not compatible with oxalyl chloride. Both MnO_2 and $KMnO_4$ were shown to be incompetent oxidants for the desired transformations (Table 4, entries 3 and 4). Dess–Martin periodane (DMP) proved to be an excellent oxidant for the desired oxidation providing a crude yield of **6** in >85% yield (Table 4, entries 5 and 6).[19] DMP and IBX have been reported in the literature to have potential shock hazards.[20] All operations were executed with a minimum 100 °C temperature window between the >130 °C decomposition temperature to ensure a safe operating window. Additionally, we employed semi-batch addition of DMP, and the reaction was quenched with sodium thiosulfate prior to further manipulation. The reaction was safely scaled to 500 g scale to afford **6** in >96% purity by GC; however, the assay was only 78% w/w and sedimentation occurred upon standing.

To improve the %w/w of isolated **6** we sought to focus our efforts on a final isolation that could be used to purify the reaction stream from the previous steps. We first attempted to form a crystalline bisulfite adduct,[21] however, were unable to successfully form the adduct which we hypothesized was due to steric interactions with the *trans*-annular *gem*-dimethyl. Since the 6,6-dimethylbicyclo[3.1.0]hexan-3-one (**6**) is a liquid we felt that the process is suited for a final distillation. We found that distillation at 1.5 mmHg between 70 to 80 °C afforded 80% yield of **6** with >99% w/w purity and was demonstrated on 0.25 kg scale.



Scheme 3 Telescoped process without chromatography

Purification of the final step was a requirement to ensure consistent and high quality **6** for use in downstream processing. We hypothesized that steps 4 and 5 could be telescoped and final purification by distillation of **6** could be successful. A batch of step 4 was executed on 100 g scale, and the crude stream was processed through step 5 (Scheme 3). A portion of the of the final crude material was distilled using conditions described above and afforded **6** in comparable purity as when step 4 was isolated by chromatography. The final two steps of the telescoped process were isolated in a combined 38% yield compared to 41% yield when chromatography was used at step 4. The telescoped process was executed on small scale, and the recovery at the final distillation would be expected to improve as scale is increased. As such, the telescoped process will be implemented in lieu of chromatography after step 4 for future manufacturing.

In conclusion we have demonstrated a refined process for the synthesis of 6,6-dimethylbicyclo[3.1.0]hexan-3-one (**6**) for readily available ≥90% (+)-3-carene. The process avoids chromatography at step 1 with a simple cooling crystallization. We have developed and demonstrated a semi-Pinacol rearrangement that avoids a large excess of silver oxide and instead uses only 1.5 equivalents of silver nitrate buffered with a tertiary amine base. The cost impact of changing the semi-Pinacol process resulted in significant savings in the cost of materials and delivers a process that no longer requires a complicated cleaning protocol. The process has been demonstrated as being capable of through

processing from step 2 to step 5 by incorporation of a final distillation to purify the desired bicyclic ketone **6**. Lastly, we have identified Dess–Martin periodinane as an alternative to using the carcinogenic CrO_3 as the final oxidant.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588484.

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(8) Current costs from sigmaaldrich.com (Item: 94415-1ML at $54.10; Item: W382108-1KG at $97).
(9) See Supporting Information for GC method details.
(10) Unidentified impurity was present at a relative retention time (RRT) of 0.87 min by gas chromatography.
(11) **(1*S*,3*R*,4*R*,6*R*)-4-Bromo-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol (2)**
To a clean and dry 45 L glass reactor was charged 1,4-dioxane (8,000 mL, 8.0 V), water (4,000 mL, 4.0 V), (+)-3-carene (1,000 g, 7.3 mol), and $CaCO_3$ (977 g, 9.8 mol), and the suspension was cooled to 10 °C. NBS (1,698 g, 9.5 mol) was added in portions over 1 h while maintaining the internal temperature. At the end of addition, the resulting mixture was warmed to 20 °C and maintained for 3 h, and the progress of the reaction was monitored by GC until (+)-3-carene was not detected. The reaction mixture was then diluted with water (20,000 mL, 20 V) and extracted twice with PE (12,000 mL, 12 V). The combined organic extracts were washed twice with 5% w/w $Na_2S_2O_3$ solution (10,000 L, 10 V), dried over anhydrous Na_2CO_4, and concentrated under vacuum at 35 °C to get the crude product.
The crude product was dissolved in hexane (4,000 mL, 4 V), cooled to –40 °C, and stirred for 30 min. The solid was filtered, washed with chilled hexane (1,000 mL, 1 V), and dried at 25 °C for 5 h to get 850 g of (1*S*,3*R*,4*R*,6*R*)-4-bromo-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol as off-white solid as main crop with 95% GC purity. The mother liquor was cooled to –40 °C, stirred for 30 min, filtered, dried, and isolated another 100 g as off-white solid (second crop) with 94% purity by GC. Both the crops material were mixed and taken forward into the next step. TLC: PE/EtOAc (8:2); Stain solution: PMA (10% EtOH), yield 950 g (56%). ^{1}HNMR of first crop (300 MHz, $CDCl_3$): δ = 0.69 (t, *J* = 7.26 Hz, 1 H), 0.80–0.88 (m, 1 H), 0.99 and 1.02 (s, 6 H), 1.30 (s, 3 H), 1.41 (d, *J* = 4.92 Hz, 1 H), 2.20 (dd, *J* = 14.63 and 9.72 Hz, 1 H), 2.34–2.49 (m, 2 H), 4.06 (dd, *J* = 10.79 and 7.95 Hz, 1 H).
(12) Current costs from sigmaaldrich.com of 99% purity silver salt: $AgNO_3$(S6506-500G at $1,071.20/0.5kg) costs $546/mol **3** using 1.5 equiv $AgNO_3$ and Ag_2O (item: 221163-1KG at $2,195.00/kg) costs $1,017/mol **3** using 2.0 equiv Ag_2O.
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(14) For examples of $AgNO_3$-mediated ring expansion, see: (a) Pauvert, M.; Dupont, V.; Guingant, A. *Synlett* **2002**, 1350. (b) Morimoto, T.; Yamazaki, A.; Achiwa, K. *Chem. Pharm. Bull.* **2004**, *52*, 1367.
(15) Throughout the investigation, an unidentified impurity was present at 0.95 RRT. The impurity had the same nominal mass by low resolution GC–MS as the desired product **3**. The impurity was present in varying amounts and is hypothesized to be the result of either elimination of HBr or epoxidation.
(16) Distillation conditions: Batch temperature 54–56 °C, pressure 5–2 mbar, isolated yield 85% on 10 g scale. Equipment: Short path distillation head with a combined cold-coil and Liebig condenser and affixed with a three-port distribution adapter.
(17) Distillation conditions: batch temperature 85–105 °C, pressure 10–1 mbar, isolated yield 88% on 7 g scale. Equipment: Short path distillation head with a combined cold-coil and Liebig condenser and affixed with a three-port distribution adapter.
(18) International Conference on Harmonization (2014). M7(R4): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.
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