Pergamon

Tetrahedron Letters 42 (2001) 3947–3949

TETRAHEDRON LETTERS

A short and efficient synthesis of enantiopure (+)-*N*-Boc-7-azabicyclo[2.2.1]heptan-2-one utilizing an asymmetric desymmetrization protocol: formal total synthesis of (−)-epibatidine

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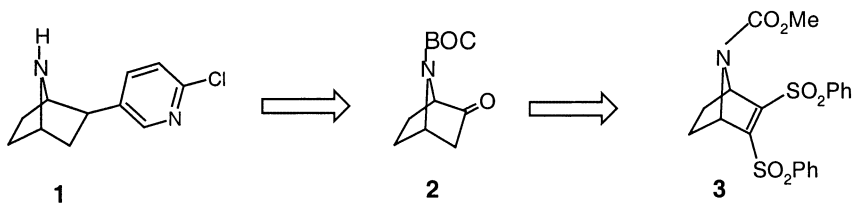
Received 8 February 2001; revised 4 April 2001; accepted 10 April 2001

Abstract—A short and efficient synthesis of optically pure (+)-*N*-Boc-azabicyclo[2.2.1]hept-2-one (**2**), a precursor in the synthesis of natural (−)-epibatidine (**1**), is reported by the asymmetric desymmetrization of *meso*-*N*-methoxycarbonyl-2,3-bis(phenylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (**3**). © 2001 Elsevier Science Ltd. All rights reserved.

Methodologies concerned with the construction of the 7-azabicyclo[2.2.1]heptane skeleton have witnessed a strong revival,[1] since the isolation of epibatidine (**1**) by Daly et al.[2] in 1992 from the extracts of the skin of an Ecuadorian poisonous frog *Epipedobates tricolor* and evaluation of its remarkable analgesic (non-opiod, 200–500 times more potent than morphine) activity, as well as its high affinity for the nicotinic receptor.[3] Although approximately 50 syntheses of racemic **1** have appeared,[4] after Broka's first contribution,[5] very few syntheses which satisfy diastereo- and enantiocontrolled construction of optically active epibatidine are known.[6] Fletcher's[7] approach of synthesizing natural non-racemic (−)-epibatidine involving (+)-*N*-Boc-7-azabicyclo[2.2.1]heptan-2-one (**2**) has aroused the attention of many groups for the synthesis of **2** in optically active form. However, most of these approaches[8] have involved multiple steps resulting in overall poor yields. Owing to our general interest in the construction of X-azabicyclo[*m*.2.1]alkanes[9] and epibatidine[10a,b] and its analogs,[10c] in particular, we were interested in developing an efficient and short synthetic route to **2**, and report herein the synthesis of enantiopure **2** by the enantiotopic discrimination of *meso*-*N*-methoxycarbonyl-2,3-bis(phenylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (**3**, Scheme 1) employing the protocol reported by De Lucchi et al.[11]

The precursor **3** was readily obtained (overall yield 43%) by the cycloaddition of ethynyl phenyl sulfone to *N*-methoxycarbonyl pyrrole, followed by the introduction of the second phenyl sulfone group onto the cycloadduct via β-metallation utilizing the procedure reported in the literature.[12]

The desymmetrization of **3** (0.35 mmol) was carried out by stirring with an equivalent amount of the disodium salt of **4** (prepared by treating **4** with NaH in THF) in



1 **2** **3**

Scheme 1.

Keywords: asymmetric desymmetrization; epibatidine; 7-azabicyclo[2.2.1]heptane.
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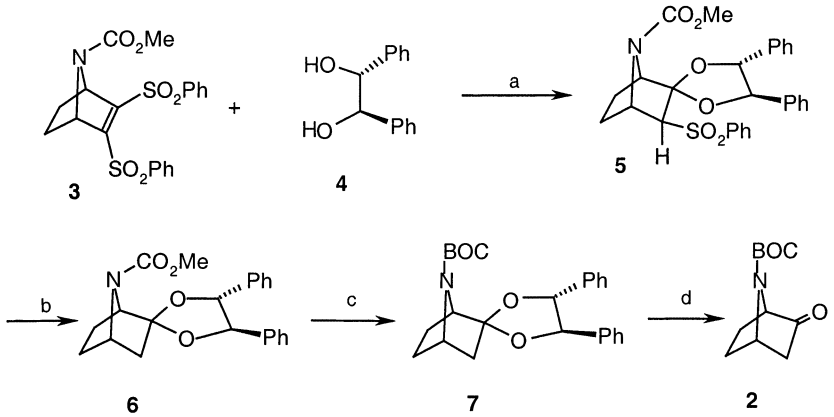
PII: S0040-4039(01)00616-5



Scheme 2. *Reagents and conditions*: (a) NaH (2.2 equiv.), THF, 0°C to rt, 2.5 h, 85%; (b) Na/Hg 6%, $NaH_2PO_4{\cdot}H_2O$, 0°C, 3 h, 95%; (c) (i) TMSCl, NaI, CH_3CN, 15 h, rt, (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 20 h, rt, 95% (two steps); (d) Pd/C, H_2, 55 psi, EtOH:EtOAc, 10 h, 90%.

THF at 0°C for about 2.5 h (Scheme 2). After allowing the reaction mixture to reach rt, it was quenched by the addition of MeOH. The crude ^1H NMR spectrum of the desymmetrized product displayed only one signal for H-3 at δ 3.65 (singlet), indicating it to be a single diastereomer, which was further confirmed by HPLC analysis (Merck, Purospher® RP-18e, 4×250 mm, CH_3CN:H_2O (3:2) isocratic, flow rate, 1 mL/min, retention time 3.56 min). Silica-gel column purification of the crude mixture gave **5** as a white fluffy solid, mp 188–189°C in 85% yield, fully characterized by ^1H and ^{13}C NMR and mass spectral analysis.[13] The stereochemistry of H-3 in **5** was established to be *endo* because we observed no coupling with the adjacent bridgehead H-4 in the ^1H NMR spectrum. It is known[9b] that no coupling is observed between bridgehead protons and adjacent *endo*-hydrogens in the 7-azabicyclo[2.2.1]alkane skeleton due to the dihedral angle of 90° between them.

Removal of the chiral acetal moiety from **5** proved somewhat troublesome. Reaction with many acidic reagents,[14] including harsh reaction conditions, such as boiling with conc. HCl, was unsuccessful. The most probable reason for the unexpected stability of this chiral acetal moiety could be either due to the high steric hindrance or long-range intramolecular hydrogen bonding after protonation. Our attempt to cleave the acetal moiety after reductive elimination of the phenyl sulfonyl group, using Na–Hg amalgam as the reagent,[15] was also unsuccessful. Reaction of **6** with TMSI cleaved only the -*N*-CO_2Me but not the acetal moiety. Therefore, left without much viable alternative at this stage, the resultant free amine product was reprotected as the corresponding *N*-Boc derivative **7** and was then subjected to catalytic hydrogenation (Pd/C, 10%, 55 psi, 10 h) to provide ketone **2**, which was characterized by IR, ^1H and ^{13}C NMR and mass spectral analysis.[16] All the spectral data was found to be in excellent agreement with that reported in the literature. $\{[\alpha]_D^{25}$ +77.3 (*c* 0.6, $CHCl_3)\}$ lit.[8a] $\{[\alpha]_D^{22}$ +73.5 (*c* 1.00, $CHCl_3)\}$.[8]

In conclusion, we have developed a short and efficient route for the synthesis of highly enantiopure (+)-*N*-Boc-azabicyclo[2.2.1]heptan-2-one, a versatile precursor for the synthesis of (−)-epibatidine. Furthermore, application of the ketone **2** to the synthesis of optically active ferruginine is in progress and will be reported elsewhere.

Acknowledgements

The authors would like to thank the Department of Science and Technology, New Delhi, for financial support. S.K.T. thanks Dr. H. R. Sonawane for support and encouragement. R.S.S. thanks the CSIR, New Delhi, for the award of a Research Associateship.

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13. Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, $J=7.7$ Hz, 2H), 7.60–7.13 (m, 13H), 5.15 (bs, 1H), 4.78 (d, $J=3.7$ Hz, 1H), 4.56 (d, $J=8.8$ Hz, 1H), 4.30 (bs, 1H), 3.65 (s, 1H), 3.58 (s, 3H), 2.05 (m, 1H), 1.9–1.58 (2m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.67, 138.56, 135.99, 134.71, 133.49, 129.89, 129.07, 128.64, 128.43, 127.60, 125.98, 113.35, 86.37, 77.43, 63.69, 58.26, 52.52, 29.11, 21.94; MS: $m/z=364$ (M^+-SO_2Ph) (24%), 258 (16%), 180 (100%), 168 (68%), 140 (48%), 125 (24%); mp 188–189°C (uncorrected); $[\alpha]_D^{25}$ −88.40 (*c* 1.00, $CHCl_3$).
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16. Compound **2**: IR ($CHCl_3$): 1764, 1699 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.56 (t, $J=4.4$ Hz, 1H), 4.26 (d, $J=4.4$ Hz, 1H), 2.48 (dd, $J=17.1$ Hz, 4.9, 1H), 2.00 (m+d, $J=17.1$ Hz, 2+1H), 1.60 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.32, 155.06, 80.80, 63.95, 56.09, 45.21, 28.20, 27.56, 24.43. GC–MS: 196 (M^+-15), 183, 138, 127, 112, 83, 68; $[\alpha]_D^{rt}$ +77.3 (*c* 0.6, $CHCl_3$), Lit.[8a] $[\alpha]_D^{22}$ +73.5 (*c* 1.00, $CHCl_3$).