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An Asymmetric Approach towards (–)-Aphanorphine and Its Analogues

Pavel A. Donets,[a] Jan L. Goeman,[b] Johan Van der Eycken,[b] Koen Robeyns,[c] Luc Van Meervelt,[c] and Erik V. Van der Eycken*[a]

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A short enantioselective approach towards the alkaloid (–)-aphanorphine and its substituted analogues is described. The enantiomerically pure starting material for the synthesis was obtained by asymmetric hydrogenation in the presence of the Rh–(*S*)-PipPhos complex. Microwave-assisted Heck cyclization selectively provided the seven-membered 3-benzazepine ring. Further, the assembly of the tricyclic core of the alkaloid was accomplished by intramolecular radical cyclization. The X-ray structure confirming the absolute configuration of the obtained products is described.

Introduction

The 3-benzazepine alkaloid (–)-aphanorphine, first isolated by Shimizu and Clardy,[1] shares structural features of benzomorphane analgesics such as pentazocine and eptazocine[2] and has been chosen as a synthetic target by many research groups[3] (Figure 1). Recently, we reported a novel approach towards the selective and facile formation of 1-substituted 3-benzazepines through intramolecular Heck reductive cyclization.[4] Herein we propose an application of the elaborated reaction for the formal asymmetric synthesis of (–)-aphanorphine and its structural analogues.

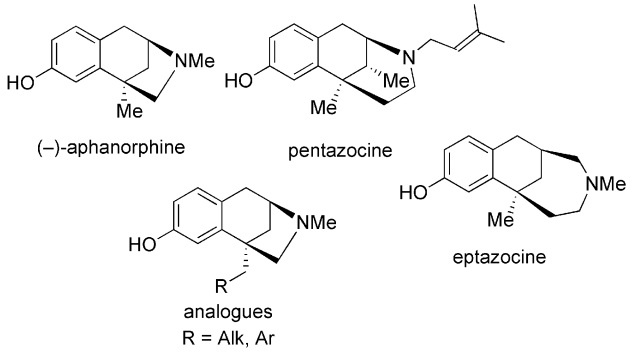


Figure 1. (–)-Aphanorphine and its structural analogues.

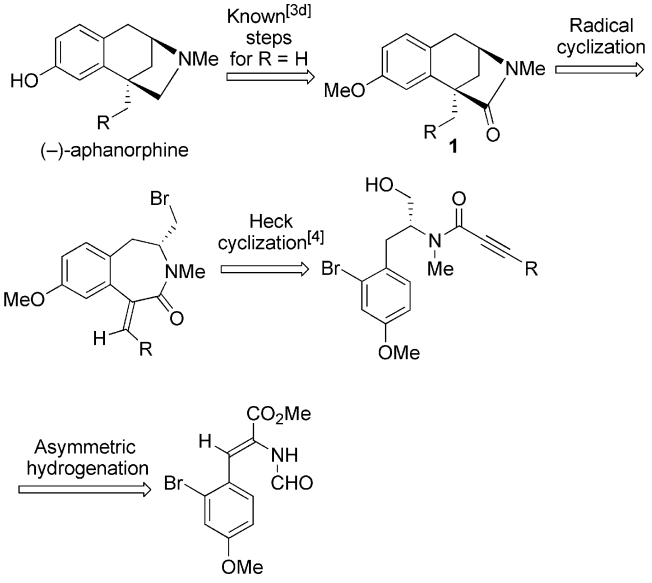
Results and Discussion

Several syntheses[3b–3e] of aphanorphine have been accomplished via intermediate **1** (R = H) (Scheme 1). Our approach towards **1** is based on three crucial stages. Intramolecular radical cyclization provides the required tricyclic framework. Heck reductive cyclization selectively creates the seven-membered 3-benzazepine ring. As we described previously,[4] the substituent R may be either an aromatic or an aliphatic group. Catalytic enantioselective hydrogenation of the appropriate *N*-formyl dehydroaminoester provides enantiomerically pure starting material.

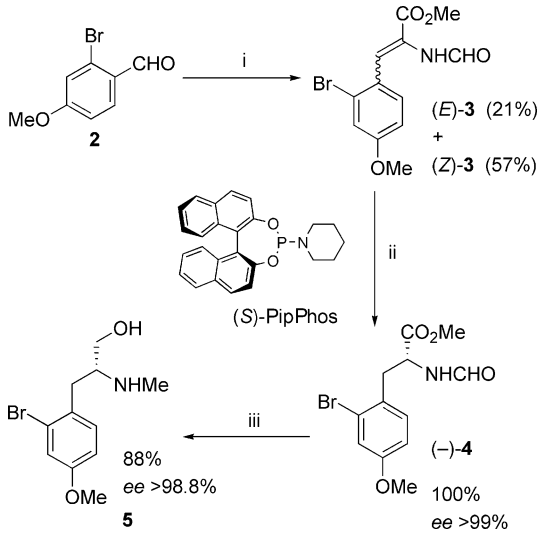
The synthesis starts with readily available bromoaldehyde **2** (Scheme 2) obtained by directed *ortho*-metalation of *p*-anisaldehyde[3b,5] followed by treatment with CBr_4. Subsequent condensation of **2** with methyl isocyanoacetate proceeds through the formation of the Schöllkopf 2-oxazoline[6] and provides after workup *N*-formyl dehydroaminoesters **3** as a mixture of two geometrical *E*/*Z* isomers. Thus, (*Z*)-**3** was isolated in 57% yield with the overall reaction yield of 78%, which was satisfactory for further elaboration. The geometry of the double bond in (*Z*)-**3** was unambiguously confirmed by the NOE effect between the amide proton and the *ortho* proton of the aryl ring.

It is necessary to mention that Gallagher and coworkers did not succeed[3b] to obtain enantiomerically pure **4** by hydrogenation of the (*E*)-**3**/(*Z*)-**3** mixture working on the synthesis of aphanorphine. In contrast, a literature survey[7] revealed that dehydroaminoesters similar to **3** have been successfully hydrogenated with a Rh catalyst and the readily available[7b] monodentate phosphoramidite ligand PipPhos.

[a] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry,
Katholieke Universiteit Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium
[b] Laboratory of Organic and Bioorganic Synthesis, Department of Chemistry, Ghent University,
Krijgslaan 281(S4), 9000 Gent, Belgium
[c] Biomolecular Architecture, Department of Chemistry, Katholieke Universiteit Leuven,
Celestijnenlaan 200F, 3001 Leuven, Belgium
Fax: +32-16-32-79-90
E-mail: erik.vandereycken@chem.kuleuven.be
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



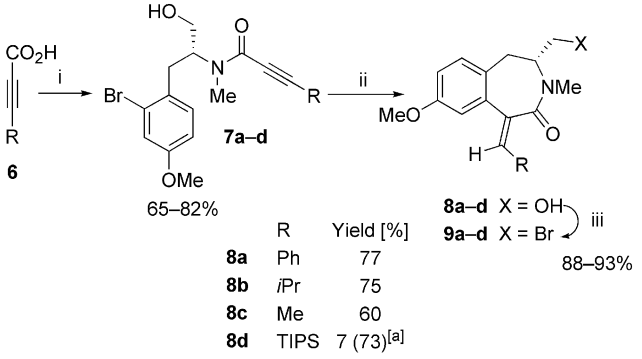
Scheme 1. Synthetic strategy towards compounds **1**.



Scheme 2. Enantioselective synthesis of amino alcohol **5**. Reagents and conditions: (i) 1) methyl isocyanoacetate, Cu_2O, Et_2O; 2) *t*BuOK; 3) AcOH; (ii) H_2 (1 atm), $Rh(cod)_2BF_4$, (*S*)-PipPhos, DCM, room temp., 24 h; (iii) BH_3·THF, THF, reflux, overnight.

It was also reported that unlike the (*Z*) isomers, the (*E*) isomers are generally difficult to reduce and give low *ee* values. Therefore, we tested the (*S*)-PipPhos ligand, which is slightly cheaper than the (*R*) form, and $Rh(nbd)_2BF_4$ (nbd = 2,5-norbornadiene) or $Rh(cod)_2BF_4$ (cod = 1,5-cyclooctadiene) complexes as Rh sources for the asymmetric hydrogenation of (*Z*)-**3**. Indeed, the Rh–PipPhos complex exhibited excellent selectivity and provided (–)-**4** with high *ee* and quantitative yield in both cases. However, $Rh(cod)_2BF_4$ proved to be more reliable and less pressure demanding, as it allowed (–)-**4** to be obtained at 1 atm of hydrogen pressure with 2 mol-% of catalyst. We failed to hydrogenate the (*E*)-**3** isomer with any appreciable enantioselectivity. However, hydrogenation of (*E*)-**3** in the presence of Wilkinson's (5 mol-%) catalyst at 25 bar provided racemic (±)-**4**, which was further used as a standard for the *ee* analysis. Compound (±)-**4** was also employed in the synthesis of racemic **1** with R = Ph in the early stages of the synthesis while exploring the general feasibility of the approach. Subsequent reduction of (–)-**4** with an excess amount of BH_3·THF complex yielded amino alcohol **5**[8] without any significant racemization, as confirmed by chiral HPLC analysis after conversion into a cyclic carbamate.

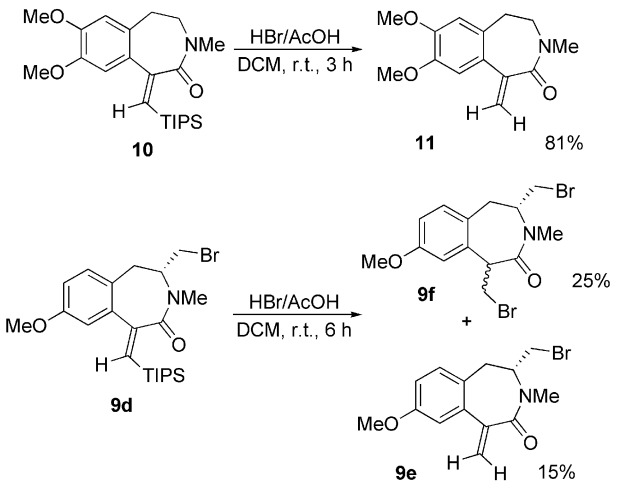
Following the synthetic plan, we further prepared amides **7a**–**d** in good yields by coupling amino alcohol **5** with NHS derivatives of corresponding propynoic acids **6** (Scheme 3). Obtained propynoic acid amides **7a**–**d** were converted into 3-benzazepinones **8a**–**d** in accordance with the previously elaborated approach by using microwave-assisted Heck reductive cyclization.[4] Experiments were carried out in a multimode Milestone MicroSYNTH microwave reactor in a sealed vial by applying a maximum power level of 300 W in the presence of Hermann's palladacycle[9] (2.5 mol-%) as a catalyst and HCO_2Na (1.5 equiv.) as the reducing reagent. For compounds **7a**–**c**, the microwave-assisted protocol worked well to provide **8a**–**c** in good yields, but **7d** containing a bulky TIPS group underwent mainly reduction with a loss of bromine; **8d** was isolated in only 7% yield. However, when subjected to the same reaction conditions at a lower temperature of 65 °C and under conventional heating, **7d** was successfully transformed into **8d** without formation of the direct reduction product (Scheme 3, yield in parenthesis). Under Appel reaction conditions, **8a**–**d** were smoothly converted into bromides **9a**–**d**, which thus served as the precursors for the subsequent intramolecular radical cyclization.



Scheme 3. Synthesis of bromides **9a**–**d**. Reagents and conditions: (i) 1) NHS, DCC, DCM; 2) **5**, DCM; (ii) Hermann's palladacycle, HCO_2Na, 110 °C, 20 min, MW. [a] for **7d**: 65 °C and conventional heating for 5 h resulted in the formation of **8d** in 73% yield; (iii) 2,6-lutidine, PPh_3, CBr_4, DCM.

Unfortunately, during our work on Heck cyclization we found out that unprotected propynoic acid amides like **7** with R = H undergo decomposition under the given reaction conditions.[4] We hoped to find conditions for protodesilylation of **8d** or **9d** to obtain 3-benzazepinone **8e** or **9e**

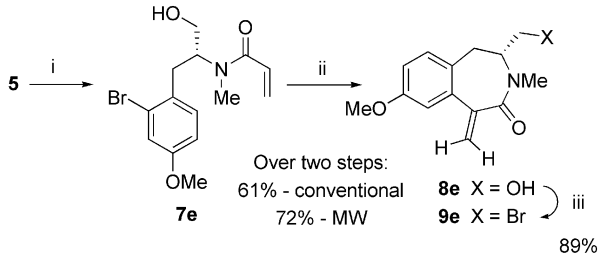
(R = H) as precursors for aphanorphine. Even though the analogous cleavage of the Si–Csp^2 bond in vinylsilanes is rather rare,[10] we first investigated this transformation on the example of compound **10** (Scheme 4), which was prepared by a similar procedure to that used for **8d**.



Scheme 4. Attempted protodesilylation of **9d**.

Treatment of **10** with aqueous HI in toluene[9b] caused only decomposition of the starting material. Having tried TfOH and $MeSO_3H$ as strong acidic additives in a DCM/TFA mixture for protodesilylation of **10**, we obtained **11** in 26 and 51% yield, respectively. The yield of **11** was further increased to 81% by using the HBr (33%)/AcOH reagent in DCM at room temperature, and this result seemed to be acceptable. Unfortunately, under these conditions we managed to isolate only the acetylation product from the reaction mixture with alcohol **8d**. However, bromide **9d** yielded required **9e** in very low yield (15%) together with dibromide **9f** (25%).

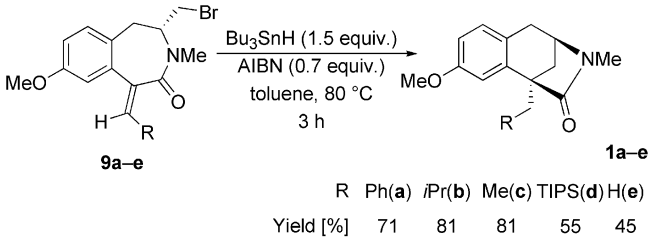
Then, we decided to obtain compound **8e** by conventional intramolecular Heck reaction of acrylamide **7e** (Scheme 5). The latter was prepared by selective acylation of **5** with acryloyl chloride in aqueous acetone in the presence of Na_2CO_3.



Scheme 5. Synthesis of bromide **9e**. Reagents and conditions: (i) acryloyl chloride, acetone/H_2O, Na_2CO_3, 0 °C, 1 h; (ii) Pd(dppf)Cl_2, Et_3N, MeCN, 110 °C; (iii) 2,6-lutidine, PPh_3, CBr_4, DCM.

Acrylamide **7e** was found to be unstable on silica during column purification and, therefore, was directly subjected to Heck reaction. The cyclization was completed in 2 h at 110 °C with conventional heating in the presence of $Pd(PPh_3)_4$ (5 mol-%) as a catalyst and Et_3N as a base and afforded **8e** in 69% yield. However, the product in this case was contaminated with inseparable Ph_3PO (24 mol-%). Application of Pd(dppf)Cl_2 as a catalyst allowed purification complications to be avoided, even though the yield dropped down to 61%. Under microwave irradiation conditions, the reaction time was greatly decreased (15 min) and the yield was improved to 72%. Bromide **9e** was subsequently obtained in excellent yield through the already used protocol.

Finally, we had all precursors **9a**–**e** at hand to proceed with the intramolecular radical cyclization (Scheme 6). During optimization of the reaction conditions on the example of bromide **9a**, the reaction was also applied to the analogous chloride and methyl xanthate obtained from **8e**. However, complete conversion of the chloride could not be reached even with a fivefold excess of Bu_3SnH. The methyl xanthate reacted similarly to the bromide, but the product purification in the case of **9a** was easier.



R	Ph(**a**)	*i*Pr(**b**)	Me(**c**)	TIPS(**d**)	H(**e**)
Yield [%]	71	81	81	55	45

Scheme 6. Radical cyclization of bromides **9a**–**e**.

By optimizing the reaction conditions for the cyclization of **9a** we found that the rate of reagent addition (Bu_3SnH and AIBN) strongly influenced the ratio of required cyclized **1a** and unwanted reduced product.[11] The best ratio (92:8) was observed with the gradual addition of Bu_3SnH (1.5 equiv.) together with AIBN (0.7 equiv.) over the course of 3 h. The overall isolated yield was 77%, which corresponds to 71% yield of **9a**. The structure of **9a** was fully confirmed with a set of 2D NMR spectroscopic experiments. We tried to improve the efficiency of the cyclization by using $(Me_3Si)_3SiH$. It is known to provide a higher ratio of cyclized and reduced products[11] than Bu_3SnH. Unfortunately, in our case, the use of $(Me_3Si)_3SiH$ resulted in a dramatic decrease in the overall yield and no expected improvement in the product ratio.

By applying the optimized reaction conditions, analogues **1b** and **1c** were obtained as the sole products in a high yield of 81% for both. In the case of **9d**, 16% of reduction products was observed, still **1d** was isolated in a moderate yield of 55%. Despite the absence of any significant amount of the reduction product in the reaction of **9e**, corresponding **1e** was obtained in 45% yield. An X-ray structure[12] of **1e** was obtained to confirm the absolute configuration (Figure 2).

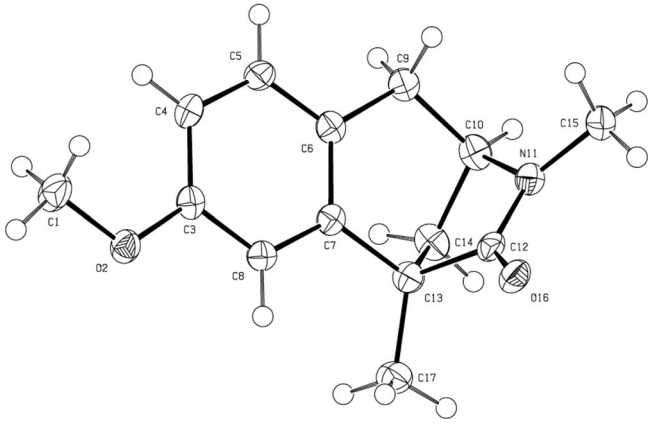


Figure 2. ORTEP representation of **1e** with thermal displacement ellipsoids drawn at the 50% probability level.

Conclusions

In summary, we developed a short asymmetric catalytic approach towards compounds **1**. As the subsequent transformations leading from **1e** to aphanorphine have already been explored,[3b–3d] our route constitutes a formal asymmetric synthesis of aphanorphine and its analogues.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data and NMR spectra for all compounds.

Acknowledgments

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[1] N. Gulavita, A. Hori, Y. Shimizu, P. Laszlo, J. Clardy, *Tetrahedron Lett.* **1988**, *29*, 4381.
[2] a) S. Shiotani, T. Kometani, K. Mitsuhashi, T. Nozawa, A. Kurobe, O. Fitsukaichi, *J. Med. Chem.* **1976**, *19*, 803; b) D. C. Palmer, M. J. Strauss, *Chem. Rev.* **1977**, *77*, 1.
[3] a) X. Yang, H. Zhai, Z. Li, *Org. Lett.* **2008**, *10*, 2457; b) J. F. Bower, P. Szeto, T. Gallagher, *J. Org. Biomol. Chem.* **2007**, *5*, 143; c) M. Katoh, H. Inoue, A. Suzuki, T. Honda, *Synlett* **2005**, *18*, 2820; d) J. R. Fuchs, R. L. Funk, *Org. Lett.* **2001**, *3*, 3923; e) R. S. Grainger, E. J. Welsh, *Angew. Chem. Int. Ed.* **2007**, *46*, 5377; f) M. Li, P. Zhou, H. F. Roth, *Synthesis* **2007**, 55; g) Z. Ma, H. Zhai, *Synlett* **2007**, 161; h) Z. Ma, H. Hu, W. Xionga, H. Zhaia, *Tetrahedron* **2007**, *63*, 7523 and references cited therein.
[4] P. A. Donets, E. Van der Eycken, *Org. Lett.* **2007**, *9*, 3017.
[5] Y. Lear, T. Durst, *Can. J. Chem.* **1997**, *75*, 817.
[6] U. Schollkopf, F. Gerhart, R. Schroder, D. Hoppe, *Justus Liebigs Ann. Chem.* **1972**, *766*, 116.
[7] a) L. Panella, A. M. Aleixandre, G. J. Kruidhof, J. Robertus, B. L. Feringa, G. Johannes, J. G. de Vries, A. J. Minnaard, *J. Org. Chem.* **2006**, *71*, 2026; b) H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943.
[8] See Supporting Information: $[a]_D^{20}$ = –20.2 (c = 0.6, $CHCl_3$), whereas the reported value has an opposite sign $[a]_D^{20}$ = +20.2 (c = 0.6, $CHCl_3$).[3b]
[9] a) W. A. Herrmann, C. Brossmer, C. P. Reisinger, T. H. Riermeier, K. Ofele, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357; b) W. A. Herrmann, C. Brossmer, K. Ofele, C. P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989; c) W. A. Herrmann, C. Brossmer, K. Ofele, C. P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844.
[10] a) M. D. Bachi, E. Bosch, *Tetrahedron Lett.* **1988**, *29*, 2581; b) K. Utimoto, W. Kitai, H. Nozaki, *Tetrahedron Lett.* **1975**, *16*, 2825.
[11] H. Togo in *Advanced Free Radical Reactions for Organic Synthesis*, Elsevier, **2004**.
[12] CCDC-705141 (for **1e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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