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Scalable Synthesis of 1-Bicyclo[1.1.1]pentylamine via a Hydrohydrazination Reaction

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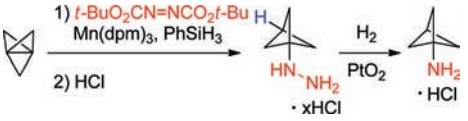
ABSTRACT



The reaction of [1.1.1]propellane with di-*tert*-butyl azodicarboxylate and phenylsilane in the presence of $Mn(dpm)_3$ to give di-*tert*-butyl 1-(bicyclo[1.1.1]pentan-1-yl)hydrazine-1,2-dicarboxylate is described. Subsequent deprotection gives 1-bicyclo[1.1.1]pentylhydrazine followed by reduction to give 1-bicyclo[1.1.1]pentylamine. The reported route marks a significant improvement over the previous syntheses of 1-bicyclo[1.1.1]pentylamine in terms of scalability, yield, safety, and cost.

Access to novel chemical space is becoming increasingly important in drug discovery.[1] One method to accomplish this is by utilizing small compounds of unique structure as building blocks, especially ones that have good drug-like properties (i.e., low lipophilicity, low clearance, and good solubility).[2] Often these compounds are associated with challenging or complex syntheses.[1,2] 1-Bicyclo[1.1.1]pentylamine (**1**) is an example of such a compound. The use of **1** has been limited because it is not commercially available. The known preparation of **1** has complications for scale-up with both a lithiation step and a Schmidt reaction that generates hydrazoic acid (extremely toxic and explosive).[3] Consequently, only a few examples showcase the successful incorporation of **1** in drug candidates (Figure 1).[4]

Improvement upon the synthesis of **1** (originally published by Wiberg[3d] over 40 years ago) has received attention from both academia and industry (Scheme 1).[5] Toops

(1) (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (b) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227.

(2) (a) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; et al. *Org. Lett.* **2008**, *10*, 3259. (b) Stocks, M. J.; Wilden, G. R. H.; Pairaudeau, G.; Perry, M. W. D.; Steele, J.; Stonehouse, J. P. *ChemMedChem* **2009**, *4*, 800. (c) Hamzik, P. J.; Brubaker, J. D. *Org. Lett.* **2010**, *12*, 1116. (d) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780. (e) Duncton, M. A. J.; Estiarte, M. A.; Johnson, R. J.; Cox, M.; O'Mahony, D. J. R.; Edwards, W. T.; Kelly, M. G. *J. Org. Chem.* **2009**, *74*, 6354.

(3) (a) Hossain, M. T.; Timberlake, J. W. *J. Org. Chem.* **2001**, *66*, 6282. (b) Barbachyn, M. R.; Hutchinson, D. K.; Toops, D. S.; Reid, R. J.; Zurenko, G. E.; Yagi, B. H.; Schaadt, R. D.; Allison, J. W. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 671. (c) Brewer, P. G., Runge, T. A., Timko, J. M., Veldman, T. J., Walker, J. A. *Preparation of 1-Bicyclopentylamine Hydrochloride, U85,879A--a Key Intermediate for the Syntheses of Quinolone Antibacterial Agents*; TR1510-91-005; Upjohn: October 3, 1991. (d) Wiberg, K. B.; Williams, V. Z., Jr. *J. Org. Chem.* **1970**, *35*, 369. (e) Della has prepared compound **1** from 1-carboxybicyclo-[1.1.1]pentane in 34% using a modified Hoffmann rearrangement; see: Della, E. W.; Kasum, B.; Kirkbride, K. P. *J. Am. Chem. Soc.* **1987**, *109*, 2746. (f) Wiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112*, 2194.

(4) (a) Since 2005, 9 of the 11 patents that contain the 1-bicyclo-[1.1.1]pentylamine moiety have been published, documenting a renewed interest in the molecule. The following are selected patent references: (b) Gammill, R. B.; Bisaha, S. N.; Timko, J. M.; Judge, T. M.; Barbachyn, M. R.; Kim, K. S. *Preparation of Antibacterial Quinolone and Naphthyridone Compounds* (Upjohn Co., USA); WO 90/06307, June 14, 1990. (c) Bennett, M. J.; Zehnder, L. R.; Ninkovic, S.; Kung, P.-P.; Meng, J. J.; Huang, B. *2-Amino-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine Derivatives as HSP-90 Inhibitors and their Preparation, Pharmaceutical Compositions and use in the Treatment of Cancer* (Pfizer Inc., USA); WO 2008/096218, Aug. 14, 2008. (d) Dessole, G.; Jones, P.; Bufi, L. L.; Muraglia, E.; Ontoria Ontoria, J. M.; Torrisi, C. *Preparation of 1,2,4-Oxadiazole Substituted Piperidine and Piperazine Derivatives as SMO Antagonists* (Istituto di Ricerche di Biologia Molecolare P. Angeletti S.p.A., Italy); WO 2010/013037, Feb. 4, 2010. (e) Kung, P.-P.; Meng, J. J. *Preparation of Pyrazolylethoxyphenyl-pyrroloyrimidinamines as Heat Shock Protein-90 (HSP-90) Inhibitors* (Pfizer Inc., USA); WO 2010/018481, Feb. 18 2010.

(5) (a) Levin, M. D.; Kaszynski, P.; Michl, J. *Chem. Rev.* **2000**, *100*, 169. (b) Toops, D. S.; Barbachyn, M. R. *J. Org. Chem.* **1993**, *58*, 6505. (c) Hossain, M. T.; Timberlake, J. W. *J. Org. Chem.* **2001**, *66*, 4409.

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and Barbachcyn showed that they could prepare **1** (characterized as the benzamide derivative) starting

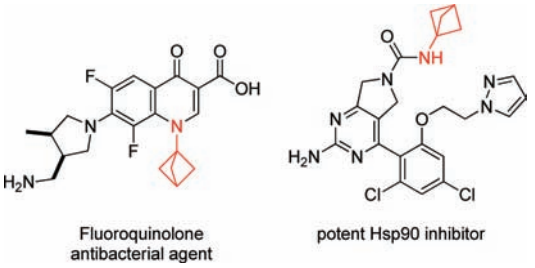
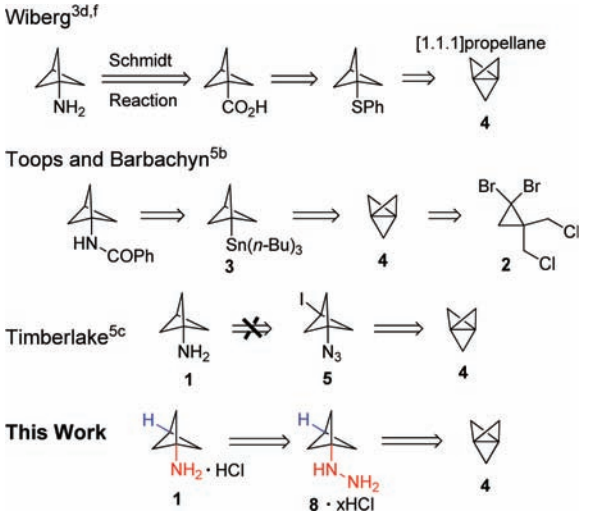


Figure 1. Select bioactive compounds containing 1-bicyclo-[1.1.1]pentyl amine moiety.

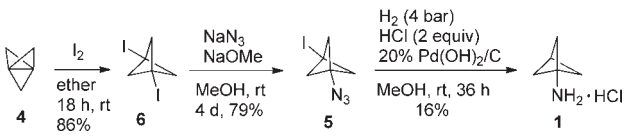
from tetrahalide (**2**) and going through 1-(tri-*n*-butylstannyl)bicyclo[1.1.1]pentane (**3**).[5b] However, besides the toxicity issue of organostannanes, this method suffered from low yield (14% from **2**), required an excess of [1.1.1]propellane (**4**), and used reversed phase chromatography to purify the organostannane. Timberlake looked at an alternate synthesis of **1** by first preparing 3-iodobicyclo[1.1.1]pentyl azide (**5**), but all reported reduction conditions (LAH, Zn/HCl, nBu$_3$SnH, Li/NH$_3$(l), etc.) failed to give compound **1**.[3a,5c]

Scheme 1



To support our ongoing drug discovery programs it became necessary to find a new route to **1** that would be amenable to scale-up. Since compound **5** is only a reduction step away from the desired product, we decided to investigate further. Other iodobicyclo[1.1.1]pentanes have been reduced using *tert*-butyl lithium.[6] To avoid the pyrophoric reagent we looked at palladium-mediated reduction of alkyl iodides.[7]

Scheme 2



Azido iodide[8] (**5**) was prepared from the diiodide (**6**) in a two-step procedure from [1.1.1]propellane (**4**) (Scheme 2).[9] In order to more quickly scope reduction conditions, microscale parallel experimentation was carried out utilizing a 96-well plate (0.01 mmol of substrate, 0.045 M concentration). The screen evaluated combinations of 41 different catalysts, two temperatures (25 and 65 °C), three solvents (MeOH, EtOAc, AcOH), three additives (HCl, AcOH, benzyl chloride), and without additive. In total, 240 reaction conditions were examined under hydrogen pressure (4 bar) for 15 h. Each reaction was analyzed by LC/MS and evaluated for product by mass ion count (TIC). From this study 20% Pd(OH)$_2$/C emerged as the leading catalyst with HCl as the additive in methanol to give **1**. These conditions were scaled-up (Scheme 2). Unfortunately, even though screening conditions indicated a higher yield (based on a standard with known concentration of **1** and comparing mass ion count), we were only able to isolate 16% of compound **1** after SFC purification. The palladium-mediated reduction route would need further optimization to become viable.

A review of the literature indicated that some of the more efficient reactions of [1.1.1]propellane (**4**) involve free radicals due to their facile addition across the central bond.[5a,10] The 1-bicyclo[1.1.1]pentyl radical is slow to ring open, and rearrange to the 3-methylenecyclobut-1-yl radical, due to a relatively large activation barrier of "at least 26 kcal mol^{-1}".[11] Additionally, [1.1.1]propellane (**4**) in many instances has shown a similar reactivity profile to that of olefins.[5a,10b] Waser and Carreira[12] have elegantly demonstrated the ability to add H−N across olefins through what is potentially a free-radical mechanism in either cobalt- or manganese-catalyzed hydrohydrazination reactions. With these considerations in mind we postulated that the

(6) (a) Hassenrueck, K.; Murthy, G. S.; Lynch, V. M.; Michl, J. *J. Org. Chem.* **1990**, *55*, 1013. (b) Mazal, C.; Paraskos, A. J.; Michl, J. *J. Org. Chem.* **1998**, *63*, 2116.

(7) (a) Ayats, C.; Camps, P.; Font-Bardia, M.; Solans, X.; Vázquez, S. *Tetrahedron* **2007**, *63*, 8027. (b) Banwell, M. G.; Chun, C.; Edwards, A. J.; Voegtle, M. M. *Aust. J. Chem.* **2003**, *56*, 861. (c) Camps, P.; Lukach, A. E.; Rossi, R. A. *J. Org. Chem.* **2001**, *66*, 5366. (d) Boukherroub, R.; Chatgilialoglu, C.; Manuel, G. *Organometallics* **1996**, *15*, 1508.

(8) Precaution should be taken when working with azides such as compound **5** as they are potentially explosive.

(9) Wiberg, K. B.; McMurdie, N. *J. Am. Chem. Soc.* **1994**, *116*, 11990.

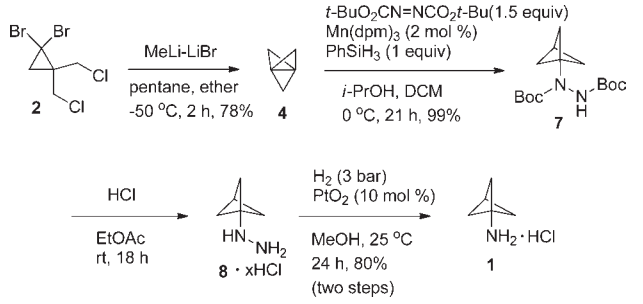
(10) (a) Della, E. W.; Lochert, I. J. *Org. Prep. Proced. Int.* **1996**, *28*, 411. (b) Kaszynski, P.; Michl, J. *Chem. Cyclopropyl Group* **1995**, *2*, 773. (c) Wiberg, K. B. *Chem. Rev.* **1989**, *89*, 975.

(11) Della, E. W.; Pigou, P. E.; Schiesser, C. H.; Taylor, D. K. *J. Org. Chem.* **1991**, *56*, 4659.

(12) (a) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (b) Waser, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 5676. (c) Waser, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4099.

1-bicyclo[1.1.1]pentyl radical would form under similar conditions and that it might be possible to trap it with an azodicarboxylate. This would effectively carry out a hydroamination[13] reaction across the bridge bond while ideally avoiding the formation of oligomers to give the known [*n*]staffanes.[5a,10b,10c]

Scheme 3



[1.1.1]Propellane (**4**) was prepared[14] as a pentane/ether solution (Scheme 3) in 78% yield (by NMR analysis of the distillate). Utilizing the previously established hydrohydrazination procedure for polymerization sensitive olefins, a cold (0 °C) *iso*-propanol solution of the catalyst tris-(dipivaloylmethanato)manganese ($Mn(dpm)_3$) was prepared and a dichloromethane solution of phenylsilane and di-*tert*-butyl-azodicarboxylate was added.[15] The crude distillate solution containing [1.1.1]propellane (**4**) (1 equiv) was then charged to the reaction mixture. LC/MS analysis of the reaction after 4 h gave a base mass ion peak of *m*/*z* 99 [$C_5H_{10}N_2 + H^+$] and fragment mass ions of *m*/*z* 143 [$C_6H_{10}N_2O_2 + H^+$] and *m*/*z* 187 [$C_7H_{10}N_2O_4 + H^+$]. A parent ion peak for compound **7** was not observed, but the mass ions of *m*/*z* 99, 143, and 187 could be expected from fragmentation of the di-*tert*-butylcarbamate substituents under the acidic LC/MS conditions. The reaction was stopped after 5 h, and following workup and flash chromatography **7** was isolated as a white solid in 73% yield. The ^{1}H NMR spectrum[16] (DMSO-d_6, 80 °C) of the sample displays the characteristic resonances of the 1-bicyclo-[1.1.1]pentyl framework at δ 2.37 (s, 1H, CH) and 1.96 (s, 6H, CH_2) and are in close agreement with the corresponding chemical shifts observed in 1-bicyclo[1.1.1]pentyl amine (**1**) (free base, $CDCl_3$)[17] at δ 2.31 (s, 1H, CH) and 1.79 (s, 6H, CH_2). Likewise, in the ^{13}C NMR spectrum (DMSO-d_6, 80 °C) of the product, the resonances at δ 54.05 (*C*N, C1), 51.61 (*C*H_2, C2), and 21.85 (*C*H, C3) were assigned to the 1-bicyclo[1.1.1]pentyl ring system and are comparable to the resonances observed in **1** (free base, $CDCl_3$) at δ 52.53 (C1), 53.17 (C2), and 21.51 (C3).[17]

As the reaction was difficult to monitor for the disappearance of [1.1.1]propellane (**4**), subsequent experiments increased the reaction time to 21 h, which led to an isolated yield of 99% of **7**.[18] Treatment of **7** with 4 M HCl in dioxane gave the hydrazine hydrochloride salt **8** as a solid (Scheme 3). Reduction of the N−N bond under hydrogenation conditions in the presence of PtO_2[19] gave the desired 1-bicyclo[1.1.1]pentylamine (**1**) in 80% yield (over two steps) as an off-white solid, which was identical in all respects to a sample of **1** prepared previously.[3]

In summary, the new route provides a dramatic improvement in scalability, yield, and safety compared to the previous route. In addition, the route gives 1-bicyclo-[1.1.1]pentylhydrazine (**8**) which can be exploited in drug design by preparing novel substrates such as 1-bicyclo-[1.1.1]pentyl pyrazoles and indoles. The new route has been successfully scaled to 20 g, the overall yield (from **2**) improved from 10% to 62% with a 50-fold reduction in costs. As work is ongoing, details of further process development will be forthcoming.[20] Work is also underway to expand the scope of the manganese-catalyzed addition reactions of [1.1.1]propellane (**4**) beyond azodicarboxylates to molecular oxygen, tosyl azide, tosyl cyanide, tosyl chloride, and related reagents.[12a,21]

Acknowledgment. We are grateful to William R. Roush (The Scripps Research Institute) for insightful disucssions as well as Pfizer colleagues Jean Cui, Javier Gonzalez, and Seiji Nukui. We are grateful to Thomas Brandt, Brian Conway, Remzi Duzguner, Alex Gontcharov, Richard Lehner, and Jeffery Raggon for their work on the scale-up and DSC measurements (Pfizer).

Supporting Information Available. Experimental procedures, differential scanning calorimetry (DSC), and characterization data of **7**, **8**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) For a review of hydroamination, see: Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(14) Shtarev, A. B.; Pinkhassik, E.; Levin, M. D.; Stibor, I.; Michl, J. *J. Am. Chem. Soc.* **2001**, *123*, 3484.

(15) Upon scale-up a large exotherm was observed when adding the prepared dichloromethane solution to the isopropanol solution. Consequently, a controlled slow addition was required to maintain the temperature at 0 °C.

(16) See Supporting Information for full characterization.

(17) Adcock, W.; Krstic, A. R. *Magn. Reson. Chem.* **2000**, *38*, 115.

(18) The yield of **7** is near quantitative within experimental error.

(19) The reduction was also successfully carried out using Raney nickel.

(20) Preliminary internal results have successfully prepared several hundred grams utilizing this new route; see Acknowledgment.

(21) (a) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294. (b) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519. (c) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758. (d) Gaspar, B.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 13214. (e) Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 1869.