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*Org. Process Res. Dev.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.9b00425 • Publication Date (Web): 12 Dec 2019



## Just Accepted



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# A fit for purpose synthesis of (*R*)-2-methyl-azepane

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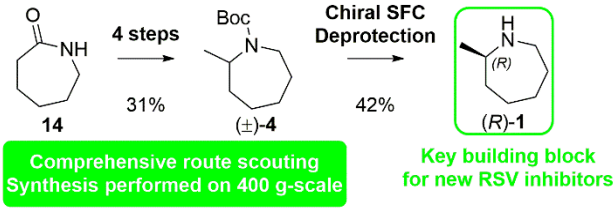



Comprehensive route scouting
Synthesis performed on 400 g-scale

Key building block
for new RSV inhibitors

ABSTRACT

Preparation of new RSV inhibitors required an efficient synthesis of (*R*)-2-methyl-azepane amenable to large-scale production to support preclinical studies. After consideration of different options, an efficient five-step synthesis relying on the preparation of the racemic *N*-Boc precursor and its purification by chiral SFC was developed and successfully implemented on four hundred gram-scale.

KEYWORDS: RSV inhibitors, (*R*)-2-methyl-azepane, Chiral SFC, route scouting

## INTRODUCTION

During the course of a project aiming at finding new Respiratory Syncytial Virus (RSV) inhibitors,[1] the 2-methyl-azepane motif **1** appeared to be one of the most promising sub-units of the newly discovered preclinical drug candidates.[2] Consequently, a larger quantity of the enantiomerically pure (*R*)-**1** key intermediate was required for further *in-vivo*

biological evaluation. In this report, we detail the route evaluation and the successful synthesis of the targeted key intermediate on multi hundred-gram scale.

## RESULTS AND DISCUSSION

Chiral amines are key structural motifs found in many natural products as well as pharmaceuticals, agrochemicals and fine chemicals.[3] A host of chemical methods have been developed to access this highly sought-after class of compounds.[3b,4] Nevertheless, only a very limited number of synthetic options are available for the particularly challenging 2-methyl-azepane core. The groups of Turner and Kroutil have described closely related whole-cell biocatalytic asymmetric reduction of cyclic imines[5] whilst Meyers and co-workers developed a chiral auxiliary approach using [5.3.0]-bicyclic lactams derived from (*R*)-phenylglycinol.[6] The former approach requires the production of a large amount of biocatalyst and was not considered for the sake of time; the latter was investigated but quickly abandoned because of low yields and inadequate enantiopurity, as described in the original paper. In addition to asymmetric reactions,

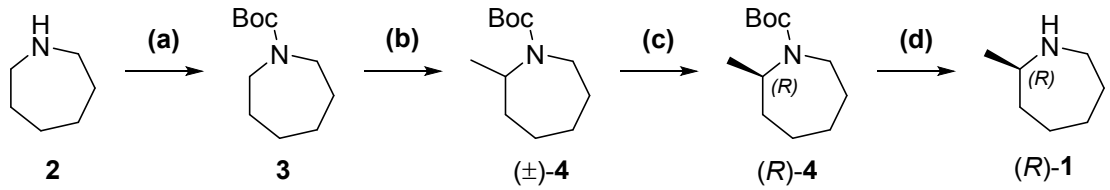
chiral hydroxamic acid-catalyzed kinetic resolution was described by Hsieh and co-workers but with moderate selectivity.[7]

The key building block **4** was initially prepared as a racemate from which the two enantiomers were found to be readily separated by preparative chiral supercritical fluid chromatography (SFC) with an excellent enantiopurity (99% e.e. by chiral HPLC). The (*R*)-enantiomer was later established as the lead to one of the candidates with the best *in-vitro* activity. Because of time pressure, the decision was taken to rely on the efficiency of the previously developed chiral separation and to find a viable synthesis that would enable consistent and timely delivery of the racemic *N*-Boc precursor **4**.

The original synthetic route (scheme 1) relies on the deprotonation of *N*-Boc protected azepane **3** under cryogenic conditions[8] and was hampered by irreproducibility and a tedious purification of (±)-**4** from unconverted **3**. Although we were able to overcome the reproducibility problem and consistently achieved conversions of greater than 95% through water removal from **3** by azeotroping with toluene, chromatographic purification

produces compound (±)-**4** in low yields. This pathway was then deemed unpracticable for implementation on a large scale.

Scheme 1: Initial synthetic route towards (*R*)-2-methyl-azepane **1**[a]

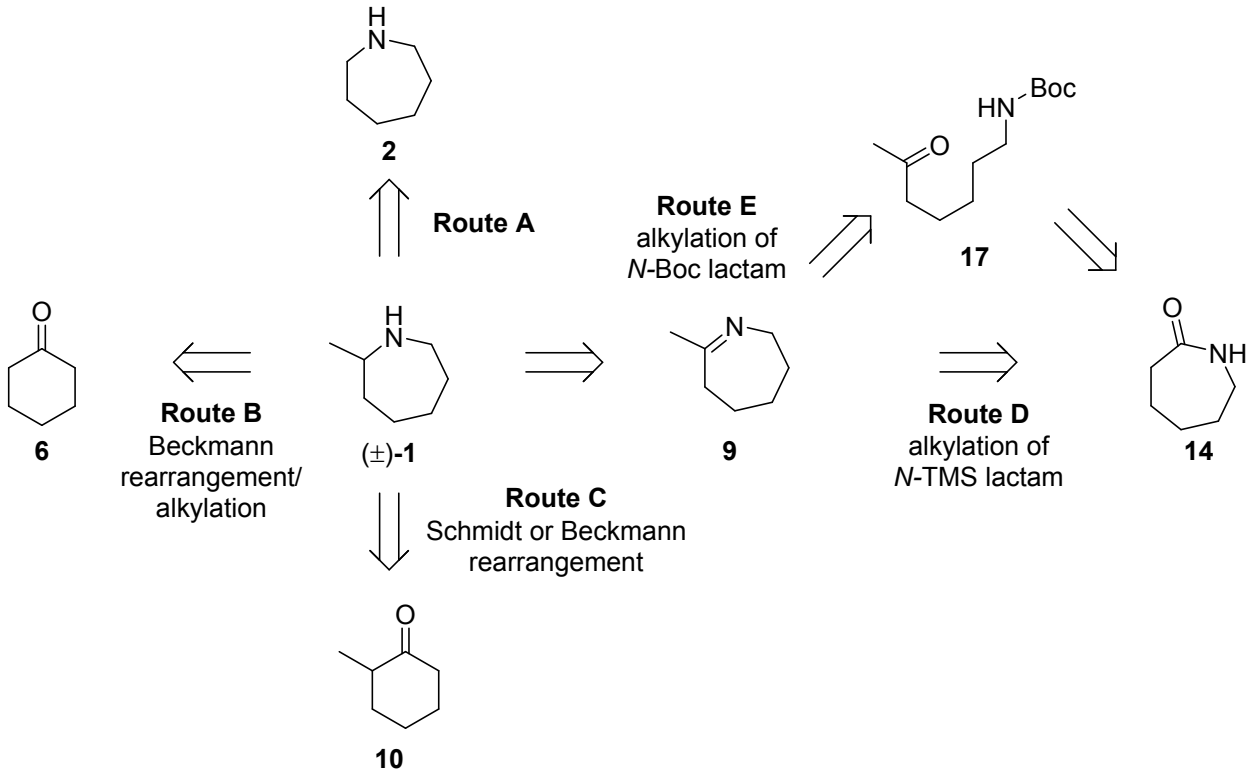



**2** **3** (±)-**4** (*R*)-**4** (*R*)-**1**

[a]: reagents and conditions: (a) $Boc_2O$, DCM, 0 °C to RT, 2 h, 100%; (b) (i) *sec*-BuLi, TMEDA, CPME, -78 °C to -40 °C (ii) $Me_2SO_4$, -78 °C to 0 °C, 90 min, 50% (c) Chiral SFC, 45%; (d) aq. HCl, MeOH, 94%.

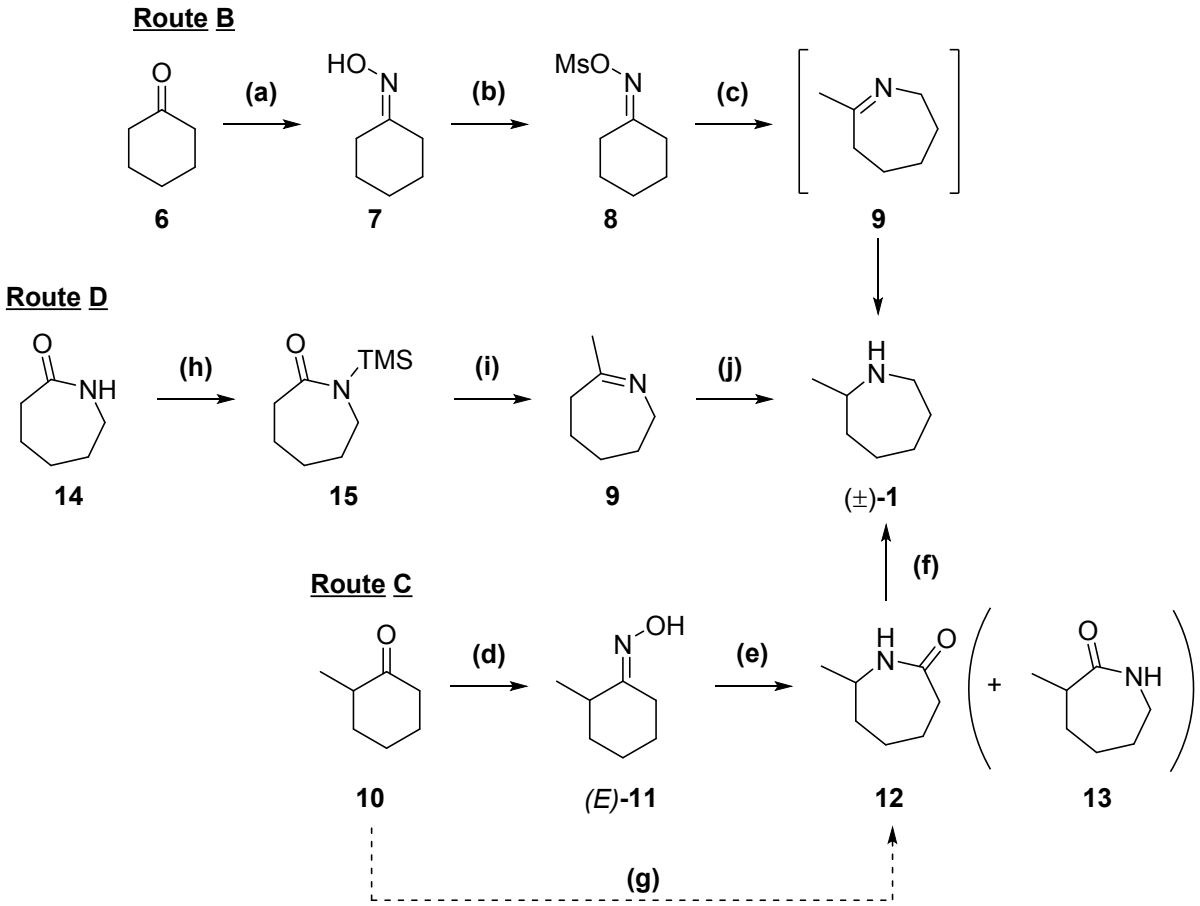
Alternative synthetic approaches to compound **1** are described in the literature. Beside route A and two reports in which the target is obtained as a minor component of the reaction mixture,[9] three main strategies have been disclosed from commercially available starting materials (scheme 2). Routes B[10] and C[6,11] rely on a rearrangement respectively from cyclohexanone **6** and 2-methylcyclohexanone **10** whilst routes D[12] and E[13] proceed through the alkylation of an *N*-protected ε-caprolactam.[14]

Scheme 2: Overview of the described strategies towards racemic 2-methyl-azepane **1**




Route E was ruled out because of the low reported yield and its overall similarity to route D with one additional step. The feasibility and practicability of the three remaining routes were assessed experimentally (scheme 3) with the objective of identifying a route that could be easily scaled-up. The route did not need to fulfill all the criteria of a commercial process at this stage of the drug discovery program, but having the potential to be developed further would be desirable.

Scheme 3: Explored synthetic pathways towards racemic 2-methyl-azepane **1**[a]




[a]: reagents and conditions: (a) $NH_2OH$, NaOAc, *i*-PrOH, RT, 30 min, 92%; (b) MsCl, $Et_3N$, DCM, -20 °C, 10 min, 100%; (c) $AlMe_3$, Toluene/DCM, -78 °C to 0 °C, 2 h then DibalH, DCM, 0 °C, 2 h, 62%. (d) $NH_2OH$, NaOAc, *i*-PrOH, 60 °C, 60 min, 66%; (e) NaOH, $PhSO_2Cl$, acetone, 0 °C to RT, 16 h, 44%; (f) $LiAlH_4$, THF, reflux, 2 h then HCl (3M/CPME), 0 °C to RT, 1 h, 73%. (g) ref 6: aq HCl, $NaN_3$, 0 °C; (h)-(j) see scheme 4

Route B relies on a well-documented organoaluminum promoted tandem Beckmann rearrangement[15] followed by alkylation.[5c] The results obtained were in line with the described procedures. This pathway was demonstrated to provide short and efficient access to the target compound in an overall yield of 25% over 3 steps. Nevertheless,

safety issues with trimethylaluminum[16] and the cumbersome work-up associated with its hydrolysis prevent the scalability of this sequence.

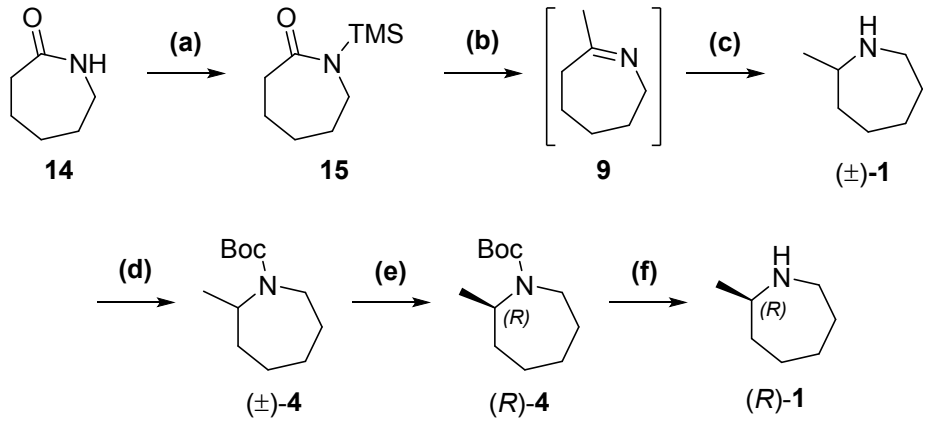
Route C was seen as advantageous as it avoids the requirement for an organometallic reagent but the initial protocol relying on a Schmidt rearrangement[6] poses a serious safety concern as large quantities of hydrazoic acid are generated.[17] Based on our previous experience, a Beckmann rearrangement[15] was envisaged as a safer alternative. A quick screening of reaction conditions (Table S1) identified the combination of sodium hydroxide and benzenesulfonyl chloride as an efficient promoter for the transformation of oxime (*E*)-**11** into **12**.[18] Unfortunately, despite the careful removal of (*Z*)-**11**, the crude reaction mixture contained 10 mol% of the regio-isomer **13** whose separation from **12** was feasible but time consuming and detrimental to the yield.

On the other hand, the feasibility of the key step of route D, methyllithium addition on 1-trimethylsilyl-azepan-2-one **15**,[12] was quickly demonstrated. Minimal optimization focusing on the reduction of imine **9** and isolation of 2-methyl-azepane **1** (table S2) was

performed. Interestingly, a palladium-catalyzed hydrogenation was substituted for stoichiometric aluminum-reagent based reduction.

One major advantage of route D is the ease of purification of the different intermediates with only *N*-Boc-2-methyl-azepane **4** requiring chromatography prior to the chiral separation. Indeed, the first intermediate, 1-trimethylsilylazepan-2-one **15**, was purified by distillation while imine **9** resulting from methyllithium addition was passed without purification to the hydrogenation step. Although, racemic 2-methyl-azepane **1** as a free base is volatile (b.p. = 150v°C at 760 mmHg)[12] and could have been distilled, it was found that hydrochloride formation followed by trituration from an ethereal solvent efficiently purged most of the by-products (mainly ε-caprolactam and trimethylsilyl derivatives) at that stage.

Scheme 4: large-scale preparation of (*R*)-2-methyl-azepane[a]




[a]: reagents and conditions: (a) TMSCl, $Et_3N$, toluene, 40 °C, 4 h, 85%; (b) MeLi, CPME, -30 °C to 22 °C, 3 h (c) $H_2$, Pd/C, EtOH/CPME, 22 °C, 18 h then HCl (4N/CPME), 54% over 2 steps (d) $Boc_2O$, $Et_3N$, 22 °C, 3 h then NaOH, DMAP, 22 °C, 1 h, 67% (e) Chiral SFC, 45%; (f) aq. HCl, MeOH, 94%.

The developed five-step sequence was successfully scaled up on 400 g-scale of 1-trimethylsilylazepan-2-one **15** (scheme 4) delivering (*R*)-2-methyl-azepane in a 13% overall yield. Although satisfactory for the rapid delivery of intermediate **1** for biological testing, further development of the current synthetic protocols would be needed before implementation on a full manufacturing scale. In particular, the development of an asymmetric method for reducing imine **9** is envisioned as a potential breakthrough since it would avoid the loss of half of the synthesized material and circumvent the protecting manipulation steps.

## CONCLUSIONS

Comprehensive route scouting allowed the identification of an efficient and readily scalable synthesis of (*R*)-2-methyl-azepane. The key racemic intermediate could be obtained in four steps from ε-caprolactam with only one chromatographic purification on a 400 g-scale. Subsequent purification by chiral SFC and deprotection afforded the enantiopure compound in high yield within a short cycle time. Further development efforts should focus asymmetric reduction of intermediate imine **9**.

## EXPERIMENTAL SECTION

**General procedures.** NMR experiment was carried out using a Bruker Avance 500 spectrometer equipped with a reverse triple-resonance ($^{1}$H, $^{13}$C, $^{15}$N TXI) probe head with z gradients and operating at 500 MHz for the proton and 125 MHz for carbon or carried out using a Bruker Avance DRX 400 spectrometer at ambient temperature, using internal deuterium lock and equipped with reverse double-resonance ($^{1}$H, $^{13}$C, SEI) probe head with z gradients and operating at 400 MHz for the proton and 100 MHz for carbon. Chemical shifts (d) are reported in parts per million (ppm). J values are expressed in Hz. The following abbreviations were used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Chemical yields refer to pure isolated product. Unless otherwise stated, all reagents were commercially purchased and used without

further purification. All solvents were purchased dry over molecular sieve from Aldrich or Acros and used without further drying or purification.

**Synthesis of 1-trimethylsilyl-azepan-2-one (15).** To a solution of ε-caprolactam **14** (1 eq., 400 g, 3534.82 mmol) and triethylamine (1.25 eq., 447.72 g, 615 mL, 4.42 mol) in dry toluene (2.2 L) in a 10 L-double jacketed reactor under mechanical stirring (500 rpm) was added at 22 °C via an addition funnel chlorotrimethylsilane (1.11 eq., 428 g, 500 mL, 3.94 mol) over 40 min (internal temperature < 25 °C). At the end of the addition, the reaction mixture was stirred at 40 °C for 4 h. The reaction was cooled to 22 °C and diluted with a mixture of diethyl ether/heptane (1:1; 7L). The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was purified by distillation under vacuum (bath temperature 135 °C; $8.10^{-1}$ mbar) to afford 1-trimethylsilyl-azepan-2-one (**15**) (556.8 g, 85%) as a colorless liquid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ ppm 3.20 (m, 2 H); 2.52 (m, 2 H); 2.45 (m, 2 H); 1.73 - 1.65 (m, 4 H); 1.59 - 1.53 (m, 2 H); 0.18 (s, 9 H) $^{13}$C NMR (100 MHz, $CDCl_3$) δ ppm 183.48 (s, 1 C) 44.68 (s, 1 C) 38.01 (s, 1 C) 30.55 (s, 1 C) 30.00 (s, 1 C) 23.66 (s, 1 C) 0.25 (s, 1 C).

**Synthesis of (±)-2-methyl-azepane ((±)-1).** To a solution of MeLi (3.1M in DME, 1.3 eq., 1 L, 3.1 mol) previously cooled to -30 °C in a 10 L-double jacketed reactor, was added via an addition funnel a solution of compound **15** (1 eq., 440 g, 2.37 mol) in CPME (1.55 L) over 45 min (internal temperature < -15 °C). The reaction mixture was stirred at -30°C for 30 min then at 22°C for 1 h. The reaction was quenched with $NH_4Cl$ solution (0.5M in water, 5.5 L). The reaction was stirred at room temperature for 1 hour. The aqueous layer was extracted with dichloromethane (3 x 1 L) The organic layers were combined, dried over sodium sulfate, filtered and evaporated to dryness. The crude reaction mixture was dissolved in a mixture of cyclopentyl methyl ether (1.5 L) and ethanol (800 mL) and purged 3 times with argon. Palladium on carbon (10% dry basis, 66 g) was added before the reaction mixture was purged 3 times with hydrogen. The reaction mixture was stirred at RT for 20 h under hydrogen (1 atm), then filtered on Celite®. The filtrate was transferred in a 10 L-double jacketed reactor, cooled to 15 °C then hydrochloric acid (4M in cyclopentyl methyl ether, 1.7 eq., 1 L, 4 mol) was slowly added (over 10 min) and the reaction was stirred at 22 °C for 30 min. The suspension was evaporated to dryness and triturated from diethyl ether (3 x 1.5 L) to afford (±)-2-methyl-azepane (**(±)-1**) (208 g;

contaminated with 7 wt wt %of ε-caprolactam **14**, 54% corrected yield) as a pink solid. $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ ppm 9.49 (br s, 1 H) 8.99 (br s, 1 H) 3.17 - 3.36 (m, 1 H) 2.89 - 3.12 (m, 2 H) 1.42 - 1.91 (m, 8 H) 1.26 (d, $J$=6.6 Hz, 3 H) $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ ppm 54.15 (s, 1 C) 44.31 (s, 1 C) 33.07 (s, 1 C) 26.64 (s, 1 C) 24.62 (s, 1 C) 24.53 (s, 1 C) 20.23 (s, 1 C).

**Synthesis of (±)-*N*-Boc-2-methyl-azepane ((±)-4).** To a suspension of compound (±)-**1** (1 eq., 207 g, 1.38 mol) in DCM (1.15 L) was added triethylamine (1.2 eq., 167.44 g, 230 mL, 1.65 mol) then a solution of di-tert-butyl dicarbonate (1.1 eq., 332 g, 1.52 mol) in DCM (300 mL) was added slowly. The reaction mixture was stirred at 22 °C for 3 h then quenched with NaOH (7.5M/$H_2O$; 1.63 eq., 300 mL, 2.25 mol) and 4-(dimethylamino)pyridine (0.0015 eq., 0.8 g, 2 mmol) and stirred at 22 °C for 1 h. The aqueous layer was extracted with DCM (2 x 300 mL). The organic layers were combined, washed with NaOH 0.5M (2 x 100 mL), dried over sodium sulfate, filtered and evaporated to dryness. The residue was then purified by flash chromatography ($SiO_2$, cyclohexane /

DCM 100:0 to 80:20) to afford (±)-*N*-Boc-2-methylazepane ((±)-**4**) (215.6 g; contaminated with 8wt % residual dichloromethane, 67%).

**Purification of (*R*)-*N*-Boc-2-methyl-azepane ((*R*)-4).** 63.8 g of compound **4** were purified via chiral SFC (Stationary phase: Whelk O1 (S,S) 5µm 250 x 21.1mm, Mobile phase: 2.5% Heptane, 95% $CO_2$, 2.5% *i*-PrOH). The fractions containing pure *(S)*-**4** were combined and evaporated in vacuo to afford *(S)*-**4** (30.6 g, 48%). The fractions containing pure *(R)*-**4** were combined and evaporated in vacuo to afford (*R*)-**4** (28.6 g, 45%). Mixture of rotamers (55:45) $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 3.98 (dt, *J*=11.9, 6.2 Hz, 0.55 H); 3.86 (dt, *J*=11.7, 6.0 Hz, 0.45 H); 3.57 (br d, 0.45 H); 3.49 (br d, 0.55 H); 2.69-2.77 (m, 1 H); 1.86 - 1.97 (m, 1 H); 1.58 - 1.73 (m, 3 H); 1.39 (s, 9 H); 1.00-1.40 (m, 4 H); 1.00 (d, *J*=6.6 Hz, 1.35 H); 0.96 (d, *J*=6.6 Hz, 1.65 H) $^{13}$C NMR (126 MHz, DMSO-d6) δ ppm 154.87 (s, 1 C) 78.31 (s, 1 C) 78.18 (s, 1 C) 62.43 (s, 1 C) 51.72 (s, 1 C) 50.48 (s, 1 C) 40.89 (s, 1 C) 40.47 (s, 1 C) 35.83 (s, 1 C) 35.66 (s, 1 C) 29.50 (s, 1 C) 29.30 (s, 1 C) 28.51 (s, 1 C) 25.85 (s, 1 C) 25.72 (s, 1 C) 25.42 (s, 1 C) 20.34 (s, 1 C) 19.93 (s, 1 C) .

**Synthesis of (*R*)-2-methyl-azepane (*(R)*-1).** In a 5 L-double jacketed reactor with mechanical stirring, aqueous HCl 37% (639 mL; 7.65 mol) was added dropwise (with monitoring of internal temperature 15 °C < T < 23 °C) to a solution of compound *(R)*-**4** (510 g; 2.39 mol) in MeOH (1 L). The reaction mixture was stirred at room temperature for 18 h and evaporated to dryness. The residue was azeotroped with EtOH (4 x 250 mL) then with $Et_2O$ (250 mL) to give a white solid. The solid was taken up in $Et_2O$ (250 mL)

and the precipitate was filtered off, washed with $Et_2O$ (4 x 200 mL) and dried under vacuum at RT for 18 h to give 336 g of pure (*R*)-2-methyl-azepane hydrochloride (94%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 9.49 (br s, 1 H) 8.99 (br s, 1 H) 3.17 - 3.36 (m, 1 H) 2.89 - 3.12 (m, 2 H) 1.42 - 1.91 (m, 8 H) 1.26 (d, *J*=6.6 Hz, 3 H) $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ ppm 54.15 (s, 1 C) 44.31 (s, 1 C) 33.07 (s, 1 C) 26.64 (s, 1 C) 24.62 (s, 1 C) 24.53 (s, 1 C) 20.23 (s, 1 C) $[\alpha]^{D}_{20}$: +8.52° (c 0.27 in DMF)

## ASSOCIATED CONTENT

**Supporting Information**.

The following files are available free of charge. Table describing the conditions screened for the synthesis of compounds **12** and (±)-**1** via route D**,** experimental procedures for routes A, B, and C, and analytical data for compounds *(R)*-**1**, (±)-**1**, (*R*)-**4**, **7**, **8**, (*E*)-**11**, **12, 15** (PDF).

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## Author Contributions

All authors contributed to the preparation of the manuscript and approved the final version.

## Funding Sources

This research was financially supported by Janssen R&D and NovAliX.

## Notes

The authors declare no competing financial interest. A patent application has been filed by some of the co-authors (David Lançois, Jérôme Guillemont, Antoine Michaut) regarding the use of the described compound as intermediate for the synthesis of new RSV inhibitors.

ACKNOWLEDGMENT

The authors acknowledge Frank Moffatt for careful proof-reading of the manuscript and Julien Marin for support throughout all the project.

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