Tetrahedron Letters 52 (2011) 953–954

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Syntheses of the opioid substructures 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine and 2,3,4,5-tetrahydro-1,5-methano-1*H*-2-benzazepine

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ARTICLE INFO

Article history:
Received 23 November 2010
Revised 15 December 2010
Accepted 16 December 2010
Available online 23 December 2010

ABSTRACT

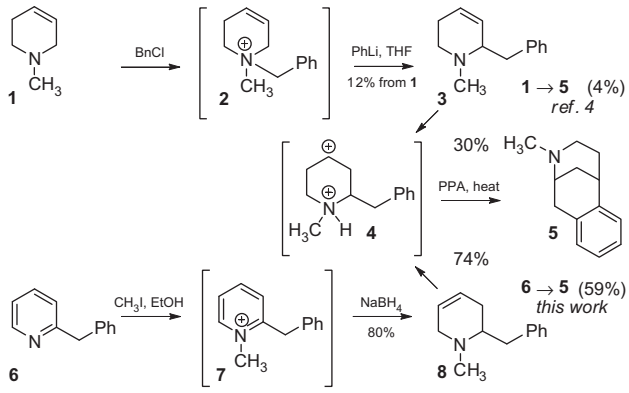
Concise syntheses of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**12**) and 2,3,4,5-tetrahydro-1,5-methano-1*H*-2-benzazepine (**18**) are described and involve an intramolecular Friedel–Crafts alkylation and an intramolecular Heck cyclization as their respective key ring-forming steps.

Natural products owe their existence to selection pressures that confer advantages to their host, giving these structures a central role in organic, natural product, and medicinal chemistry research.[1] Linking their pharmacological action to structure often inspires medicinal research to develop the safest and most beneficial treatments for disease.

The 1970s witnessed considerable synthetic effort in the opioid field intended to elucidate the structural features responsible for morphine's antinociceptive properties.[2] The objective was and remains to identify molecules capable of providing pain relief with reduced reinforcement and addictive qualities. Advancing an understanding of the distinct structure–pharmacology relationships necessary for addiction and antinociception is central to this research effort. The minimum structural requirements that elicit the desired pharmacology are defined through the study of molecular topology, ligand–receptor interactions, and biological systems interactions.[3] The continued study of these interrelationships requires available sources of material for further experimentation. To support this we describe herein efficient syntheses of two known opioid substructures, benzomorphan, or 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**12**) and 2,3,4,5-tetrahydro-1,5-methano-1*H*-2-benzazepine (**18**).

Our approach to benzomorphan **12** (Scheme 1) refines the approach described by Kanematsu involving an intramolecular Friedel–Crafts alkylation to access *N*-methyl benzomorphan **5** (Scheme 1) by improving the yield from 4% to 59%.[4] Kanematsu's key intramolecular cyclization of tetrahydropyridine **3** presumably involves a dicationic 4-piperidinium species **4** that places the two cations as remotely as possible. Kanematsu accessed intermediate **3** in low yield via Stevens rearrangement (**2** → **3**).

Our related route to **5** involves alternative access to transition structure **4** via tetrahydropyridine isomer **8** giving greatly enhanced overall yields (**6** → **8** → **5**, 59%). The alkylation of 2-benzylpyridine **6** with iodomethane forms *N*-methyl pyridinium salt **7**



Scheme 1. Approaches to benzazocine **5**.

which was reduced with $NaBH_4$ to give Δ^4-isomer **8** in a one-pot protocol (80%).[5] It should be noted that May reported a similar pyridinium salt reduction which gave a 4:1 mixture of the Δ^3- and Δ^4-isomers.[6] In our hands, the Δ^4-tetrahydropyridine was the only reduction product formed in this reaction. Friedel–Crafts cyclization of alkene **8** in hot PPA furnished benzomorphan **5**, completing a high-yielding and scalable preparation of this bicyclic ring system. In further attempts to improve the cyclization yield we investigated amide and carbamate *N*-protection to circumvent doubly protonated intermediates (i.e., **4**), which in theory would reduce cyclization temperatures by enhancing the stability of reactive intermediates. These reactions returned only complex mixtures or starting materials. Even the *N*-benzyl derivative of **7** failed to cyclize, possibly due to poor solubility in hot PPA. These results suggest the facility of the Friedel–Crafts cyclization arises from the highly reactive nature of dicationic species **4**.

N-Methyl benzomorphan **5** was demethylated via the trichloroethyl carbamate (Troc) intermediate **11** (Scheme 2).[7] Standard conditions (Troc–Cl, DCE, 80 °C) gave a mixture of desired product and a co-eluting material $(M+14)^+$, the elimination product **10**. Addi-

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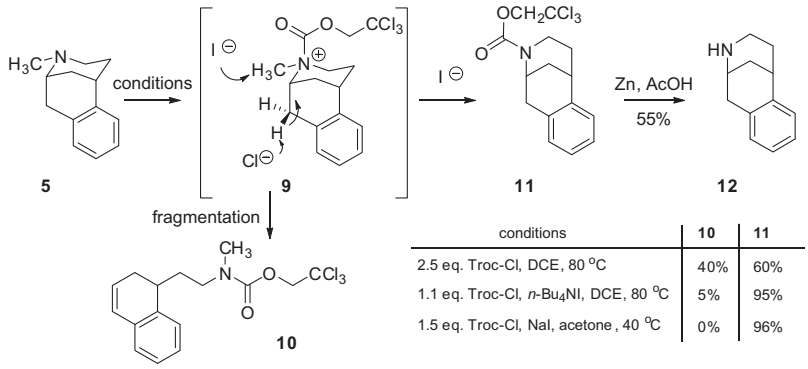
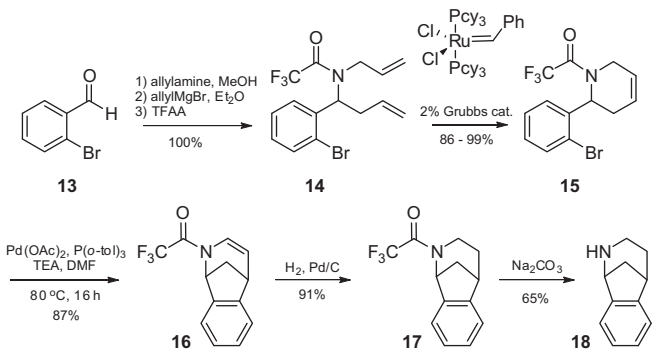
doi:10.1016/j.tetlet.2010.12.072



conditions	10	11
2.5 eq. Troc-Cl, DCE, 80 °C	40%	60%
1.1 eq. Troc-Cl, *n*-Bu_4NI, DCE, 80 °C	5%	95%
1.5 eq. Troc-Cl, NaI, acetone , 40 °C	0%	96%

Scheme 2. Troc-mediated N-demethylation of **5**.



Scheme 3. Metathesis–Heck route to bicyclic **18**.

tional Troc–Cl was necessary to completely consume **5**, as the HCl formed in the pathway to **10** presumably protonates the starting amine thereby protecting it from reaction with Troc–Cl. To enhance the nucleophilic pathway to **11** we introduced iodide ion, which successfully circumvented the elimination pathway under two conditions (see table, Scheme 2).[8] Both reactions were complete in less than 1 h with no elimination observed under the Finkelstein conditions.[9] Troc removal under standard conditions (Zn, AcOH) provided 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**12**) in four synthetic operations from **1** in 31% yield overall.

Benzazepine (**18**), a homolog of benzomorphan (**12**), was prepared by a Heck-based sequence to generate the bicyclic core (Scheme 3).[10] The original preparation of **18** proceeded in eight-steps and 3% yield overall.[11] In our synthesis, 2-bromobenzaldehyde **13** was condensed with allylamine in MeOH and stripped of solvent. After dissolving the residue in Et_2O, the mixture was cooled to −78 °C and then treated with allylMgBr. The resulting salt was trapped in situ with trifluoroacetic anhydride to generate **14** in quantitative yield. Ring-closing metathesis converted this crude material to tetrahydropyridine **15** reproducibly in excellent yield. Standard Heck conditions afforded [3.2.1]-bicyclic adduct **16**. The enamide was reduced by hydrogenation and the trifluoroacetamide was removed to give 2,3,4,5-tetrahydro-1,5-methano-1*H*-2-benzazepine (**18**) in five steps and 50% overall yield for the sequence.

We used these compounds to examine their pharmacology as described in the original work of the 1970s[2] and in our effort to discover varenicline.[2a] By modifying the original approach to benzomorphan **12** and applying modern methodology to the preparation of benzazocine **19**, efficient syntheses have been realized.

Acknowledgments

J.W.C. thanks Bertrand L. Chenard and Art Nagel for helpful suggestions inspiring these approaches.

Supplementary data

Supplementary data (experimental procedures and supporting data for all compounds) associated with this article can be found at doi:10.1016/j.tetlet.2010.12.072.

References and notes

1. (a) Cragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod.* **1997**, *60*, 52–60; (b) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022–1037; (c) Kingston, D. G.; Newman, D. J. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 207–227; (d) Koehn, F. E.; Carter, G. T. *Nat. Rev. Drug Disc.* **2005**, *4*, 206–220; (e) Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451–453; (f) Jones, W. P.; Chin, Y. W.; Kinghorn, A. D. *Curr. Drug Targets* **2006**, *7*, 247–264; (g) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329–8351; (h) Baker, D. D.; Chu, M.; Oza, U.; Rajgarhia, V. *Nat. Prod. Rep.* **2007**, *24*, 1225–1244.
2. (a) Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Wirtz, M. C.; Arnold, E. P.; Huang, J.; Sands, S. B.; Davis, T. I.; Lebel, L. A.; Fox, C. B.; Shrikhande, A.; Heym, J. H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R. S.; Chambers, L. K.; Rovetti, C. C.; Schulz, D. W.; Tingley, F. D., III; O'Neill, B. T. *J. Med. Chem.* **2005**, *48*, 3474–3478; (b) Malec, D.; Langwinski, R. *J. Pharm. Pharmacol.* **1980**, *32*, 72–73; (c) Ossipov, M. H.; Kovelowski, C. J.; Nichols, M. L.; Hruby, V. J.; Porreca, F. *Pain* **1995**, *62*, 287–293; (d) Baxter, M. G.; Follenfant, R. L.; Miller, A. A.; Sethna, D. M. *Br. J. Pharmacol.* **1977**, *59*, 523; (e) Bloom, A. S.; Dewey, W. L.; Harris, L. S.; Brosius, K. K. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 33–41; (f) Blundell, C.; Slater, P. *J. Pharm. Pharmacol.* **1977**, *29*, 306–307; (g) Chesher, G. B.; Dahl, C. J.; Everingham, M.; Jackson, D. M.; Marchant-Williams, H.; Starmer, G. A. *Br. J. Pharmacol.* **1973**, *49*, 588–594; (h) Dewey, W. L.; Harris, L. S. *J. Pharmacol. Exp. Ther.* **1971**, *179*, 652–659; (i) Gispen, W. H.; Van Wimersma Greidanus, T. B.; Waters-Ezrin, C.; Zimmermann, E.; Krivoy, W. A.; De Wied, D. *Eur. J. Pharmacol.* **1975**, *33*, 99–105.
3. Fliri, A. F.; Loging, W. T.; Volkmann, R. A. *Trends Pharmacol. Sci.* **2010**, *31*, 547–555.
4. Kanematsu, K.; Takeda, M.; Jacobson, A. E.; May, E. L. *J. Med. Chem.* **1969**, *12*, 405–408.
5. 2-Benzylpyridine is commercially available (CAS 101-82-6). For its preparation, see: (a) Jerchel, D.; Noetzel, S.; Thomas, K. *Chem. Ber.* **1960**, *93*, 2966–2970; (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240–1241; (c) Panizzon, L. *Helv. Chim. Acta* **1944**, *27*, 1748–1756; (d) Yamashita, S.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *Eur. J. Org. Chem.* **2009**, *8*, 1173–1180.
6. Thyagarajan, G.; May, E. L. *J. Heterocycl. Chem.* **1971**, *8*, 465–468.
7. Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52 1*, 19–28.
8. For a related approach see Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719–9721.
9. Baughman, T. W.; Sworen, J. C.; Wagener, K. B. *Tetrahedron* **2004**, *60*, 10943–10948.
10. Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Tetrahedron* **2009**, *65*, 6454–6469.
11. (a) Mokotoff, M.; Jacobsen, A. E. *J. Heterocycl. Chem.* **1970**, *7*, 773–778; (b) Jacobsen, A. E.; Mokotoff, M. *J. Med. Chem.* **1970**, *13*, 7–9.