Short, asymmetric synthesis of *epi*-morphine ACNO analogues†

Nicolas Heureux,[a] Johan Wouters,[b] Bernadette Norberg[b] and István E. Markó*[a]

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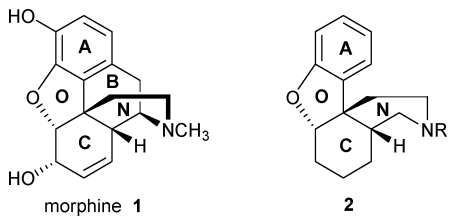
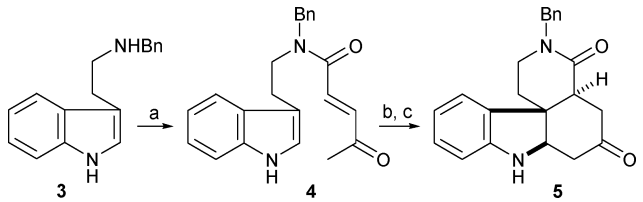
A concise and efficient asymmetric synthesis of ACNO analogues of morphine is reported.

Morphine **1**, an alkaloid isolated from *Papaver somniferum*, is one of the oldest drugs on record. However, due to its molecular complexity and addictive side-effects, approaches based upon simplification of the morphine skeleton for the discovery of novel analgesics have been adopted by generations of medicinal chemists. Nevertheless, there remain several interesting classes of morphine fragments, including the ACNO partial polycyclic system **2**, which have not been developed for clinical use, either due to inefficiency of their synthesis or inadequate structure–activity relationship studies (Scheme 1).[1]



Scheme 1

For some time, we have been interested in novel cascade-like transformations,[2] and we have recently reported on the rapid construction of the tetracyclic compound **5** using a silica-gel/^{t}BuOK polycyclisation sequence. Adduct **5** could then be transformed efficiently into Büchi's ketone (Scheme 2).[3]



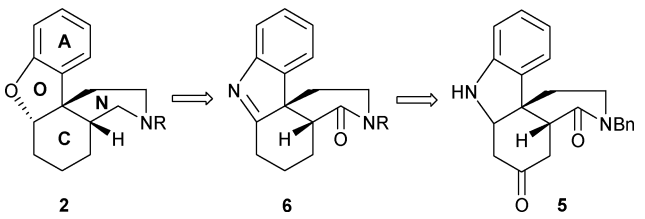
Scheme 2 *Reagents and conditions*: a) (*E*)-4-oxopent-2-enoic acid, BOPCl, Et_3N, DCM, 10 °C; b) SiO_2, DCM, rt, 79%; c) ^{t}BuOK, THF, −78 °C, 85%.

[a]*Unité de Chimie Organique et Médicinale, Université Catholique de Louvain, Place Pasteur 1, 1348, Louvain-la-Neuve, Belgium. E-mail: marko@chim.ucl.ac.be; Fax: +32 10472788; Tel: +32 10472782*
[b]*Laboratoire de Chimie Biologique Structurale, Facultés Universitaires Notre-Dame de la Paix, Rue Grafé 2, 5000, Namur, Belgium. E-mail: johan.wouters@fundp.ac.be; Fax: +32 81724530; Tel: +32 81724550*

† Electronic supplementary information (ESI) available: Experimental details for the preparation of compounds **6–10**, **6′**, **14**, **15** and **5**, as well as full spectroscopic data; crystal structure data for compounds **8** and **14**. See DOI: 10.1039/b610148h

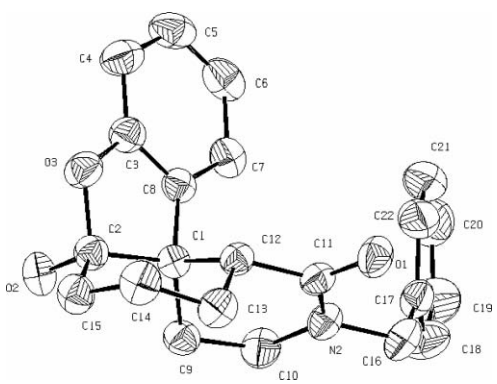
The close similarity between the ACNO analogue **2** and our tetracycle **5** prompted us to investigate the conversion of **5** into **2**. In this communication, we wish to report our results on the short synthesis of ACNO analogues of morphine, as well as on the development of an asymmetric version of this polycyclisation methodology.

Our retrosynthetic analysis of **2**, leading to tetracyclic intermediate **5**, is depicted in Scheme 3. Thus, the oxygenated five-membered ring of compound **2** could be derived from the imine **6**, which itself might originate from tetracycle **5** by oxidation of the aniline nitrogen and chemoselective removal of the ketone function.



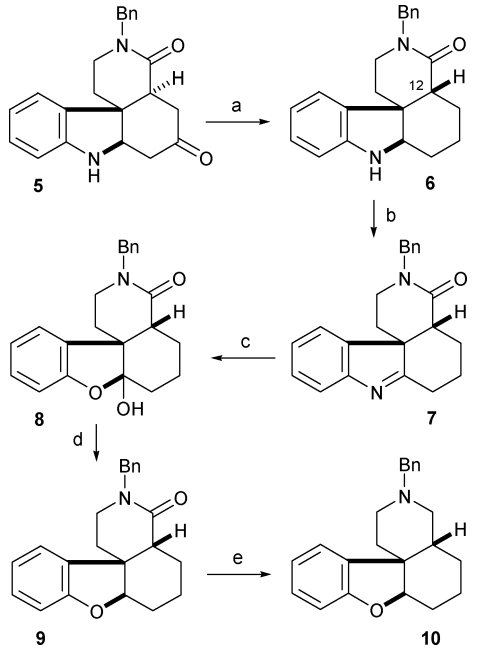
Scheme 3

Our approach towards **2** began with the Huang–Minlon modification of the Wolff–Kishner reduction[4] of ketone **5**. As confirmed later on in the synthesis, this reaction proceeded with epimerisation at C12, thus giving an easy entry to the *epi*-morphane family. The crucial amine oxidation was then performed using $KMnO_4$ in the presence of $BnNMe_3Cl$ as a phase transfer catalyst, and the relatively stable imine **7** was obtained in 71% yield. Following a beautiful procedure developed by the group of J. Lévy,[1e] treatment of imine **7** with $NaNO_2$ in acidic aqueous media afforded hemi-ketal **8** in 91% yield. The structure and relative stereochemistry of racemic **8** was unambiguously established by single crystal X-ray diffraction analysis‡ (Scheme 4). Triethylsilane-mediated transformation of the hemi-ketal to an ether and amide reduction



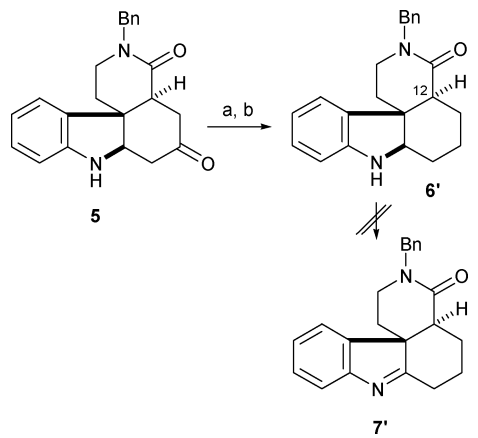
Scheme 4 50% ORTEP plot of compound **8**.

finally led, in quantitative yields, to the *epi*-ACNO analogue **10** (Scheme 5).



Scheme 5 *Reagents and conditions*: a) $HO(CH_2)_2OH$, Na, N_2H_4, Δ, 70%; b) $KMnO_4$, $BnNMe_3Cl$, DCM, −40°C, 71%; c) HCl (aq.), $NaNO_2$, rt, 91%; d) TFA, Et_3SiH, DCM, rt, 99%; e) $LiAlH_4$, Et_2O, Δ, 98%.

The tetracyclic compound **6′**, possessing the correct C12-β-stereochemistry of the ACNO ring system, has been synthesised using a Raney-Ni-mediated reduction of the corresponding dithiocetal derivative. Unfortunately, we have been unable for the moment to transform **6′** into the corresponding indolenine **7′**. Efforts are ongoing towards developing mild oxidation conditions that will enable us to access the ACNO analogues of morphine *via* **6′** (Scheme 6).



Scheme 6 *Reagents and conditions*: a) $HS(CH_2)_2SH$, $BF_3{\cdot}OEt_2$, AcOH, 65 °C; b) Ra-Ni, MeOH, Δ, 64%.

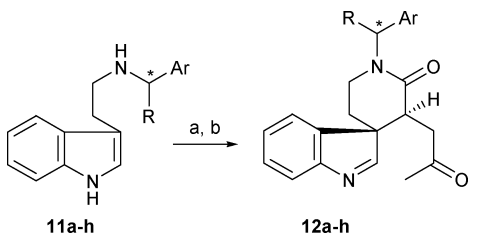
Having established a short, efficient and diastereoselective route to analogues of *epi*-morphanes, starting from the racemic tetracycle **5**, we next turned our attention towards delineating an enantioselective version of this methodology for the rapid assembly of ACNO analogues.

Table 1 Diastereoselective spirocyclisation precursors to **11a–h**

Entry	R	Ar	dr[a]
a	Me	Ph	2 : 1[b]
b	Me	*p*-F–C_6H_4-	1.6 : 1
c	Me	*p*-Cl–C_6H_4-	2 : 1
d	Me	*p*-Br–C_6H_4-	1.2 : 1
e	Me	*p*-Me–C_6H_4-	1 : 1
f	Me	1-Naphthyl	2 : 1[c]
g	Me	2-Naphthyl	2.2 : 1
h	Et	Ph	2.4 : 1

[a] Measured in the crude reaction mixture. [b] Yield of purified product: 61%. [c] Yield of purified product: 90%.

Initially, chiral equivalents of benzyltryptamine **11a–h** were synthesised using described procedures[5] and coupled with (*E*)-4-oxopent-2-enoic acid in the presence of BOPCl.[6] The corresponding precursors were then cyclised under heterogeneous SiO_2/DCM conditions, and the spirocyclic compounds **12a–h** were obtained as a mixture of diastereoisomers (Scheme 7).[7] Whilst the electronic effects of the *para*-substituent of the aromatic ring on the diastereomeric ratio are negligible (Table 1, entries a–e), small improvements in the dr are obtained using more hindered derivatives (entries f–h).

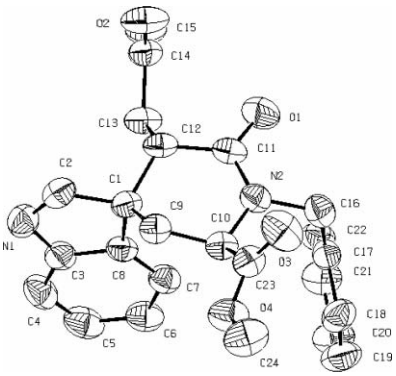


Scheme 7 *Reagents and conditions*: a) (*E*)-4-oxopent-2-enoic acid, BOPCl, Et_3N, DCM, 0 °C → rt; b) SiO_2, DCM, 0 °C → rt.

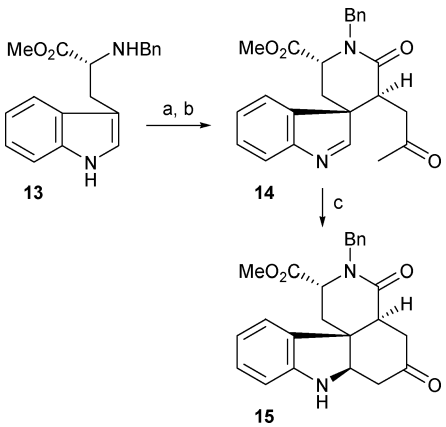
Given that the stereogenic centre in the chiral auxiliary is quite remote from the reactive electrophilic site of the Michael acceptor and that it is not directly attached to the 6-membered ring involved in the transition state, these modest results were not really surprising.

The situation changed dramatically when we shifted to precursors derived from the cheap, natural amino acid L-tryptophan. Thus, optically pure benzylated methyl ester **13** was coupled with (*E*)-4-oxopent-2-enoic acid and reacted with silica-gel overnight. Much to our delight, the completely diastereoselective formation of the spiro-imine **14** was observed. Adduct **14** was obtained in a good overall yield of 64% (from **13**).[8] Base-catalysed imino-aldol cyclisation proceeded smoothly in the presence of LiOH, affording tetracycle **15** as a single diastereoisomer (Scheme 9).[9] The structure and relative stereochemistry of **14** was unambiguously established by single crystal X-ray diffraction analysis§ [10] (Scheme 8).

At this point, all that remained to complete the asymmetric synthesis of intermediate **5** was the removal of the carboxymethyl auxiliary. Many methods described in the literature were tested without success,[11] and only the radical decarboxylation of selenoester **16**,[12] obtained in one step from **15** by using $Me_2AlSeMe$,[13] proved to be efficient. Following this protocol, tetracycle **5** could be isolated in an overall yield of 67% from

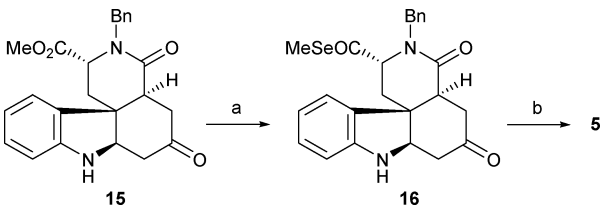


Scheme 8 50% ORTEP plot of compound **14**.



Scheme 9 *Reagents and conditions*: a) (*E*)-4-oxopent-2-enoic acid, BOPCl, Et_3N, DCM, 0°C → rt; b) SiO_2, DCM, rt, 64% overall yield, dr >95 : 5; c) LiOH, THF, rt, 79%, dr >95 : 5.

15. The enantiomeric excess of **5**, measured by HPLC, was equal to 94% (Scheme 10).



Scheme 10 *Reagents and conditions*: a) $Me_2AlSeMe$, DCM, rt; b) Bu_3SnH, AIBN, benzene, Δ, 67% overall yield, 94% ee.

In summary, we have developed a short and efficient route towards analogues of *epi*-morphine (8 steps, 29% overall yield). This approach hinges upon two key-steps: a one-pot silica-gel/base-catalysed polycyclisation sequence and an indoline-to-benzofuran transformation. We have also developed a practical synthesis of the optically enriched, key tetracyclic compound **5** (5 steps, 34% overall yield, 94% ee), using a modified LiOH-mediated imino-aldol cyclisation. Current efforts are now directed towards accessing fully functionnalised morphine analogues and applying this methodology to the synthesis of naturally occurring opioids.

Acknowledgements

The Université Catholique de Louvain and the Fonds National de la Recherche Scientifique are gratefully acknowledged for their financial support. István E. Markó is grateful to Merck Sharp & Dohme for its continuous support and SHIMADZU Benelux for their support in the purchase of the FTIR-8400S equipment.

Notes and references

‡ Crystal data for compound **8** (recrystallised from isopropanol): $C_{22}H_{23}NO_3$, $M = 349.41$, monoclinic, $a = 11.9450(10)$, $b = 11.653(2)$, $c = 16.339(2)$ Å, $\beta = 127.717(7)°$, $T = 293$ K, space group $P2_1/c$ (no. 14), $Z = 4$, $\mu = 0.684$, 3857 reflections measured, 3464 of which were used in all calculations; the final wR_1 was 0.0423 (all data). CCDC reference number 608856. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610148h.

§ Crystal data for compound **14** (recrystallised from isopropanol): $C_{24}H_{24}N_2O_4$, $M = 404.45$, monoclinic, $a = 17.576(3)$, $b = 15.667(2)$, $c = 7.4650(10)$ Å, $\beta = 90.561(11)°$, $T = 293$ K, space group Cc (no. 9), $Z = 4$, $\mu = 0.727$, 2287 reflections measured, 2235 of which were used in all calculations; the final wR_1 was 0.0387 (all data). CCDC reference number 608857. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610148h.

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7 Diastereoisomeric mixtures **12a** and **12f** were easily separated using classical flash chromatography techniques.
8 No traces of the other diastereoisomer has been detected in the crude mixture.
9 The use of ^{t}BuOK led, in this case, to extensive degradation of the substrate **14**.
10 The crystal that was selected for the X-ray analysis proved, rather surprisingly, to be the racemic product *rac*-**14**, originating from the crystallisation of the small amount of *ent*-adduct **14** with the major enantiomer of **14**. However, this is of no consequence, since this X-ray analysis gave us the required information about the relative stereochemistry of all the chiral centres present in the molecule. Since we employed optically active methyl ester **13** to prepare **14** and **5**, which was obtained with an optical purity of 94%, and since we know the absolute configuration of **13**, we can transpose our relative stereochemistry into an absolute one.
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