View Article Online / Journal Homepage / Table of Contents for this issue

A Novel Asymmetric Synthesis of 3-Benzyl-1,2,3,4,5,6-hexahydro-11-alkyl-2,6-methano-3-benzazocines

Xu Bai,[a] S. Wayne Mascarella,[a] Wayne D. Bowen[b] and F. Ivy Carroll*[a]

[a] *Chemistry and Life Sciences, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709, USA*

[b] *Laboratory of Medicinal Chemistry, NIDDK, NIH, Bethesda, MD 20892, USA*

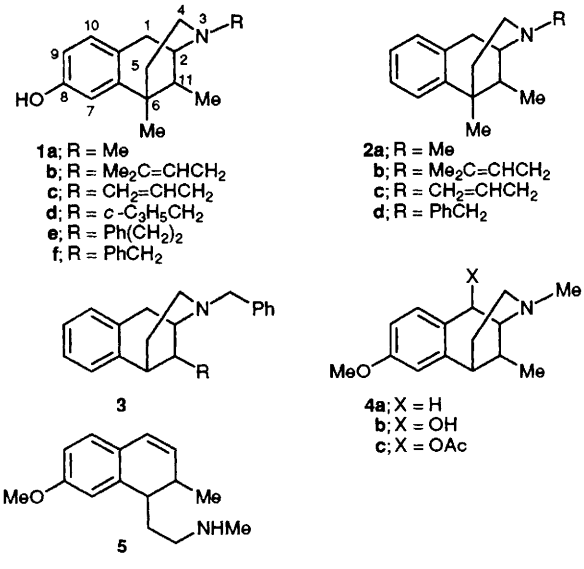
9-Alkyl 6,7-benzomorphans (1,2,3,4,5,6-hexahydro-11-alkyl-2,6-methano-3-benzazocines) are important selective ligands of sigma receptor sites; their asymmetric synthesis starting with (1*R*,2*R*)- or (1*S*,2*S*)-1-hydroxymethyl-2-alkyl-1,2-dihydronaphthalene is described.

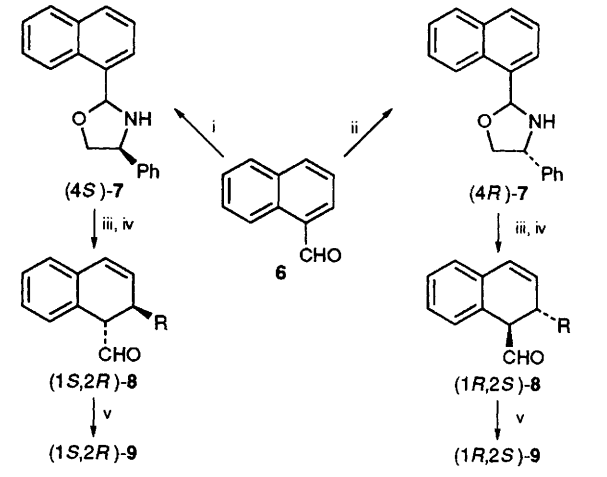
Published on 01 January 1994. Downloaded by State University of New York at Stony Brook on 28/10/2014 07:13:25.

Metazocine **1a**, pentazocine **1b**, *N*-allyl-*N*-normetazocine **1c**, cyclazocine **1d** and phenazocine **1e** are (2*RS*,6*RS*,11*RS*)-(±)-3-alkyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-ols† which are well known for their opioid activity.[1,2] The (2*S*,6*S*,11*S*)-(+)-isomers, (+)-**1b** and (+)-**1c**, have also proven extremely useful in the characterization of the sigma-1 binding site.[3] Recently, we reported that (2*S*,6*S*,11*S*)-(+)-3-benzyl-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol (+)-**1f** was a potent and selective ligand for the sigma-1 binding site.[4] We also reported that compounds **2a–c** possessed sigma-1 affinity essentially identical to that of **1a–c**, showing that the 8-hydroxy group was not required for high affinity for the sigma-1 binding site.[5] In a separate study, we reported that (2*R*,6*R*,11*R*)-(−)-**2d** was devoid of opioid binding affinity and was a useful ligand for studying the sigma-2 binding site.[6] As a continuation of these structure–activity relationship (SAR) studies and in particular to gain information concerning the effect of the 11-methyl group of these disubstituted hexahydro-2,6-methano-3-benzazocines to sigma binding affinity, we were interested in the syntheses of (2*S*,6*S*,11*S*)-(+)- and (2*R*,6*R*,11*R*)-(−)-3-benzyl-1,2,3,4,5,6-hexahydro-11-alkyl-2,6-methano-3-benzazocines **3**.

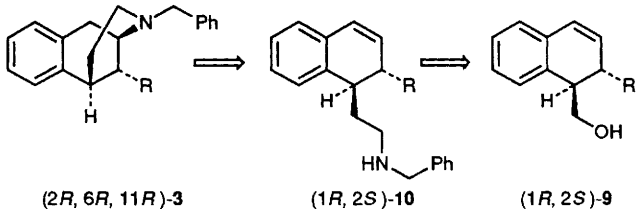
Inoue and May reported that mercury(II) acetate–sodium borohydride cyclization of the dihydronaphthalene **5** gave a mixture of **4b** and **4c**.[7] Compound **4c** could be converted to **4b**, and reduction of **4b** with palladium in acetic acid containing perchloric acid gave the desired (2*RS*,6*RS*,11*RS*)-(±)-1,2,3,4,5,6-hexahydro-3,11-dimethyl-8-methoxy-2,6-methano-3-benzazocine **4a**. The synthesis of Inoue and May suffers the disadvantage of providing racemic material and requiring several steps to prepare the key intermediate **5**.[7] Recently, Pridgen *et al.*[8] reported that either optical antipode of *trans*-1-hydroxymethyl-2-alkyl-1,2-dihydronaphthalene [(1*S*,2*R*)- or (1*R*,2*S*)-**9**] could be prepared in high chemical and optical purity by the route shown in Scheme 1. Thus, the addition of the appropriate alkylmagnesium halide to the oxazolidine **7**, derived from (*R*)- or (*S*)-phenylglycinol and naphthaldehyde **6**, followed by acid-catalysed cleavage of the chiral auxiliary and reduction of the resulting aldehyde **8** provided the required optically active alcohols **9** in either optical form depending on the phenylglycinol used. The ready availability of the optically active alcohols **9** suggested the retrosynthesis of (2*R*,6*R*,11*R*)- and (2*S*,6*S*,11*S*)-**3** outlined in Scheme 2 as a way of overcoming the disadvantages of the Inoue and May synthesis of 11-substituted hexahydro-2,6-methano-3-benzazocines.[7]

Scheme 3 outlines the routes we used to convert (1*S*,2*R*)-**9** to ethyl, isopropyl and butyl substituted (2*S*,6*S*,11*S*)-**3**. For example, tosylation of the (1*S*,2*R*)-**9a** {$[\alpha]_D^{18}$ −297 (*c* 0.1, $CHCl_3$), δ ($-CH_2-O$) 3.46–3.60 (m)} with toluene-*p*-sulfonyl chloride followed by treatment of the resulting tosylate with potassium cyanide in dimethyl sulfoxide at 105 °C yielded the nitrile (1*S*,2*R*)-**11a** {$[\alpha]_D^{21}$ −319 (*c* 0.17, $CHCl_3$), δ ($-CH_2-$





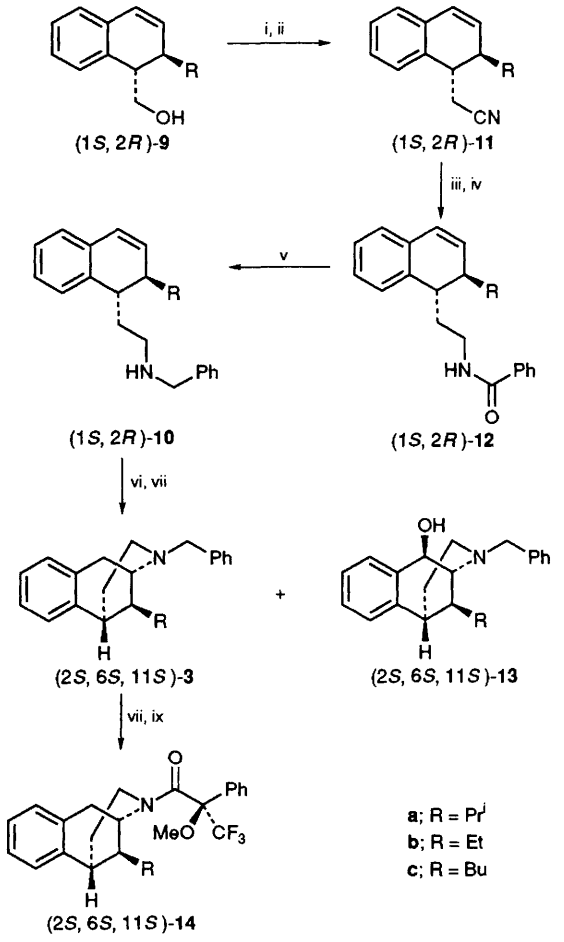
Scheme 1 *Reagents and conditions*: i, (*S*)-phenylglycinol, $MgSO_4$; $CHCl_3$, reflux; ii, (*R*)-phenylglycinol, $MgSO_4$, $CHCl_3$, reflux; iii, RMgCl; iv, 3 mol l^{-1} HCl; v, $NaBH_4$, MeOH, 0 °C



Scheme 2 Retrosynthetic analysis of **3**. Illustrated for the (2*R*,6*R*,11*R*)-isomer.

View Article Online

Published on 01 January 1994. Downloaded by State University of New York at Stony Brook on 28/10/2014 07:13:25.



Scheme 3 *Reagents and conditions*: i, TsCl–pyridine, 0 °C; ii, KCN–DMSO, 105 °C; iii, $LiAlH_4$–Et_2O; iv, PhCOCl, triethanolamine–CH_2Cl_2; v, $LiAlH_4$–THF, reflux; vi, $Hg(OAc)_2$–THF, 50 °C, vii, $NaBH_4$–1 mol l^{-1} NaOH (aq); viii, H_2, Pd–C, MeOH; ix, (*R*)MTPACl, Et_3N, CH_2Cl

CN) 2.39–2.56 (m), 67% yield}. Lithium aluminium hydride reduction of **11a** in diethyl ether followed by benzoylation of the intermediate amine provided the amide **12a** (81% yield). Reduction of **12a** with lithium aluminium hydride in tetrahydrofuran (THF) gave the benzylamine (1*S*,2*R*)-**10a** {$[\alpha]_D^{20}$ −279 (*c* 0.15, $CHCl_3$), δ (–CH_2–CH_2–NH–CH_2–Ph) 1.66–1.78 (m), 2.53–2.70 (m) and 3.74 (s), 90% yield}. Unexpectedly, treatment of **10a** with mercury(II) acetate in THF followed by reduction with sodium borohydride gave the benzomorphan (2*S*,6*S*,11*S*)-**3a** directly as the major product {$[\alpha]_D^{20}$ +78.5 (*c* 0.14, EtOH), 50% yield} with a trace of **13a** evident by NMR analysis [δ (aryl–CH–OH) 4.98 (s)].[7] The conversion of **10a** to **3a** was indicated by the loss of vinyl protons [(1*S*,2*R*) **10a**: δ 6.40 (d, *J* 9.7 Hz) and 5.92 (ddd, *J* 1.0, 6.1, 9.7 Hz)] and the appearance of the typical benzylic 1-H methylene protons [(2*S*,6*S*,11*S*)-**3a**: δ 2.56 (dd, *J* 6.0, 18.6 Hz) and 3.08 (d, *J* 18.6 Hz)]. The (2*R*,6*R*,11*R*)-(−)-isomer of **3a**, as well as both the (2*S*,6*S*,11*S*)-(+)- and (2*R*,6*R*,11*R*)-(−)-isomers of **3b** and **3c** were prepared by the method described above. The structural assignment of benzomorphans **3a–c** is based on the elemental analysis of the hydrochloride salts and ^1H NMR, ^{13}C NMR, 2D ^1H–^1H correlation NMR and 2D ^1H–^{13}C correlation NMR data of the free bases.

The absolute configurations of the starting alcohols **9** produced by the method shown in Scheme 1 are known[9,10] and were verified by comparison with the published optical rotation for each enantiomer.[8,11] As the stereochemistry of all three stereogenic centres in the product is determined by the stereochemistry of the alcohol starting material, the absolute stereochemistry of the benzomorphans **3a–c** can be established. The optical purity of **3a–c** was shown to be ≥96% by gas chromatography–mass spectral analysis of the (*R*)-2-methoxy-2-trifluoromethylphenylacetyl amides **14a–c**. The amides **14a–c** were prepared by catalytic debenzylation of **3** followed by acylation of the intermediate *N*-nor analogue with (*R*)-2-methoxy-2-trifluoromethylphenylacetyl chloride [(*R*)MTPACl].

The K_i values for the sigma-1 binding affinity of (3*R*,6*R*,11*R*)-(−)-**3b** and (3*S*,6*S*,11*S*)-(+)-**3b** are 3.36 and 26.7 nmol l^{-1}, respectively. Thus, the enantioselectivity is opposite to that for all reported *N*-substituted-*N*-normetazocines.[4]

In summary, we have developed a convenient enantioselective synthesis of (+)- and (−)-3-benzyl-1,2,3,4,5,6-hexahydro-11-alkyl-2,6-methano-3-benzazocines **3** starting from naphthaldehyde. Debenzylation provides the *N*-nor analogue which will allow the synthesis of other *N*-substituted analogues. Starting with 7-methoxynaphthaldehyde will lead to 8-methoxy substituted analogues of **3**, which are of importance for their opioid activity. The scope of this useful route to other benzomorphans is currently being explored. The biochemical and pharmacological significance of the unexpected reversal of enantioselective sigma-1 binding affinity of the benzomorphans **3** is also under investigation.

This research was supported by Grant DA05721 from the Natonal Institute on Drug Abuse.

Received, 8th August 1994; Com. 4/04873C

Footnote

† These compounds are also referred to in the literature as *N*-substituted-*cis*-2′-hydroxy-5,9-dimethyl-6,7-benzomorphans or *N*-substituted-*cis*-*N*-normetazocines.

References

1 G. R. Lenz, D. E. Walters, S. M. Evans, A. J. Hopfinger and D. L. Hammond, *Opiates*, Academic Press, Orlando, 1986, p. 250.
2 A. F. Casy and R. T. Parfitt, *Opioid Analgesics. Chemistry and Receptors*, Plenum Press, New York and London, 1986, p. 153.
3 J. M. Walker, W. D. Bowen, F. O. Walker, R. R. Matsumoto, B. De Costa and K. C. Rice, *Pharmacol. Rev.*, 1990, **42**, 355.
4 F. I. Carroll, P. Abraham, K. Parham, X. Bai, X. Zhang, G. A. Brine, S. W. Mascarella, B. R. Martin, E. L. May, C. Sauss, L. Di Paolo, P. Wallace, J. M. Walker and W. D. Bowen, *J. Med. Chem.*, 1992, **35**, 2812.
5 F. I. Carroll, X. Bai, X. Zhang, G. A. Brine, S. W. Mascarella, L. Di Paolo, P. Wallace, J. M. Walker and W. D. Bowen, *Med. Chem. Res.*, 1992, **2**, 3.
6 J. M. Walker, W. D. Bowen, S. L. Patrick, W. E. Williams, S. W. Mascarella, X. Bai and F. I. Carroll, *Eur. J. Pharmacol.*, 1993, **231**, 61.
7 H. Inoue and E. L. May, *J. Med. Chem.*, 1976, **19**, 259.
8 L. N. Pridgen, M. K. Mokhallalati and M.-J. Wu, *J. Org. Chem.*, 1992, **57**, 1237.
9 A. I. Meyers and D. Hoyer, *Tetrahedron Lett.*, 1984, **25**, 3667.
10 A. I. Meyers, G. P. Roth, D. Hoyer, B. A. Barner and D. Laucher, *J. Am. Chem. Soc.*, 1988, **110**, 4611.
11 A. I. Meyers and B. A. Barner, *J. Org. Chem.*, 1986, **51**, 120.