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Aza-Prins-Pinacol Approach to 7-Azabicyclo[2.2.1]heptanes: Syntheses of (±)-Epibatidine and (±)-Epiboxidine

Alan Armstrong,* Yunas Bhonoah, and Stephen E. Shanahan†

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, U.K.

A.Armstrong@imperial.ac.uk

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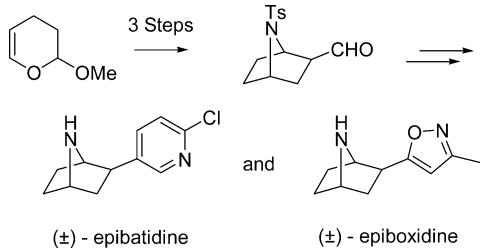
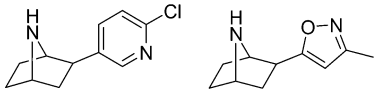


The syntheses of (±)-epibatidine and (±)-epiboxidine have been accomplished from commercial 2-methoxy-3,4-dihydro-2*H*-pyran. A recently developed aza-Prins-pinacol rearrangement was employed for the construction of the key 7-azabicyclo[2.2.1]heptane skeleton of these targets.

Introduction

Epibatidine **1** is a structurally unique alkaloid isolated from the skin of the Equadorian poison frog *Epipedobates tricolor*.[1]



epibatidine **1** epiboxidine **2**

It is a powerful analgesic, mediating its action at nicotinic cholinergic receptors[2] and has stimulated intense interest in the synthetic chemistry community.[3] The two enantiomers of the natural product are almost equipotent in their activities. However, the high toxicity of epibatidine precludes its therapeutic application.[4] Much effort has been invested in the design, synthesis, and biological screening of analogues;[5] notable strategies include variation of the heteroaromatic group[4,6] and movement of the ring nitrogen around the alicyclic skeleton.[7] These studies have identified epiboxidine **2**—a less potent but 20-fold less toxic analogue—as a more viable template for further development.[4] Compounds bearing substituents on the 7-azabicyclo[2.2.1]heptane skeleton were, until recently,[8] relatively unknown, predominantly due to a lack of robust methodologies for their preparation.

We recently reported[9] a novel stereocontrolled route toward substituted pyrrolidines via the aminative rearrangement of 2-alkoxydihydropyrans **3** (Scheme 1). The latter compounds are easily accessible via hetero-Diels−Alder methodologies. The product pyrrolidines **4** contain both an aldehyde and a latent N-sulfonyl iminium moiety and are potentially bifunctional electrophiles. An exploitation of this bifunctional nature was subsequently undertaken;[10] addition of vinyl Grignard reagents to the aldehyde **4** gave the desired allylic alcohols **5** as a mixture of diastereomers. Upon treatment with $SnCl_4$, these rearranged to give a single 7-azabicyclo[2.2.1]heptane **6** with the aldehyde

† Current address: Chemical Development, GlaxoSmithkline, Old Powder Mills, Tonbridge, TN11 9AN, UK.

(1) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478.

(2) Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, *45*, 563−569.

(3) (a) For reviews of epibatidine syntheses, see (i) Chen, Z. M.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179−1193. (ii) Olivo, H. F.; Hemenway, M. S. *Org. Prep. Proc. Int.* **2002**, *34*, 1−26. (b) For recent syntheses, see (i) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009−3012. (ii) Lee, C. L. K.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2965−2967. (iii) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516−5519.

(4) Badio, B.; Garraffo, H. M.; Plummer, C. V.; Padgett, W. L.; Daly, J. W. *Eur. J. Pharmacol.* **1997**, *321*, 189−194.

(5) For a review, see Carroll, F. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1889−1896.

(6) For recent examples, see (a) Che, D. Q.; Wegge, T.; Stubbs, M. T.; Seitz, G.; Meier, H.; Methfessel, C. *J. Med. Chem.* **2001**, *44*, 47−57. (b) Seerden, J.-P. G.; Tulp, M. T. M.; Scheeren, H. W.; Kruse, C. G. *Bioorg. Med. Chem.* **1998**, *6*, 2103−2110.

(7) (a) Cox, C. D.; Malpass, J. R. *Tetrahedron* **1999**, *55*, 11879−11888. (b) Cox, C. D.; Malpass, J. R.; Gordon, J.; Rosen, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2372−2379. (c) Malpass, J. R.; Cox, C. D. *Tetrahedron Lett.* **1999**, *40*, 1419−1422.

(8) Wei, Z. L.; Xiao, Y. X.; George, C.; Kellar, K. J.; Kozikowski, A. P. *Org. Biomol. Chem.* **2003**, *1*, 3878−3881.

(9) Armstrong, A.; Cumming, G. R.; Pike, K. *Chem. Commun.* **2004**, 812−813.

(10) Armstrong, A.; Shanahan, S. E. *Org. Lett.* **2005**, *7*, 1335−1338.

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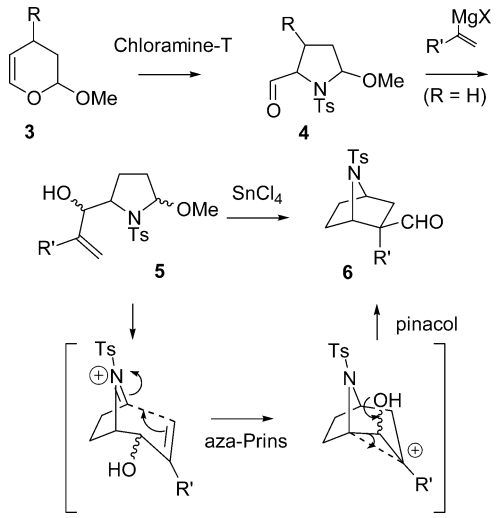
SCHEME 1. Aza-Prins-Pinacol Rearrangement



functionality exclusively in the exo orientation. We proposed an aza-Prins-pinacol mechanism to account for the remarkable diastereoselectivity of this rearrangement and the lack of dependence on the configuration of the precursor allylic alcohols **5**.[10]

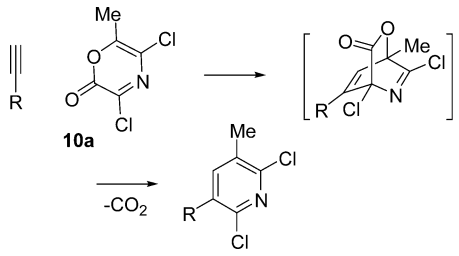
We envisaged that a concise synthesis of the bicyclic alkaloid (±)-epibatidine and its analogue (±)-epiboxidine could be achieved using this new approach toward 7-azabicyclo[2.2.1]-heptanes. Herein we describe the successful realization of these goals.

Results and Discussion

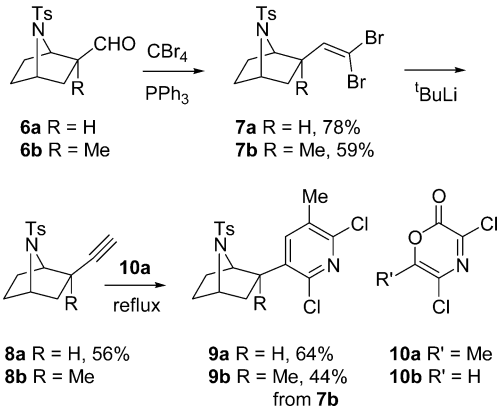
De novo synthesis of the chloropyridine moiety of epibatidine is relatively rare; most syntheses of the natural product generally attach a fully formed pyridine onto the bicyclic skeleton. Our route to 7-azabicyclo[2.2.1]heptanes generates a valuable aldehyde moiety on the azabicycle (Scheme 1), and we anticipated that this functionality could be elaborated into the desired chloropyridine. The initial strategy focused on the [4+2] cycloaddition of oxazinones to acetylenes as the methodological basis for the pyridine construction; the initial cycloadduct formed during such reactions spontaneously lose CO_2 to afford pyridines. Interestingly, Hoornaert and co-workers[11,12] have shown that good levels of regiocontrol for pyridine formation are obtained with alkyl-substituted terminal acetylenes reacting with dichloro-oxazinone **10a** under thermal conditions (Scheme 2). While the origin of such regioselectivity was not rationalized, we anticipated that this methodology would set up the correct regioisomeric pyridine for a potential synthesis of epibatidine.

For initial studies, we selected the methyl-substituted oxazinone **10a**[13] since this is most well-precedented in such cycloadditions. The requisite acetylene dienophiles **8** were readily prepared from the aldehyde precursors **6**[10] by the two-step Corey−Fuchs methodology via the corresponding 1,1-dibromoolefins (Scheme 3). Cycloaddition of acetylene **8a** with oxazinone **10a** in refluxing toluene proceeded smoothly to afford the desired pyridine regioselectively. With methyl-substituted acetylene **8b**, the reaction was more sluggish and gave the

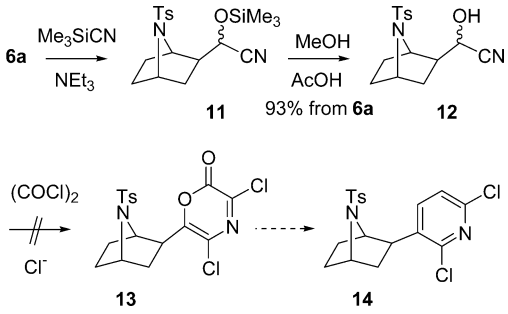
SCHEME 2. Pyridine Formation by [4+2] Cycloaddition



SCHEME 3. Oxazinone Cycloaddition



SCHEME 4



corresponding pyridine in slightly lower yield. This approach represents the first regioselective de novo synthesis of chloropyridines on 7-azabicyclo[2.2.1]heptanes.

Having established the validity of the cycloaddition strategy, we set about preparing the methyl-unsubstituted oxazinone **10b** required for the synthesis of epibatidine. Disappointingly, this could not be achieved; the cyanohydrin precursor, glycolonitrile, proved very difficult to dry and failed to give any oxazinone product under the conditions of Hoornaert.[13] A slight modification to the current strategy was thus made; it was envisaged that interchanging the reactive functionalities of the two cycloaddition partners would circumvent the above issue. Furthermore, only one possible regiochemical outcome **14** would be possible from reaction of **13** with ethyne as the dienophile partner. The required precursor cyanohydrin **12** (Scheme 4) was prepared in two steps from aldehyde **6a** in excellent yield as a mixture of two diastereomers. Unfortunately, subjection of **12** to oxazinone-forming conditions failed to provide any of the desired product **13**.[14]

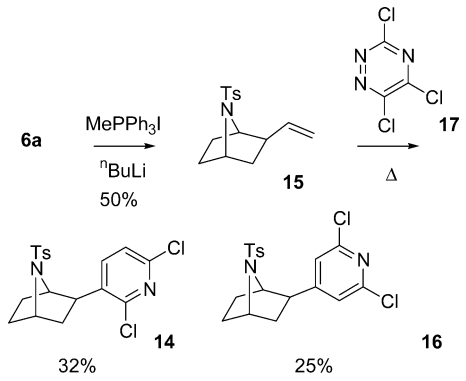
(11) Meerpoel, L.; Hoornaert, G. *Tetrahedron Lett.* **1989**, *30*, 3183−3186.

(12) Meerpoel, L.; Toppet, S. M.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **1991**, *47*, 10065−10076.

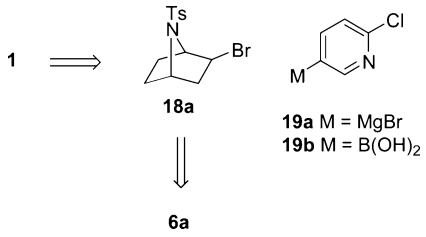
(13) Meerpoel, L.; Hoornaert, G. *Synthesis* **1990**, 905−908.

(14) Hoornaert[13] has observed that significantly bulky cyanohydrins such as that derived from pivaldehyde failed to cyclise to the desired oxazinones. The bulkiness of the *N*-Ts-azabicycle in our case may account for the failure of the reaction.

SCHEME 5. Triazine Cycloaddition



SCHEME 6. Cross-Coupling Strategy toward Epibatidine

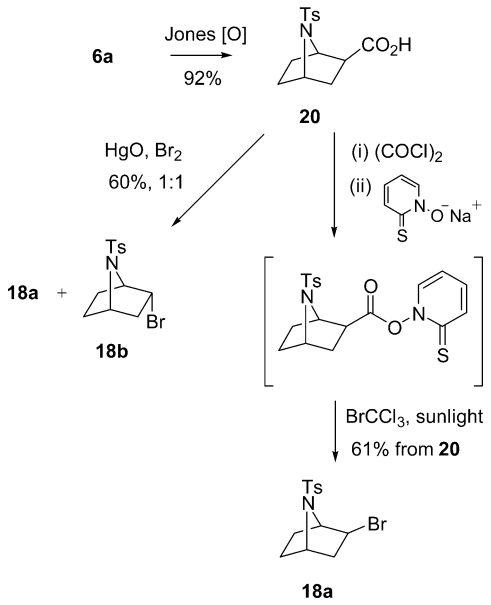


The partial success with the oxazinone cycloaddition chemistry prompted us to examine alternative aza-dienes as cycloaddition partners. 1,2,4-Triazines substituted with electron-withdrawing groups are reported to react with enamines and enol ethers to provide pyridines.[15] More interestingly, trichloro-1,2,4-triazine **17** has been shown to undergo [4+2] cycloaddition to unactivated alkenes with concomitant loss of nitrogen followed by a [1,5]-sigmatropic hydrogen shift and loss of HCl to afford chlorinated pyridines.[16] With this precedent, we decided to attempt such a cycloaddition with our bicyclic system. The required terminal alkene **15** was easily prepared by a standard Wittig reaction in 50% yield as a single diastereomer (Scheme 5). Trichlorotriazine **17** was available in two steps from commercial 6-azauracil.[17] Under thermal conditions, the reaction of **15** with **17** gave pyridine products **14** and **16** in moderate yields but poor regioselectivities. An attempted reaction under microwave conditions proved unsuccessful.

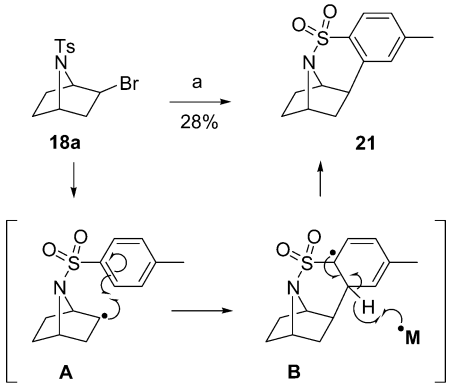
The poor regioselectivity and the anticipated difficulty in the selective removal of the extra chlorine atom from pyridine **14** led to the abandonment of this approach as a route to epibatidine. However, these two cycloaddition strategies do show promise in the synthesis of diverse pyridine analogues—a number of oxazinones[13] and triazines[15] are known and these could, in principle, provide a means of varying the heteroaromatic portion of the natural product.

The approaches described so far aimed to construct the pyridine system from the exo aldehyde functionality of azabicycle **6a**. Conceptually, a more attractive strategy may be to attach a fully formed pyridine directly onto the azabicycle—such an approach would, however, require deletion of the aldehyde carbon. Our revised plan is shown in Scheme 6. We anticipated that N-protected epibatidine could be accessed via a key sp^2-sp^3 cross-coupling between bicyclic bromide **18a** and a pyridyl species **19**. The area of cross-coupling of unactivated primary and secondary alkyl halides has seen some spectacular advances over the past few years;[18] several catalyst systems are now available which would effect these transformations. However, most of the methodologies to date employ relatively simple unfunctionalised alkyl halides. The required bromide **18a**, in turn, would be derived from aldehyde **6a**. Such a strategy would allow diversity to be installed not only on the bicyclic skeleton but also on the heteroaromatic mioety.

SCHEME 7. Bromodecarboxylation of Acid 20



SCHEME 8. Unexpected Intramolecular Cyclization of 18a



[a] Conditions: $Ni(COD)_2$ (4 mol %), bathophenanthroline (8 mol %), KO^{t}Bu, boronic acid **19b**, ^{s}BuOH.

Jones oxidation of aldehyde **6a** furnished the corresponding acid **20** in excellent yield (Scheme 7). Barton bromodecarboxy-

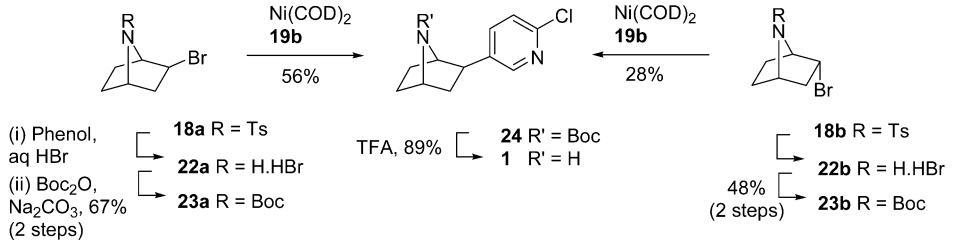
(15) (a) Boger, D. L. W. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press, Inc.: New York, 1987. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781−793.

(16) (a) Barlow, M. G.; Haszeldine, R. N.; Simpkin, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1245−1249. (b) Barlow, M. G.; Sibous, L.; Suliman, N. N. E.; Tipping, A. E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 519−524.

(17) (a) Dudfield, P. J.; Le, V. D.; Lindell, S. D.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2929−2936. (b) Loving, B. A.; Snyder, C. E.; Whittier, G. L.; Fountain, K. R. *J. Heterocycl. Chem.* **1971**, *8*, 1095.

(18) (a) For nickel-catalyzed processes, see (i) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532. (ii) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341. (iii) Gonzalez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360−5361. (b) For iron-catalyzed processes, see (i) Furstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863. (ii) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, B. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687. (iii) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297−1299. (c) For cobalt-catalyzed processes, see (i) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886−1889. (ii) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374−5375.

SCHEME 9. Ni(0)-Catalyzed Suzuki Cross-Coupling



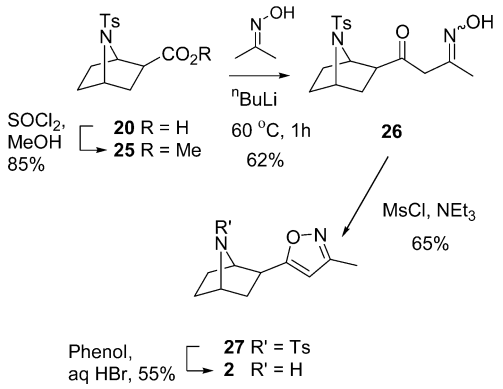
lation[19] via the thiohydroxamate ester gave the desired bromide **18a** in good yield as a single exo diastereomer. It was found that exposure of the ester to strong sunlight was crucial for the success of the reaction; irradiation with a tungsten lamp only led to poor yields of the desired product. These highly specific, restrictive conditions led us to seek alternative, more general methods to effect the bromodecarboxylation. The Cristol−Firth modification[20] of the Hunsdiecker reaction employing HgO proved to be the most effective, albeit giving a 1:1 mixture of separable diastereomers **18**.

With the bromide **18a** in hand, our attention turned to the critical cross-coupling reaction. Several methodologies were evaluated but were unsuccessful.[21] Interestingly, an attempt with Fu's Ni(0)-catalyzed Suzuki coupling[18a(ii)] employing pyridylboronic acid **19b**[22] led to the isolation of the tricycle **21**. This result was quite intriguing, and a possible mechanistic scenario is shown in Scheme 8; the putative radical intermediate **A**[23] can undergo a 6-endo-trig cyclization onto the tosyl group to afford intermediate **B**. Subsequent hydrogen abstraction by some radical species, **M**, in the reaction mixture affords the observed product. Interestingly, such an intramolecular cyclization does not occur during the Barton bromodecarboxylation described above, where **A** would also be an intermediate, presumably due to rapid quenching by the bromide source.

The interference of the tosyl group in the Suzuki reaction prompted us to modify our strategy with the inclusion of an extra deprotection/reprotection sequence; we anticipated that the N-Boc bromide **23a** (Scheme 9) should successfully react in the cross-coupling. The removal of the tosyl group was achieved using aq HBr and phenol; the deprotected amine was isolated as its hydrobromide salt with the bromine moiety of the azabicycle intact. Subsequent Boc-protection gave the key bromide **23a** in good yield. With the latter compound in hand, a second attempt at the cross-coupling with $Ni(COD)_2$ was made. Gratifyingly, the desired coupled product **24** was isolated in good yield as a single diastereomer; no trace of the alternative endo isomer was observed.

The postulated intermediacy of radical species in the cross-coupling reaction led us to progress the endo tosylbromide **18b** through the same sequence of steps as the exo counterpart (Scheme 9). Coupling with chloropyridylboronic acid **19b** under Ni(0) catalysis furnished exclusively the exo product **24**.

SCHEME 10. Synthesis of (±)-Epiboxidine



However, we found that the endo-Boc-bromide **23b** was more sluggish and only low yields of the desired product could be isolated; a significant amount of the starting bromide was recovered unchanged. Increasing the catalyst loading and reaction temperatures did not improve the yields. Nevertheless, we have shown that the cross-coupling methodology could be applied to complex secondary bromides and pyridylboronic acids and gives only the exo-coupled products on azabicyclic bromides such as **23**.[24] The isolation of the intramolecular cyclization product **21** lends further support to a radical-based mechanism[23] operating in this Suzuki reaction, although the participation of the metal in this cyclization cannot be completely excluded. The final step in our synthesis entailed the deprotection of N-Boc-epibatidine **24**. This was achieved in good yield with trifluoroacetic acid. The structure of synthetic (±)-epibatidine was confirmed by comparison to reported literature data (^{1}H, ^{13}C NMR).[25]

With the epibatidine synthesis completed, attention turned to our second target, (±)-epiboxidine. We planned to install the isoxazole moiety by the classical acetoxime dianion addition to a bicyclic ester followed by cyclization.[4,26] The ester precursor was anticipated to be accessible via acid **20** employed in our epibatidine route.

A standard esterification with thionyl chloride and methanol gave the desired ester **25** in good yield (Scheme 10). The construction of the isoxazole proved problematic; indeed, this transformation is reported to be generally low-yielding.[26] The direct dianion addition followed by in situ cyclization with HCl failed to give significant amounts of the isoxazole product. We

(19) Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675−684.

(20) Cristol, S.; Firth, J. W. *J. Org. Chem.* **1961**, *26*, 280.

(21) Attempted systems include $CoCl_2$[18c(i)], $FeCl_3$[18b(ii)], $Fe(acac)_3$[18b(i),(iii)], and NiI_2[18a(iii)].

(22) This was initially prepared according to Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885−2890. **19b** is now commercially available.

(23) (a) The exo selectivity of the Suzuki reaction with both endo and exo bromonorbornane has led Fu et al.[18a] to postulate the involvement of radicals. (b) For similar radical cyclisation on simpler N-tosylpiperidines, see Kohler, J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 631−634.

(24) For a recent application of this Suzuki coupling to other azabicyclic systems, see Malpass, J. R.; Handa, S.; White, R. *Org. Lett.* **2005**, *7*, 2759−2762.

(25) Zhang, C. M.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189−7191.

(26) (a) Pandey, G.; Sahoo, A. K.; Gadre, S. R.; Bagul, T. D.; Phalgune, U. D. *J. Org. Chem.* **1999**, *64*, 4990−4994.(b) Elliott, R. L.; Kopecka, H.; Lin, N. H.; He, Y.; Garvey, D. S. *Synthesis* **1995**, 772−774. (c) Avenoza, A.; Busto, J. H.; Cativiela, C.; Dordal, A.; Frigola, J.; Peregrina, J. M. *Tetrahedron* **2002**, *58*, 4505−4511.

found, however, that a two-step sequence with isolation of the intermediate *β*-keto oxime **26** followed by MsCl-mediated cyclization[26b] led to good yields of the desired heterocycle **27**; heating the reaction mixture following dianion addition proved crucial in obtaining reasonable yields of the oxime adducts. Subjection of compound **27** to tosyl deprotection conditions (aq HBr/phenol) led to the isolation of (±)-epiboxidine **2** with the isoxazole ring intact.

Conclusion

In summary, concise syntheses of (±)-epibatidine and its significant analogue (±)-epiboxidine have been achieved from commercial 2-methoxy-3,4-dihydro-2*H*-pyran. The approaches described feature the recently developed aza-Prins-pinacol rearrangement for the construction of the key 7-azabicyclo[2.2.1]-heptane systems. We have shown that the nickel(0)-catalyzed Suzuki coupling can be applied to relatively complex bicyclic bromides with complete exo selectivity. We have also demonstrated the first de novo synthesis of chloropyridines on these azabicycles using [4+2] cycloadditions. These methodologies would potentially allow the synthesis of epibatidine analogues with diversity installed on both the alicyclic skeleton, as well as the heteroaromatic fragment.

Experimental Section

(±)-*exo*-2-[(2′,6′-Dichloro-5′-methyl)-3-pyridyl]-2-methyl-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane (9b). The dibromoolefin **7b** (43 mg, 0.096 mmol) was dissolved in THF (2 mL) and the solution cooled to −78 °C. *tert*-Butyl lithium (0.17 mL, 1.7M in pentane, 0.30 mmol) was added, producing a yellow/green color. The reaction was stirred at −78 °C for 5 min, before raising the temperature to 0 °C for a further 5 min. The color was observed to change to orange. The reaction was quenched by addition of saturated aq NH_4Cl (10 mL). The mixture was extracted with diethyl ether (2 × 20 mL), and the combined ethereal fractions dried over Na_2SO_4. Filtration and evaporation of solvent in vacuo afforded the *acetylene* **8b** (26 mg) as a colorless oil which was used without further purification.

The acetylene **8b** (39 mg, 0.13 mmol) and oxazinone **10a**[13] (97 mg, 0.54 mmol) were dissolved in toluene (0.8 mL) and the mixture heated to reflux for 4 days. Solvent was removed in vacuo, and the crude residue subjected to flash column chromatography (3:1 hexane/Et_2O rising to 2:1). The desired *pyridine* **9b** (27 mg, 44% from **7b**) was isolated as a white crystalline solid: mp 211−212 °C; IR (neat) 2979, 2928, 1598, 1536 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.68 (d, J = 4.0 Hz, 1H), 4.12 (t, J = 5.0 Hz, 1H), 2.42 (s, 3H), 2.34 (ddd, J = 13.0, 5.0 and 2.1 Hz, 1H), 2.26 (s, 3H), 2.13−1.82 (m, 3H), 1.65 (d, J = 13.0 Hz, 1H), 1.57−1.47 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 146.5, 143.8, 141.1, 139.2, 137.1, 130.8, 129.6, 127.5, 65.2, 61.1, 47.4, 46.7, 29.3, 24.0, 22.7, 21.5, 18.9; MS (CI) *m*/*z* 425 (MH^+, 100%); HRMS calcd for $C_{20}H_{23}N_2O_2Cl_2S$ (MH^+) 425.0857; found, 425.0869.

(±)-*exo*-2-[(2′,6′-Dichloro-5′-methyl)-3-pyridyl]-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane (9a). The acetylene **8a** (23 mg, 0.084 mmol) and oxazinone **10a**[13] (60 mg, 0.33 mmol) were dissolved in toluene (0.7 mL) and the mixture heated to reflux for 24 h. The resulting mixture was concentrated in vacuo and subjected to flash column chromatography (3:1 petrol/Et_2O rising to 2:1). The desired *pyridine* **9a** (22 mg, 64%) was isolated as a white crystalline solid: mp 201−203 °C; IR ($CHCl_3$) 2984, 2958, 2927, 2881, 1597, 1544 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 4.35 (t, J = 4.0 Hz, 1H), 4.21 (d, J = 4.0 Hz, 1H), 3.16 (dd, J = 9.0 and 4.8 Hz, 1H), 2.43 (s, 3H), 2.23 (s, 3H), 2.07 (dd, J = 12.5 and 9.0 Hz, 1H), 1.91−1.78 (m, 2H), 1.73−1.66 (m, 1H), 1.63−1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 146.1, 143.9, 139.2, 137.4, 137.3, 131.6, 129.7, 127.5, 63.5, 59.5, 43.8, 40.1, 29.5, 29.2, 21.5, 18.9; MS (CI) *m*/*z* 411 (MH^+, 100%); HRMS calcd for $C_{19}H_{21}{}^{35}Cl_2N_2O_2S$ (MH^+), 411.0701; found, 411.0712.

(±)-*exo*-2-(2,6-Dichloro-pyridin-3-yl)-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane (14) and (±)-*exo*-2-(2,6-Dichloro-pyridin-4-yl)-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane (16). A solution of the alkene **15** (50 mg, 0.181 mmol) and 3,5,6-trichloro-1,2,4-triazine **17**[17] (166 mg, 0.903 mmol, 5 equiv) in toluene (1 mL) in a sealed tube was heated to 120 °C for 14 days. The reaction mixture was then evaporated under reduced pressure and the residual brown oil taken up in Et_2O (100 mL). The suspension was filtered and the filtrate evaporated under reduced pressure. Flash chromatography (1:9 EtOAc/petrol rising to 2:8) afforded the following products after trituration with petrol (containing ∼1% dichloromethane).

The more-polar regioisomer **16** (18 mg, 25%) as a white solid: mp 174 °C; IR (nujol) 1533, 1323, 1056, 880, 807, 673, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.00 (s, 2H), 4.39 (t, J = 4.5 Hz, 1H), 4.01 (d, J = 4.0 Hz, 1H), 2.77 (dd, J = 9.0 and 5.0 Hz, 1H), 2.44 (s, 3H), 2.10−2.07 (m, 2H), 1.97 (dd, J = 12.5 and 9.0 Hz, 1H), 1.80−1.75 (m, 1H), 1.59−1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 150.5, 144.2, 137.0, 129.9, 127.4, 121.5, 64.3, 59.2, 47.4, 40.4, 29.8, 29.4, 21.6; MS (CI) *m*/*z* 397 (MH^+, 100%); HRMS calcd for $C_{18}H_{19}N_2Cl_2O_2S$ (MH^+), 397.0544; found 397.0551.

The less-polar regioisomer **14** (23 mg, 32%) as a white solid: mp 176 °C; IR (film) 1546, 1429, 1329, 1218,1053, 818, 674, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 1H), 4.31 (t, J = 4.0 Hz, 1H), 4.26 (d, J = 4.0 Hz, 1H), 3.19 (dd, J = 9.0 and 5.0 Hz, 1H), 2.44 (s, 3H), 2.07 (dd, J = 12.0 and 9.0 Hz, 1H), 1.78−1.67 (m, 3H), 1.63−1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.3, 147.8, 144.2, 138.5, 137.4, 137.0, 129.7, 127.6, 123.3, 63.2, 59.4, 44.0, 40.1, 29.3, 28.9, 21.6; MS (CI) *m*/*z* 397 (MH^+, 100%); HRMS calcd for $C_{18}H_{19}N_2Cl_2O_2S$ (MH^+), 397.0544; found, 397.0548.

(±)-*exo*-2-Bromo-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]-heptane (18a). The acid **20** (104 mg, 0.35 mmol) was suspended in dichloromethane (3 mL) and treated with oxalyl chloride (0.30 mL, 3.50 mmol). The mixture was heated to reflux until all the acid had dissolved (*c*. 20 min). Volatiles were removed in vacuo to afford a crude foam. The reaction flask was wrapped in aluminum foil and in the absence of direct lighting were added bromotrichloromethane (3 mL) and the sodium salt of 2-mercaptopyridine-1-oxide (52 mg, 0.35 mmol). The mixture was heated to 90 °C for 1 h, then allowed to cool to room temperature (rt). The aluminum foil was removed and the strongly yellow-green-colored solution exposed to sunlight for 5 min. The mixture decolorized to straw yellow and gas evolution was observed. The resulting solution was concentrated in vacuo and purified by flash column chromatography (3:1 petrol/Et_2O rising to 2:1) to give bromide **18a** (70 mg, 61%) as a white powder: mp 110−113 °C; IR (film) 2984, 2956, 2923, 2881, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.26 (t, J = 4.5 Hz, 1H), 4.23 (d, J = 5.0 Hz, 1H), 3.92 (dd, J = 7.5 and 3.0 Hz, 1H), 2.44 (s, 3H), 2.28−2.23 (m, 1H), 2.17−1.92 (m, 3H), 1.50−1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.4, 129.5, 127.6, 67.0, 59.3, 48.2, 44.4, 28.8, 28.0, 21.6; MS (CI) *m*/*z* 349, 332 (MH^+), 250; HRMS calcd for $C_{13}H_{17}NSO_2{}^{81}Br$ (MH^+), 332.0143; found, 332.0150.

(±)-*exo*-2-Bromo-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]-heptane (18a) and (±)-*endo*-2-Bromo-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane (18b). A suspension of the bicyclic acid **20** (400 mg, 1.36 mmol) and HgO (294 mg, 1.36 mmol, 1 equiv) in dibromomethane (10 mL) was heated to 90 °C. A solution of Br_2 (90 μL, 281 mg, 1.76 mmol, 1.3 equiv) in dibromomethane (1.5 mL) was then added dropwise over 10 min. Upon completion of addition, the reaction mixture was stirred at 90 °C for 2 h. The

heterogeneous solution was then cooled and filtered and the filtrate washed successively with 10% aq KI (50 mL) and brine and then dried (Na_2SO_4). Flash chromatography (3:1 petrol/Et_2O) afforded the following compounds.

Exo isomer **18a** (139 mg, 31%) as a white amorphous solid identical in all respects to that obtained using the Barton protocol above,

Endo isomer **18b** (138 mg, 31%) as a colorless oil: IR (nujol) 1329, 1149, 1093, 1041, 812, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 6.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.31−4.26 (m, 1H), 4.23 (t, J = 4.0 Hz, 1H), 4.13 (t, J = 4.0 Hz, 1H), 2.62−2.54 (m, 1H), 2.43 (s, 3H), 2.36−2.32 (m, 1H), 1.82−1.73 (m, 2H), 1.54−1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 137.2, 129.7, 127.5, 63.0, 60.1, 46.6, 41.6, 30.1, 24.8, 21.6; MS (CI) m/z 349 (MNH_4^+), 347 (MNH_4^+), 332 (MH^+), 330 (MH^+), 267; HRMS calcd for $C_{13}H_{17}NSO_2{}^{81}Br$ (MH^+), 332.0143; found, 332.0150.

(±)-4-Methyl-8-thia-9-aza-tetracyclo[8.4.0^{1,10}.0^{2,7}.0^{9,13}]tetradeca-2,4,6-triene-8,8-dioxide (21). According to the reported procedure,[18a(ii)] ^{s}BuOH (2 mL) was added to a mixture of $Ni(COD)_2$ (4.10 mg, 15.0 μmol, 4 mol %), bathophenanthroline (10.1 mg, 30.0 μmol, 8 mol %), 2-chloro-5-pyridylboronic acid **19b** (71.7 mg, 0.456 mmol, 1.2 equiv), and KO^{t}Bu (68.2 mg, 0.608 mmol, 1.6 equiv) under Ar. The mixture was stirred at rt for 10 min. To this was then added a solution of bicyclic bromide **18a** (124 mg, 0.38 mmol, 1.0 equiv) in ^{s}BuOH (1 mL) and the reaction stirred for 5 h at 60 °C. It was then passed through a plug of silica, washing with Et_2O. The filtrate was concentrated and purified by flash chromatography (3:1 petrol/Et_2O) to give tricycle **21** (32 mg, 28%) as a white amorphous solid: mp 110 °C; IR (nujol) 1600, 1318, 1168, 1136, 977, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 1H), 7.18 (br d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 4.31 (t, J = 5.0 Hz, 1H), 4.26 (d, J = 5.5 Hz, 1H), 2.96 (dd, J = 7.5 and 1.5 Hz, 1H), 2.36 (s, 3H), 2.15−2.04 (m, 2H), 2.01−1.92 (m, 1H), 1.86−1.81 (m, 1H), 1.61−1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 132.9, 128.9, 126.5, 126.0, 66.3, 60.2, 44.6, 38.8, 30.6, 27.8, 21.5; MS (CI) m/z 267 (MNH_4^+, 100%), 250 (MH^+), 191; HRMS calcd for $C_{13}H_{16}NO_2S$ (MH^+), 250.0902; found, 250.0906.

(±)-*exo*-2-(6-Chloro-pyridin-3-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylic acid *tert*-butyl Ester (24). Adapting the reported procedure,[18a(ii)] ^{s}BuOH (1 mL) was added to a mixture of $Ni(COD)_2$ (3 mg, 11.0 μmol, 10 mol %), bathophenanthroline (7 mg, 21.0 μmol, 20 mol %), 2-chloro-5-pyridylboronic acid **19b** (20 mg, 0.126 mmol, 1.2 equiv), and KO^{t}Bu (19 mg, 0.168 mmol, 1.6 equiv) under Ar. The mixture was stirred at rt for 10 min upon which a deep purple coloration was observed. To this solution was then added a solution of bicyclic bromide **23a** (29 mg, 0.105 mmol, 1.0 equiv) in ^{s}BuOH (2 mL) and the reaction stirred on at 60 °C. The mixture was then cooled and passed through a plug of silica, washing with Et_2O (50 mL). The filtrate was concentrated and purified by flash chromatography (3:1 petrol/Et_2O) to give the title compound (18 mg, 56%, 15% SM recovered) as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 4.37 (br s, 1H), 4.15 (br s, 1H), 2.85 (dd, J = 9.0 and 5.0 Hz, 1H), 1.99 (dd, J = 12.5 and 9.0 Hz, 1H), 1.82−1.77 (m, 3H), 1.55 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 149.4, 148.7, 140.1, 137.3, 124.1, 79.9, 62.0, 56.0, 44.9, 40.4, 29.7, 28.8, 28.3; MS (CI) m/z 309 (MH^+, 100%); HRMS calcd for $C_{16}H_{22}N_2ClO_2$ (MH^+), 309.1370; found, 309.1376

(±)-*exo*-1-[7-(Toluene-4-sulfonyl)-7-azabicyclo[2.2.1]hept-2-yl]-butane-1,3-dione 3-Oxime (26). ^{n}BuLi (0.34 mL, 0.78 mmol, 2.3M in hexanes, 4 equiv) was added dropwise to a solution of acetone oxime (28 mg, 0.39 mmol, 2 equiv) in THF (1 mL) at 0 °C and the resulting mixture warmed to 25 °C and stirred for 35 min. A solution of the bicyclic ester **25** in THF was then added dropwise over 15 min. The reaction mixture was then heated to 60−65 °C for 1 h, then cooled to 0 to −5 °C, and ice-cold 10% aq HCl was carefully added. The organic layer was separated and the aqueous layer neutralized with solid Na_2CO_3 (effervescence) and extracted with EtOAc (3 × 5 mL). The EtOAc and previous organic layers were combined, dried ($MgSO_4$), and evaporated. Flash chromatography (1:1 EtOAc/petrol) gave the title compound (42 mg, 62%) as an inseparable mixture of geometric isomers as a colorless oil: IR (film) 3449, 2957, 1330, 1156, 191, 816, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (* denotes minor isomer) δ 7.79 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H*), 7.30 (2 overlapping d, 2H and 2H*), 4.40 (d, J = 4.0 Hz, 1H), 4.31 (t, J = 4.0 Hz, 1H), 4.26 (br m, 1H*), 4.05 (d, J = 4.5 Hz, 1H*), 3.63 (s, 1H), 3.30 (d, J = 18.0 Hz, 1H*), 2.96 (s, 1H*), 2.90 (d, J = 18.0 Hz, 1H), 2.61 (d, J = 18.0 Hz, 2H), 2.59 (d, J = 18.0 Hz, 2H*), 2.43 (s, 3H and 3H*), 2.14−2.09 (m, 1H and 1H*), 1.96 (s, 3H), 1.94 (s, 3H*), 1.80−1.78 (m, 2H), 1.72−1.68 (m, 1H and 3H*), 1.64−1.59 (m, 1H and 1H*), 1.46−1.37 (m, 2H and 2H*); ^{13}C NMR (100 MHz, $CDCl_3$) 157.0, 156.6, 144.1, 143.9, 137.2, 137.1, 129.9, 129.8, 127.44, 127.35, 108.7, 108.4, 60.9, 60.8, 59.6, 59.3, 49.6, 49.4, 46.5, 45.4, 35.5, 34.1, 29.5, 29.3, 29.1, 28.6, 21.6, 21.5, 13.44, 13.39; MS (CI) m/z 368 (MNH_4^+), 350 (M^+, 100%), 333, 282; HRMS calcd for $C_{17}H_{22}N_2O_4S$ (MNH_4^+), 368.1644; found, 368.1647.

(±)-*exo*-2-(3-Methyl-isoxazol-5-yl)-7-(toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane (27). To a solution of the ketooxime **26** (29 mg, 0.08mmol) in dichloromethane (1.2 mL) at 0 °C was added Et_3N (16 μL, 0.12 mmol, 1.4 equiv) followed dropwise by mesyl chloride (8.4 μL, 0.11 mmol, 1.3 equiv). The resulting mixture was allowed to warm to rt and stirred overnight, then quenched with H_2O (5 mL) and extracted with dichloromethane (3 × 15 mL). Organics were combined, dried (Na_2SO_4), and evaporated. Flash chromatography (2:1 Et_2O/hexane) gave the title compound (18 mg, 65%) as a white amorphous solid: mp 146−150 °C; IR (nujol) 1599, 1325, 1157, 109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 5.76 (s, 1H), 4.31 (br m, 1H), 4.24 (d, J = 4.0 Hz, 1H), 2.99 (t, J = 6.5 Hz, 1H), 2.42 (s, 3H), 2.21 (s, 3H), 1.93−1.91 (m, 2H), 1.88−1.83 (m, 2H), 1.58−1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 159.8, 143.7, 137.3, 129.5, 127.5, 100.9, 63.2, 58.8, 40.9, 38.4, 29.2, 29.0, 21.5, 11.4; MS (CI) m/z 350 (MNH_4^+, 100%), 333 (MH^+); HRMS calcd for $C_{17}H_{21}N_2O_3S$ (MH^+), 333.1273; found, 333.1279.

(±)-*exo*-2-(3-Methyl-isoxazol-5-yl)-7-azabicyclo[2.2.1]-heptane (2). A mixture of *N*-Ts-epiboxidine **27** (24 mg, 0.07 mmol, 1 equiv) and phenol (34 mg, 0.36 mmol, 5 equiv) in 48% aq HBr (0.7 mL) was heated to reflux for 3 h under ambient atmosphere. The reaction mixture was then cooled, diluted with H_2O (3 mL), and extracted with Et_2O (3 × 10 mL). The aqueous layer was separated, rendered basic with saturated aq $NaHCO_3$, and extracted with dichloromethane (3 × 10 mL). Combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatography (97:2:1 $CHCl_3$/MeOH/NH_3) gave the title compound (7 mg, 55%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.77 (t, J = 4.5 Hz, 1H), 3.72 (d, J = 4.0 Hz, 1H), 3.00 (dd, J = 9.0 and 5.0 Hz, 1H), 2.25 (s, 3H), 1.91 (dd, J = 12.5 and 9.0 Hz, 1H), 1.81 (br s, 1H), 1.73−1.67 (m, 3H), 1.49−1.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 160.0, 100.8, 61.4, 56.1, 41.1, 38.0, 29.6, 29.2, 11.4; MS (CI) m/z 179 (MH^+, 100%); HRMS calcd for $C_{10}H_{15}N_2O$ (MH^+), 179.1184; found, 179.1189.

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Supporting Information Available: Experimental procedures and characterization data for compounds **7a**, **7b**, **8a**, **12**, **15**, **20**, **23a**, **23b**, **25**, and **1**. Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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