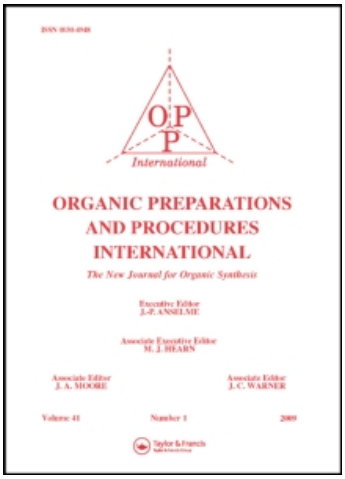


Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

EFFICIENT SYNTHESIS OF *EXO*-1-AZABICYCLO[2.2.1]HEPTAN-3-OL

Stephen D. Barrett[a]; Juan C. Jaen[a]; Bradley W. Caprathe[a]; Anthony J. Thomas[a]; Haile Tecle[a]
[a] Division of Warner-Lambert, Parke-Davis Pharmaceutical Research, Ann Arbor, MI, USA

To cite this Article Barrett, Stephen D. , Jaen, Juan C. , Caprathe, Bradley W. , Thomas, Anthony J. and Tecle, Haile(1997) 'EFFICIENT SYNTHESIS OF *EXO*-1-AZABICYCLO[2.2.1]HEPTAN-3-OL', Organic Preparations and Procedures International, 29: 3, 330 — 335
To link to this Article: DOI: 10.1080/00304949709355206
URL: http://dx.doi.org/10.1080/00304949709355206

15. a) G. A. Olah, G. K. S. Prakash, P. S. Iyer, M. Tashiro and T. Yamato, *J. Org. Chem.*, **52**, 1881 (1987); b) T. Yamato, C. Hideshima, M. Tashiro, G. K. S. Prakash and G. A. Olah, *ibid.*, **56**, 6248 (1991).

16. a) G. A. Olah, P. S. Iyer and G. K. S. Prakash, *Synthesis*, **1986**, 513; b) T. Yamato, *J. Synth. Org. Chem. Jpn*, **53**, 487 (1995) and references therein.

****

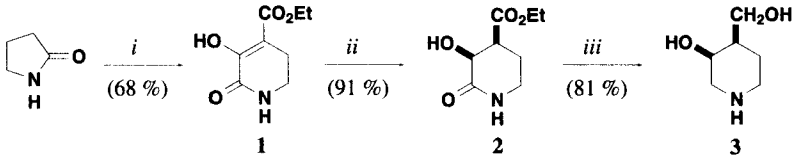
EFFICIENT SYNTHESIS OF *EXO*-1-AZABICYCLO[2.2.1]HEPTAN-3-OL

Submitted by (11/07/96) Stephen D. Barrett*, Juan C. Jaen, Bradley W. Caprathe Anthony J. Thomas and Haile Tecle

Parke-Davis Pharmaceutical Research, Division of Warner-Lambert 2800 Plymouth Road, Ann Arbor, MI 48105, USA

The 1-azabicylo[2.2.1]heptane ring system is found in a number of useful therapeutic agents.[1-4] Since substitution on either of the two-carbon bridges imparts chirality to this ring, an efficient route to the versatile optically active 1-azabicyclo[2.2.1] heptane synthons was required. Enantiomeric (R)-(-)- or (S)-(+)-*exo*-1-azabicyclo[2.2.1]heptan-3-ol (**5**), are such synthons. For example, (-)-**5** is a key intermediate in the synthesis of PD 151832, an m1-selective muscarinic agonist.[5] A previously described cyclodehydration of piperidinediol **3** over basic alumina gave only a modest yield (33%) of racemic **5**.[6] We found this procedure impractical for the procurement of the large quantities of **5** needed and describe here a practical synthesis of racemic **5** on a multigram scale in 86-96% overall yield from **3**.

In our hands, condensation of pyrrolidinone with diethyl oxalate (sequential ring-opening and reclosure under Claisen conditions) on a two hundred-gram scale afforded β-ketoester **1** in 68% yield.[6,7] Catalytic hydrogenation of **1** and recrystallization of the crude product from toluene furnished the *cis* diastereomer of β-hydroxyester **2** as the sole product in excellent yield.



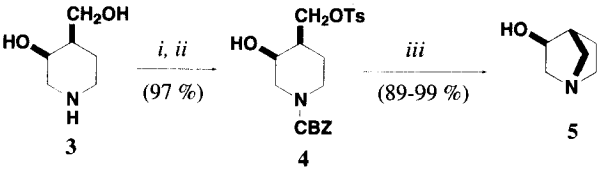
1 **2** **3** (1)

i) $(CO_2Et)_2$, KOEt, $PhCH_3$, Δ, 18 hrs; *ii*) H_2, 10% Rh/C, AcOH; *iii*) LAH, THF, Δ, 48 hrs

Lithium tetrahydoaluminate reduction on the 40 gram scale provided the *cis* diol **3** with no detectable amount of the *trans* diastereomer in 81% yield. An attempt to reduce **2** with borane-tetrahy-

drofuran complex in boiling tetrahydrofuran for 63 hrs produced none of the desired product.

Having obtained **3** from pyrrolidinone in comparable overall yield (42% to 50%) to the established literature procedure, a protection-deprotection strategy for the preparation of the key intermediate **5** was chosen. Although three steps were required (Eq. 2), a facile transformation from **3** to **5** amenable to scaleup with greatly improved the overall yield was achieved.



(2)

i) CBZ-O-Succ, H_2O, $NaHCO_3$; *ii*) TsCl, pyridine; *iii*) H_2, Pd/C.

Carboxybenzyl-protection of the piperidine nitrogen proceeded quantitatively. Selective tosylation of the primary hydroxyl function of the CBZ-protected piperidine diol with *p*-toluenesulfonyl chloride followed by aqueous acid workup and trituration of the crude viscous product residue with pentane afforded the analytically pure solid **4** in nearly quantitative yield. Hydrogenolysis of **4** was carried out in absolute ethanol over 20% Pd on carbon. Removal of the solvent followed by aqueous basic workup and continuous overnight chloroform extraction provided excellent yield of the desired racemic azabicyclic amino alcohol **5** in satisfactory purity.

Two alternative attempts at ring closure gave less favorable results. First, intramolecular piperidine nitrogen atom displacement of the primary hydroxyl group of **3** *via* dehydration using the Mitsunobu reagent (Ph_3P/DEAD)[8,9] in THF afforded **5** in low yield (33%) after a tedious purification. Second **3** was N-benzylated (BnBr/$NaHCO_3$) in methanol in modest yield (58%). The N-protected diol was treated with one equivalent of tosyl chloride in pyridine to affect tosylation of only the primary hydroxyl group. Under these conditions rapid ring closure by intramolecular displacement of tosylate by nitrogen was facilitated. The tosylated intermediate was thus never isolated. However, difficulties in the purification of the resulting quaternary salt and poor yields in the subsequent N-deprotection step make this method impractical for scale-up.

The resolution of racemic **5** *via* its tartrate salt and its subsequent oxidation to the optically active ketone have been described in the literature.[10] We determined enantiomeric excesses by chiral HPLC and UV detection of the O-benzoate derivatives of the optically active alcohols.

EXPERIMENTAL SECTION

Proton nuclear magnetic resonance (^{1}H NMR) were determined at 400 MHz on a Varian Unity 400 NMR spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) were recorded at 100 MHz on a Varian Unity 400 NMR spectrometer. Chemical shifts are reported in parts per million (δ) from an internal standard of tetramethylsilane (0.00 ppm) for ^{1}H NMR and from an internal standard of either residual chloroform (77.00 ppm) or dimethylsulfoxide (39.50 ppm) for ^{13}C NMR. NMR peak multiplicities are denoted as follows: s(singlet), d(doublet), t(triplet), q(quartet), ddd(doublet of doublet-of-doublets), and m(multiplet). Coupling constants (J) are given in Hz. Infrared spectra were recorded on

a Mattson Cygnus 100 FTIR as KBr pellets. Wavenumbers are given in cm^{-1}. Electron ionization (EI) and chemical ionization (CI) mass spectra were obtained on a VG Trio 2 mass spectrometer. Melting points were determined on either a Thomas Hoover or a Mel-temp. melting point apparatus and are not corrected. Elemental analyses were performed on a Lehman Labs 440 instrument. All experiments that required dry conditions were carried out under a nitrogen or argon (if indicated) atmosphere using reagent grade solvents. Deionized (reverse osmosis) water was used in all cases.

5-Hydroxy-6-oxo-1,2,3,6-tetrahydropyridine-4-carboxylic Acid Ethyl Ester (1).- To a vigorously stirried suspension of pentane-washed (3 x 400 mL) potassium hydride (123 g of pre-washed KH in mineral oil; 1.07 mol) in 1.20 L of toluene in an oven-dried 5 L three-neck, round-bottom reaction flask was added dropwise *via* addition funnel 300 mL (5.1 mol) of absolute ethanol over a fifteen minute period. (The use of commercially available (Aldrich) potassium ethoxide both eliminated the intrinsic safety risks associated with the handling of potassium hydride on a large scale and afforded comparable (61-73%) yields). The resulting warm homogeneous solution was allowed to cool to 40°. To this stirred mixture was added a solution of 79 mL (1.04 mol) of pyrrolidinone and 144 mL (1.06 mol) of diethyl oxalate in 250 mL of toluene with a slow steady-stream addition. Toluene (300 mL) and ethanol (200 mL) were added to dilute the thick yellow suspension that had formed. The reaction mixture was stirred at 90° for 18 hrs followed by cooling to 40° before quenching with 6 N HCl (400 mL). After vigorous mixing, the phases were separated. The aqueous phase was extracted also with dichloromethane (2 x 500 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was purified by recrystallization (ethyl acetate) and the purified material was recovered by vacuum filtration. Drying overnight in the vacuum oven (50°) afforded 131.18 g (68%) of a yellow crystalline solid, mp. 142-148°, lit.[7] 148°; ^{1}H NMR (400 MHz; $CDCl_3$): δ 11.45 (s, 1H), 7.92 (s, 1H), 4.31 (q, 2H, 7.2 Hz), 3.42 (m, 2H), 2.60 (t, 2H, 7.1 Hz), 1.35 (t, 3H, 7.2 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.99, 162.55, 155.47, 105.63, 61.67, 39.03, 21.47, 14.20; IR (KBr): 3298, 1697, 1661, 1613, 1476, 1383, 1304, 1256, 1238, 1159, 1032, 945, 812, 777, 619 cm^{-1}; MS (EI) M+1=186.

(±)-*cis*-3-Hydroxy-2-oxopiperidine-4-carboxylic Acid Ethyl Ester (2).- The hydrogenation of **1** (941 g; 5.08 mol) was carried out in 6.0 L of glacial acetic acid over 50 g of catalyst (10% rhodium on carbon) at 54 psi of hydrogen gas for 20 hrs. The catalyst was removed by vacuum filtration and the filtrate was concentrated *in vacuo*. The crude solid was purified by recrystallization (toluene) and the purified material was recovered by vacuum filtration. Drying overnight in the vacuum oven (54°) afforded 733.83 g of a crystalline solid. The filtrate from the recrystallization was likewise concentrated *in vacuo* and the crude concentrate recrystallized (toluene). This process could be repeated one more time to afford a total of 863.28 g (91%) of crystalline material, mp. 117-125°, lit.[6] 122-123°; ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.84 (s, 1H),4.19 (m, 3H), 4.10 (s, 1H), 3.43 (m, 1H), 3.31 (m, 1H), 3.23 (q, 1H, 5.2 Hz), 2.15 (m, 2H), 1.27 (t, 3H, 7.2 Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ 173.36, 171.57, 67.52, 60.98, 43.67, 39.67, 22.82, 14.16; IR (KBr): 3327, 3208, 1734, 1672, 1182 cm^{-1}; MS (EI) M+1=188.

(±)-*cis*-4-Hydroxymethylpiperidin-3-ol (3).- To a stirred commercially available (Aldrich) solution (800 mL) of lithium tetrahydroaluminate in tetrahydrofuran (1.0 M; 0.80 mol) under a slight positive pressure of argon and cooled to 13° with an ice-water bath was added 40.0 g (0.214 mol) of the solid **2** in portions. It should be noted here that reducing metal hydrides react explosively with peroxides that are commonly found in ether solvents. Only fresh tetrahydrofuran free of these peroxides should be used in combination with lithium tetrahydroaluminate. The careful addition caused the reaction temperature to rise to 35° as hydrogen gas was liberated. The vigorously stirred reaction mixture was then brought to reflux for 48 hrs. The reaction mixture was cooled to 5° with an ice-water bath. The mixture was quenched using the traditional procedure.[11] Water (30 mL) was added dropwise with vigorous stirring. Aqueous sodium hydroxide (30 mL; 15% by weight) was then added dropwise followed by addition of 90 mL of water. With continual stirring excess anhydrous potassium carbonate was added followed by vacuum filtration of the mixture. The solids were washed with 500 mL of hot tetrahydrofuran followed by additional ambient tetrahydrofuran (1.5 L). The filtrate was concentrated *in vacuo* and the solid was dried under high vacuum (23°) to afford 22.83 g (81%) of a white powder, mp. 123-126.5°, lit.[6] 126-127°. The bulk of the product was carried on to the next step without further purification. A small portion (0.60 g) was recrystallized (ethyl acetate) to give 0.57 g of a white crystalline solid used for characterization, mp. 129-130°; ^{1}H NMR (400 MHz; DMSO): δ 3.78 (broad s, 3H), 3.62 (s, 1H), 3.42 (m, 1H), 3.23 (s, 1H), 2.80 (m, 2H), 2.50 (m, 1H), 2.37 (m, 1H), 1.54 (m, 1H), 1.34 (m, 2H); ^{13}C NMR (100 MHz; DMSO): δ 64.72, 63.59, 52.87, 45.91, 43.16, 24.88,; IR (KBr): 3368, 3375, 3061, 2951, 2920, 2893, 2859, 2822, 2718, 2585, 1441, 1370, 1101, 1051, 1028, 988, 856 cm^{-1}; MS (EI) M+1=132.

(±)-*cis*-3-Hydroxy-4-hydroxymethylpiperidine-1-carboxylic Acid Benzyl Ester.-To a stirred solution of 272.7 g (2.079 mol) of **3** in 2.5 L of saturated aqueous sodium bicarbonate was added a solution of 509.1 g (2.043 mol) of N-(benzyloxycarbonyloxy)succinimide (Aldrich) in 1.4 L of tetrahydrofuran. The biphasic reaction mixture was stirred vigorously for 18 hrs. The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 1 L). The combined organic phases were dried (K_2CO_3) and concentrated to afford 546.2 g of a brown viscous glass which was used in the next step without further purification; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.34 (m, 5H), 5.14 (s, 2H), 4.24 (m, 2H), 4.08 (s, 1H), 3.75 (m, 2H), 2.94 (d, 1H, *J* = 13.6 Hz), 2.83 (t, 1H, *J* = 13.2 Hz), 2.20 (broad s, 3H; disappears with D_2O wash), 1.83 (ddd, 1H), 1.70 (m, 1H), 1.43 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 136.61, 128.47, 128.45, 127.99, 127.82, 67.26, 65.14, 50.46, 43.97, 41.28, 30.31, 22.37; IR ($CDCl_3$): 3445, 3013, 2949, 2904, 1688, 1472, 1437, 1287, 1236, 1125, 698 cm^{-1}; MS (EI) M+1=266.

(±)-*cis*-3-Hydroxy-4-(toluene-4-sulfonyloxymethyl)piperidine-1-carboxylic Acid Benzyl Ester (4).- To a stirred solution of 542 g of (±)-*cis*-3-hydroxy-4-hydroxymethylpiperidine-1-carboxylic acid benzyl ester (2.04 mol) in 1.0 L of anhydrous pyridine cooled to -15° was added 391.8 g (2.035 mol) of *p*-toluenesulfonyl chloride. The reaction mixture was stirred for 1 hr and was quenched slowly with 1750 mL of 6 N hydrochloric acid while maintaining the temperature between 5° and 30°. Dichloromethane (800 mL) was next added and the biphasic mixture was stirred vigorously for

several hours. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 1.5 L). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford an off-white oily solid. Trituration with pentane caused complete solidification of the crude solid. The solid was dissolved in 2.8 L of hot ethyl acetate and this solution reconcentrated to an oil, but not to dryness. Pentane was then added and the two-layered mixture was scratched vigorously with a glass rod until the entire oily (bottom) layer had formed a tan solid. The solid was collected by vacuum filtration and was dried under vacuum overnight to afford 823.44 g (97%) of the desired product ; mp. 67-73°; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.78 (d, 2H, *J* = 8.4 Hz), 7.33 (m, 7H), 5.10 (s, 2H), 4.23 (m, 2H), 4.09 (t, 1H, *J* = 8.0 Hz), 3.89 (m, 2H), 2.85 (m, 1H), 2.75 (m, 1H), 2.44 (s, 3H), 2.26 (s, 1H), 1.94 (m, 1H), 1.52 (ddd, 1H), 1.41 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 144.87, 136.49, 132.74, 129.86, 129.76, 128.57, 128.46, 128.00, 127.84, 71.13, 67.28, 63.79, 50.04, 43.49, 39.78, 22.04, 21.64; IR (KBr): 3461, 2924, 1684, 1352, 1175, 961, 554 cm^{-1}; MS (EI) M+1=420.

Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34; S, 7.64

Found: C, 60.03; H, 5.89; N, 3.24; S, 7.51

(±)-*exo*-1-Azabicyclo[2.2.1]heptan-3-ol (5).- The hydrogenolysis of **4** (72.38 g; 0.1726 mol) was carried out in 1.0 L of absolute ethanol over 5 g of catalyst (20% palladium on carbon) at 50 psi of hydrogen gas for 3.33 hrs. The catalyst was removed by vacuum filtration and to the filtrate was added 21.80 g (0.2595 mol) of sodium bicarbonate. The stirred mixture was brought to 50-60° for 5 hrs and the solvent was removed *in vacuo*. The crude residue was dissolved in saturated aqueous potassium carbonate. Continuous chloroform extraction for 18 hrs using a liquid-liquid extractor apparatus followed by drying the organic phase (K_2CO_3), concentration *in vacuo*, and drying under high vacuum (23°) afforded 19.03 g (97%) of a white powder, mp. 123.5-135°, lit.[6] 128-129°; ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.45 (broad s, 1H), 3.62 (d, 1H, *J* = 5.8 Hz), 2.73 (m, 3H), 2.51 (d, 1H, *J* = 12.8 Hz), 2.41 (d, 1H, *J* = 4.8 Hz), 2.26 (m, 2H),1.57 (m, 1H), 0.97 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 73.37, 65.32, 56.51, 53.12, 44.47, 25.40; IR (KBr): 3098, 2885, 1684, 1349, 1114, 1023, 976, 828 cm^{-1}; MS (CI) M+1=114. Sublimation of a small portion of this product afforded clear prisms, mp. 130-130.5°. The bulk of the material was carried on to resolution of the enantiomers *via* fractional crystallization with tartaric acid by an established procedure[10] and needed no further purification.

REFERENCES

1. J. Saunders, A. M. MacLeod, K. Merchant, G. A. Showell, R. J. Snow, L. J. Street and R. Baker, *Chem. Commun.*, 1618 (**1988**).

2. C. J. Swain, R. Baker, C. Kneen, J. Moseley, J. Saunders, E. M. Seward, G. Stevenson, M. Beer, J. Stanton and K. Watling, *J. Med. Chem.*, **34**, 140 (1991).

3. B. S. Orlek, F. Cassidy, M. S. G. Clark, R. E. Faulkner, E. J. Collings, J. Hawkins and G. J. Riley, *Bioorg. & Med. Chem. Lett.*, **4**, 1411 (1994).

4. H. Tecle, D. J. Lauffer, R. E. Davis, T. Mirzadegan, D. W. Moreland, R. D. Schwarz, A. J. Thomas, C. Raby, D. Eubanks, M. R. Brann and J. C. Jaen, *ibid.*, **5**, 637 (1995).

5. J. Jaen, S. Barrett, M. Brann, M. Callahan, R. Davis, P. Doyle, D. Eubanks, D. Lauffer, L. Lauffer, W. Lipinski, D. Moreland, C. Nelson, C. Raby, R. Schwarz, C. Spencer and H. Tecle, *Life Sciences*, **55**, 845 (1995).

6. D. O. Spry and H. S. Aaron, *J. Org. Chem.*, **34**, 3674 (1969).

7. K. Hasse and A. Wieland, *Chem. Ber.*, **93**, 1686 (1960).

8. O. Mitsunobu, *Synthesis*, 1 (**1981**). Hughes [D. L. Hughes, *Org. Prep. Proced. Int.*, **28**, 127 (1996)] has written a recent review of the progress in the Mitsunobu reaction.

9. R. C. Bernotas and R. V. Cube, *Tetrahedron Lett.*, **32**, 161 (1991).

10. J. Boelsterli, U. Eggnauer, E. Pombo-Villar, H. Weber, M. Walkinshaw and R. O. Gould, *Helv. Chim. Acta*, **70**, 1065 (1987).

11. V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

****

TETRAHYDROFURAN RING-OPENING WITH ACID ANHYDRIDES CATALYZED BY SAMARIUM TRIIODIDE

Submitted by (06/05/96)

Weiliang Bao, Taokai Ying, Yongmin Zhang* and Mingxin Yu

Department of Chemistry, Hangzhou University
Hangzhou, Zhejiang 310028, P. R. CHINA

The application of lanthanide compounds to organic synthesis has recently emerged as a valuable synthetic method.[1] Some lanthanide compounds such as $CeCl_3$ and SmI_2 have gained much attention and have become versatile reagents in organic synthesis.[2] However, liftte attention has been paid to the use of samarium(III) compounds. We reported that samarium triiodide catalyzes the formation of dithioacetals and dithioketals[3] and carbon-carbon double bonds between α-halo ketones and aldehydes.[4] More recently we have also found that tetrahydrofuran ring opening with acid chlorides is promoted by SmI_3.[5] We now report that tetrahydrofuran can be opened with cyclic and acyclic anhydrides in the presence of a catalytic amount of samarium triiodide under mild conditions to give the corresponding 4-iodobutyl esters.