Asymmetric synthesis of 2-azabicyclo[3.3.1]nonanes by a microwave-assisted organocatalysed tandem desymmetrisation and intramolecular aldolisation†

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The six-membered nitrogen-containing ring of the morphan scaffold, ubiquitous in natural products, is formed by an intramolecular aldol process of an aza-tethered dicarbonyl compound, leading to the first asymmetric synthesis of a morphan derivative using organocatalysis.

Many biologically active natural products such as the immunosuppressant FR901483,[1] the cytotoxic agents aspernomine[2] and madangamine A,[3] the serine protease inhibitor suomilide,[4] as well as the classical alkaloids morphine,[5] strychnine,[6] and *Daphniphyllum*[7] contain the 2-azabicyclo[3.3.1]nonane (morphan) scaffold within their frameworks (Fig. 1). Nevertheless, very few methods are currently available to synthesise enantiopure morphans.[8] Of these, only the Eschenmoser approach relies on an asymmetric procedure, which involves a Diels–Alder catalysed by TADDOL in the key step.[8b] Thus, the development of catalytic enantioselective methods in the field of morphan synthesis remains challenging.

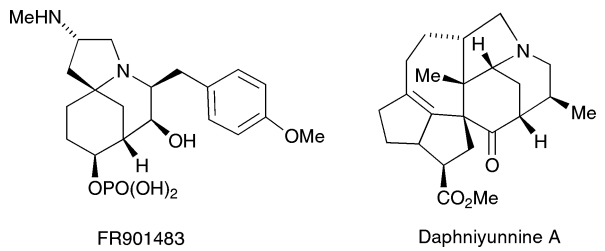
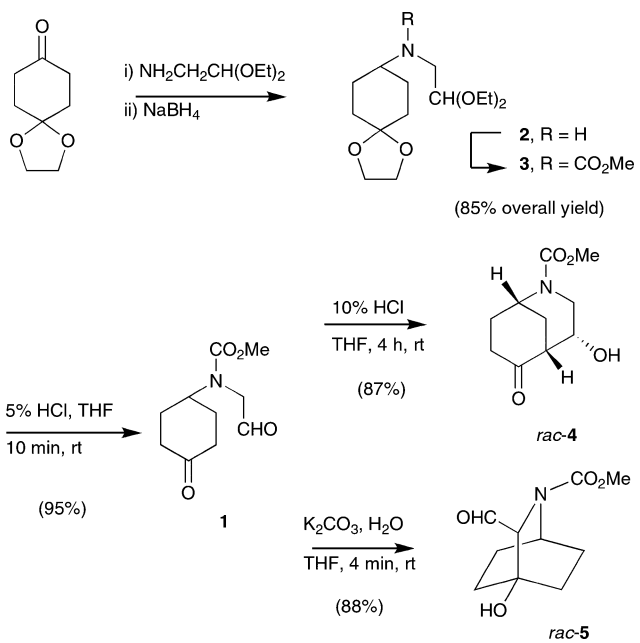


Fig. 1 Challenging morphan-containing alkaloids.

Here we report a direct, catalytic, highly diastereoselective and enantioselective approach to morphans using a proline-type organocatalysed intramolecular aldol reaction.[9–12] Although the bridged azabicyclic nucleus, when embedded in a more complex structure (e.g. FR901483[13,14] and dasycarpidan skeleton[15]), has been achieved by an aldol process, to date no general protocol has been developed to synthesise its scaffold using a classical aldol reaction upon an aminotethered keto aldehyde, even for racemic compounds. This could be partly attributed to the lability of the required 2-aminoacetaldehydes.[16,17]

In order to proceed with our studies, we required an achiral keto aldehyde of type **1**, which is unprecedented in the literature.[18] Reductive amination of 1,4-cyclohexanedione monoethylene acetal with aminoacetaldehyde diethyl acetal gave the secondary amine **2**, which was converted to the carbamate **3** (85% overall yield, Scheme 1). After several hydrolytic studies, we found that the treatment of **3** with 5% aqueous HCl in THF for 10 min at room temperature furnished the key intermediate keto aldehyde **1** (95%). If the acid treatment was performed (10% HCl) for a period of 4 h concomitant to the hydrolytic process the aldol cyclisation stereoselectively gave the bridged hydroxy ketone *rac*-**4** (87%). However, if the acid treatment was shortened to 25 min, the major compound isolated after the basic work-up was the isoquinuclidine *rac*-**5**. These results *a priori* suggested that **5** was produced by a kinetic-controlled process, while **4** derived from a thermodynamic control. Yet when **5** was submitted to acid treatment no reversion was observed and the isoquinuclidine was recovered. Thus, the formation of *rac*-**5** in a short reaction time was likely to be the result of the basic treatment in the work-up of the unreacted keto aldehyde. In fact, a few minutes of exposure of **1** to an aqueous K_2CO_3 solution gave compound **5** in good yield (88%).



Scheme 1 The regiodivergent synthesis of racemic **4** and **5**.

With the achiral keto aldehyde **1** and the racemic azabicyclic compounds *rac*-**4** and *rac*-**5** in hand, we turned our attention to the organocatalysed cyclisation of **1** and the deracemisation of the bridged β-hydroxy carbonyl compounds **4** and **5** to obtain the targeted enantioenriched morphan **4**. Starting from *rac*-**5** the best

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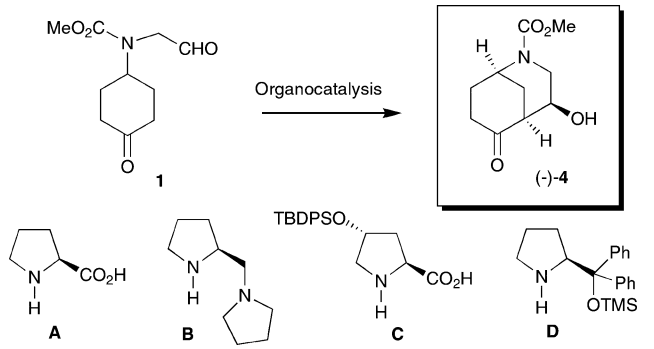
† Electronic supplementary information (ESI) available: Experimental and NMR data of all compounds and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b906835j

Table 1 Catalyst screening[a]



Entry	Catalyst	*t*/h	Cat. mol%	Yield (%)[b]	ee (%)[c]	**5** (%)
1	**A**[d]	48	50	10	8	35
2	**A**[e]	48	50	56	18	16
3	**B**[f]	48	50	38	-2	
4	**C**[g]	48	30	18	40	
5	**C**[h]	48	50	70	72	
6	**C**[i]	48	25	46	70	24
7	**D**[j]	48	20	20	3	50
8	**C**[k]	30 min	20	41	70	

[a] Unless otherwise noted, the reaction was carried out from 100 mg of keto aldehyde **1** at room temperature. [b] Yield of isolated product **4**. [c] Determined by chiral HPLC with a DAICEL Chiralpak IC column. [d] DMSO as the solvent. [e] CH_3CN as the solvent. [f] Trifluoroacetate salt of B was used. [g] H_2O as the solvent. [h] CH_3CN (2 mL), 10 equiv H_2O. [i] 50 mg scale. [j] CH_2Cl_2; benzoic acid (30%). [k] 100 °C, sealed tube.

result was observed using L-Pro (50%) in CH_3CN, compound (–)-**4** being obtained in 52% yield after one week, although with a low ee (33%). On the contrary, compound *rac*-**4** was found to be inert under the same reaction conditions.

The organocatalysed intramolecular reaction of **1** was studied with four proline derivatives (**A**–**D**) as shown in Table 1. L-Proline (**A**) catalysed the formation of **4** in very poor yield in DMSO, but in CH_3CN the conversion clearly improved (56%), although once again the ee was very low (entries 1,2). The bifunctional catalyst diamine **B**/TFA was also ineffective (entry 3). Treatment of keto aldehyde **1** with the proline-substituted catalyst **C**, using CH_3CN as a solvent in the presence of water,[19] gave the best results, producing (–)-**4** in 70% overall yield and 72% ee with total diastereoselectivity (entry 5). Catalyst **D** gave poor results in this aldol process, isoquinuclidine **5** being isolated in 50% yield (entry 7).

In order to assess if the rotamer ratio of the keto aldehyde **1** (2:1 at room temperature) had any effect upon the enantioselectivity of the process, the aldol reaction was carried out at 100 °C for 30 min using 20 mol% of catalyst **C**. Although the chemical yield of **4** was low (entry 8), the enantioselectivity was maintained, which ruled out the influence of the ratio rotamers.[20]

Since the best reaction conditions at room temperature were lengthy and required high catalyst loading (Table 1, entry 5), and considering that the enantioselectivity was maintained when working at 100 °C (entry 8), we decided to accelerate the process using microwave activation.[21] Indeed, as can be seen in Table 2, (–)-**4** was obtained in 70% yield, with total diastereoselectivity and the same enantioselectivity, after only 15 min and a lower amount of catalyst (entry 1).‡ When the reaction was carried

Table 2 Results of the microwave-assisted aldol reaction of **1** in the presence of L-4-(*tert*-butyldiphenylsilyloxy)proline **C**[a]

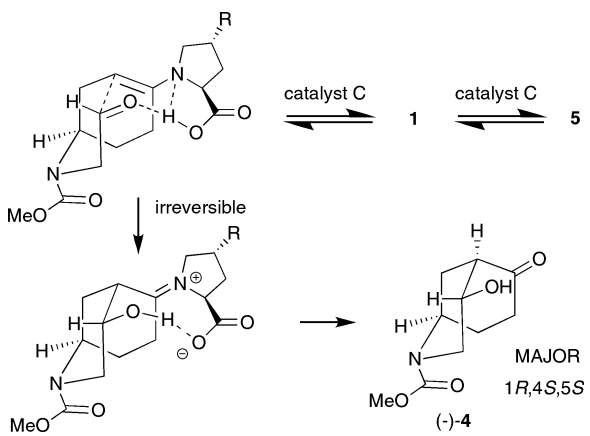
Entry	Time/min	Cat. mol%	Yield (%)[b]	ee (%)[c]	**5**
1	15	25	70	70	—
2[d]	15	25	78	54	—
3	15	20	70	65	—
4[e]	15	20	66	62	—
5	15	10	77	62	—
6	15	5	74	54	10
7	15	2.5	50	39	38
8	5	10	65	63	13

[a] All reactions were carried out in sealed 10 mL tubes. Maximal irradiated power 300 W. Maximal temperature 100 °C. CH_3CN was used as the solvent and H_2O (10 equiv) was added unless noted. [b] Yields of isolated compounds. [c] Determined by HPLC with a DAICEL Chiralpack IC column. [d] H_2O was omitted. [e] BINOL (3%) was used as an additive

out without water, the ee clearly diminished (entry 2). Decreasing the catalyst loading from 25% to 20% had practically no effect (entry 3), but further reductions to 10%, 5%, and 2.5% led to a drop in ee (entries 5–7). The use of L-BINOL (3%) as an additive did not improve the results (66% yield, 62% ee). Finally, it is also worth mentioning that when using catalyst **C** (10%) under microwave conditions, isoquinuclidine *rac*-**5** was converted to (–)-**4** (74% yield, 60% ee) while, as expected, *rac*-**4** and enantioenriched **4** remained unchanged.

A remaining task was to determine the absolute configuration of the major heterocyclic ring formed. Thus, a sample of enantioenriched (–)-**4** was converted to the corresponding OAc-mandelic derivatives[22] (see ESI†), which were separated by column chromatography. NMR analysis of both diastereomers of **4**.AcMA allowed us to assign the configuration 1*R*,4*S*,5*S* to the major enantiomer.

The proposed mechanism for the synthesis of enantioenriched aldol **4** through reaction of the prochiral keto aldehyde **1** is illustrated in Scheme 2. The kinetically formed isoquinuclidine **5** evolves to morphan **4**, since the first aldol process (**1** → **5**), in which the aldehyde and ketone act as a nucleophile and electrophile, respectively, is reversible. The transformation (**1** → **4**) involves two successive steps: an asymmetric desymmetrisation for the enamine formation, and a diastereoselective and enantioselective aldol cyclisation of the generated enamine. The results suggest that the asymmetric induction in the initial enamine formation



Scheme 2 The organocatalyzed synthesis of (–)-**4**.

was not very high, while the diastereoselectivity of the second aldol process was excellent. Since the treatment under proline-type catalysis of *rac*-**4** and (–)-**4** gave the starting material unchanged, we can conclude that the reverse aldolisation was not operative in these reaction conditions. Thus, the observed enantioselectivity was determined by an irreversible kinetically-controlled step in which the ketone acts as a nucleophile (Scheme 2). Additionally, it is worth mentioning that water plays an effective role in the process,[23] probably with a favourable hydrophilic interaction in the transition state leading to (–)-**4** (compare entries 1 and 2 in Table 2).

In summary, we have described the first nitrogen-containing ring synthesis by means of an asymmetric aldol reaction using organocatalysis. The desymmetrisation of a prochiral 4-*N*-protected aminocyclohexanone[24] through its intramolecular aldolisation, as reported here, still has some outstanding enantioselectivity issues to be resolved. With the aim of improving the enantioselectivity of the process and applying it to natural product synthesis, studies with additional chiral amines are ongoing.

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Notes and references

‡ Reaction procedure: in a 10 mL vessel were placed keto aldehyde **1** (100 mg, 0.47 mmol), catalyst **C** (43 mg, 0.12 mmol, 25%), acetonitrile (1 mL) and water (0.08 mL, 4.7 mmol). The mixture was heated with stirring to 100 °C using microwave irradiation for 15 min. After concentration, the reaction mixture was purified by chromatography (dichloromethane/ethyl acetate 1:1) to give **4** (70 mg, 70%) as a viscous colourless oil: HPLC (Daicel Chiralpak IC, dichloromethane/methanol 99:1, 1 mL min^{-1}, $\lambda = 290$ nm; major isomer t = 8.48 min; minor isomer 9.63 min); IR (NaCl, neat): 3413, 1698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, gCOSY) 1.90–2.24 (m, 4H), 2.46 (dt, 1H, $J = 18$, 8.4 Hz, H-7ax), 2.59 (ddd, 1H, $J = 18$, 9.2, 4.8 Hz, H-7eq), 2.82 (br s, 1H, H-5), 2.89 (t, 1H, $J = 12.4$ Hz, H-3ax), 3.24 and 3.27 (2d, 1H, $J = 5.6$ Hz, OH), 3.73 (s, 3H, CH_3), 3.98 (br s, 1H, H-4), 4.23 and 4.37 (2dd, 1H, $J = 13.2$, 6 Hz, H-3eq), 4.45 and 4.61 (2brs, 1H, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz, gHSQC) 27.7 and 28.6 (C-9), 29.4 and 29.9 (C-8), 38.3 (C-7), 43.4 and 43.7 (C-1), 45.9 and 46.1 (C-3), 49.4 (C-5), 52.8 (CH_3), 67.4 and 67.7 (C-4), 156.0 (CO), 212.3 and 213.2 (C-6). HRMS (ESI-TOF) Calcd for $C_{10}H_{16}NO_4$: 214.1073 ($M + H^+$), Found 214.1074.

1 (*a*) J. Bonjoch and F. Diaba, *Studies in Natural Products Chemistry*, 2005, **32**, 3–60; (*b*) C. A. Carson and M. A. Kerr, *Org. Lett.*, 2009, **11**, 777–779 and references therein.
2 G. M. Staub, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *J. Am. Chem. Soc.*, 1992, **114**, 1015–1017.
3 J. Quirante, L. Paloma, F. Diaba, X. Vila and J. Bonjoch, *J. Org. Chem.*, 2008, **73**, 768–771 and references therein.
4 C. S. Schindler, C. R. J. Stephenson and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 8852–8855.
5 (*a*) J. Zezula and T. Hudlicky, *Synlett*, 2005, 388–405; (*b*) H. Tanimoto, R. Saito and N. Chida, *Tetrahedron Lett.*, 2008, **49**, 358–361 and references therein.
6 (*a*) J. Bonjoch and D. Solé, *Chem. Rev.*, 2000, **100**, 3455–3482; (*b*) J. Boonsombat, H. Zhang, M. J. Chughtai, J. Hartung and A. Padwa, *J. Org. Chem.*, 2008, **73**, 3539–3550 and references therein.
7 D. Solé, X. Urbaneja and J. Bonjoch, *Org. Lett.*, 2005, **7**, 5461–5464 and references therein.
8 (*a*) J. Quirante, M. Torra, F. Diaba, C. Escolano and J. Bonjoch, *Tetrahedron: Asymmetry*, 1999, **10**, 2399–2410; (*b*) G. Karig, A. Fuchs, A. Büsing, T. Brandstetter, S. Scherer, J. W. Bats, A. Eschenmoser and G. Quinkert, *Helv. Chim. Acta*, 2000, **83**, 1049–1078; (*c*) J. Quirante, F. Diaba, X. Vila, J. Bonjoch, E. Lago and E. Molins, *C. R. Acad. Sci*, 2001, **4**, 513–521; (*d*) M. Amat, M. Pérez, A. T. Minaglia and J. Bosch, *J. Org. Chem.*, 2008, **73**, 6920–6923.
9 For some reviews about asymmetric aminocatalysis of aldol processes, see: (*a*) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong and K. N. Houk, *Acc. Chem. Res.*, 2004, **37**, 558–569; (*b*) G. Guillena, C. Nájera and D. J. Ramon, *Tetrahedron: Asymmetry*, 2007, **18**, 2249–2293; (*c*) C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2008, **47**, 42–47; (*d*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138–6171.
10 Apart from the studies in the Wieland–Miescher ketone and analogs synthesis,[11] few examples of asymmetric intramolecular aldol processes using organocatalysis have been reported[12].
11 (*a*) T. Bui and C. F. Barbas III, *Tetrahedron Lett.*, 2000, **41**, 6951–6954; (*b*) B. List, L. Hoang and H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5839–5842 and references therein; (*c*) S. G. Davies, A. J. Russell, R. L. Sheppard, A. D. Smith and J. E. Thompson, *Org. Biomol. Chem.*, 2007, 3190–3200; (*d*) D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056–5068; (*e*) T. Kanger, K. Kriis, M. Laars, T. Kailas, A.-M. Müürisepp, T. Pehk and M. Lopp, *J. Org. Chem.*, 2007, **72**, 5168–5173; (*f*) G. Guillena, C. Nájera and S. F. Viózquez, *Synlett*, 2008, 3031–3035.
12 (*a*) C. Pidathala, L. Hoang, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2003, **42**, 2785–2788; (*b*) N. Itagaki, M. Kimura, T. Sugahara and Y. Y. Iwabuchi, *Org. Lett.*, 2005, **7**, 4185–4188; (*c*) Y. Hayashi, H. Sekizawa, J. Yamaguchi and H. Gotoh, *J. Org. Chem.*, 2007, **72**, 6493–6499; (*d*) J. Zhou, V. Wackchaure, P. Kraft and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 7656–7658.
13 For racemic compounds, see: (*a*) J.-H. Maeng and R. L. Funk, *Org. Lett.*, 2001, **3**, 1125–1128; (*b*) T. Kan, T. Fujimoto, S. Ieda, Y. Asoh, H. Kitaoka and T. Fukuyama, *Org. Lett.*, 2004, **6**, 2729–2731.
14 For enantiopure compounds by diastereoselective processes, see: (*a*) B. B. Snider and H. Lin, *J. Am. Chem. Soc.*, 1999, **121**, 7778–7786; (*b*) G. Scheffler, H. Seike and E. J. Sorensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4593–4596; (*c*) M. Ousmer, N. A. Braun, C. Bavoux, M. Perin and M. A. Ciufolini, *J. Am. Chem. Soc.*, 2001, **123**, 7534–7538; (*d*) S. Kaden and H.-U. Reissig, *Org. Lett.*, 2006, **8**, 4763–4766.
15 S. Patir, P. Rosenmund and P. H. Goetz, *Heterocycles*, 1996, **43**, 15–22.
16 For *N*-dealkylations of aminoacetaldehyde derivatives, see: D. Solé, J. Bosch and J. Bonjoch, *Tetrahedron*, 1996, **52**, 4013–4028 and references therein.
17 For the use of a protected aminoacetaldehyde in organocatalytic asymmetric intermolecular aldol reactions, see: R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2004, **6**, 3541–3544.
18 A search in SciFinder reveals that the structure of 4-(2-oxoethyl)aminocyclohexanone (**1**) has not been reported for any *N*-substituent-type.
19 Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 8103–8104.
20 The influence of the protecting group on the nitrogen atom was unexplored. In any case, the use of a phthalimido protecting group, which was the key in Barbas' work (ref. 17), is structurally impossible in the synthesis of nitrogen-containing rings.
21 For some organocatalyzed asymmetric reactions *via* microwave activation: (*a*) B. Westermann and C. Neuhaus, *Angew. Chem., Int. Ed.*, 2005, **44**, 4077–4079; (*b*) B. Rodríguez and C. Bolm, *J. Org. Chem.*, 2006, **71**, 2888–2891; (*c*) S. Mossé and A. Alexakis, *Org. Lett.*, 2006, **8**, 3577–3580; (*d*) M. Hosseini, N. Stiasni, V. Barbieri and C. O. Kappe, *J. Org. Chem.*, 2007, **72**, 1417–1424.
22 (*a*) I. Chataigner, J. Lebreton, D. Durand, A. Guingant and J. Villiéras, *Tetrahedron Lett.*, 1998, **39**, 1759–1762; (*b*) J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17–117.
23 For a review about water in stereoselective organocatalytic reactions, see: M. Gruttadauria, F. Giacalone and R. Notoa, *Adv. Synth. Catal.*, 2009, **351**, 33–57.
24 The only precedent of a 4-aminocyclohexanone asymmetric desymmetrization is upon the $N(Boc)_2$ derivative and using Simpkins' base: V. K. Aggarwal and B. Olofsson, *Angew. Chem., Int. Ed.*, 2005, **44**, 5516–5519.