Enantioselective Synthesis of a (1*R*,5*R*,9*R*)-2-Azabicyclo[3.3.1]nonane-9-carboxylic Acid with an Embedded Morphan Motif: A Multipurpose Product

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Abstract: A convenient asymmetric synthesis of (1*R*,5*R*,9*R*)-2-azabicyclo[3.3.1]nonane-9-carboxylic acid is described, starting from (2*E*,7*E*)-dimethyl nonadienedioate. The route involves a stereoselective domino Michael–Dieckman process that furnishes a 1,2,3-trisubstituted cyclohexane derivative bearing three adjacent stereocenters with full stereochemical control. A subsequent chemoselective transformation of one of the side-chain ester groups allows an effective second cyclization leading to the morphan motif. The versatility of this novel amino acid for the generation of molecular complexity was tested by elaborating a tripeptide in homogeneous phase.

Key words: β-amino acids, asymmetric synthesis, Michael addition, morphan, GABA uptake inhibitors

Amino acids are one of the most widespread and biologically relevant families of substances. Within this group, β-amino acids are gaining importance, as a result of their multiple advantages (higher resistance to enzyme degradation, higher conformational freedom) over their natural homologues, leading to a wide variety of interesting applications.[1] Nowadays, great efforts are being directed at finding ways to introduce new scaffolds and additional functionalities in these compounds, allowing their use as building blocks for the construction of peptidomimetics. The inclusion of bridged bicyclic backbones is a striking example. This transformation restricts the conformational space of the molecule, which can be exploited to reach several goals, such as restricting the flexibility of peptides[2] or stabilizing the helical secondary structure and helix-bundle quaternary structures that organize helical folding by replacing flexible β[3]-residues with their cyclic analogues.[2b]

The 2-azabicyclo[3.3.1]nonane skeleton is present in several important narcotic analgesics like (–)-morphine[3] (**1**, Figure 1) and its derivatives; in (+)-aspernomine (**2**), an insecticide, antifungal, and cytotoxic natural product;[4] the madangamines[5] (**3**), a family of marine alkaloids from *Xestospongia ingens*, and the novel aeroginusin family of serine protease inhibitors headed by (+)-suomilide[6] (**4**). In the literature, this bicyclic system has been synthesized employing nonstereoselective radical[7] and Mannich[8] reactions; organocatalytic[9] approaches have also been employed, with moderate enantioselection.

Our research group has experience[10] in the asymmetric addition of chiral lithium (α-methylbenzyl)benzylamide [(*R*)-**6** or (*S*)-**6**] to binary Michael systems **5**. Using (2*E*,6*E*)-octadienedioate, (2*E*,7*E*)-nonadienedioate, and (2*E*,8*E*)-decadienedioate as either symmetric diesters or orthogonal acceptors, a collection of cyclic (**7**, **9**, **10**) or linear (**8**, **11**, **12**) derivatives has been assembled, with total stereochemical control in all cases (Scheme 1).

The *E* stereochemistry of the double bonds in the substrates has a key role in avoiding the potential competition between addition and γ-deprotonation.[10] Thus, when the

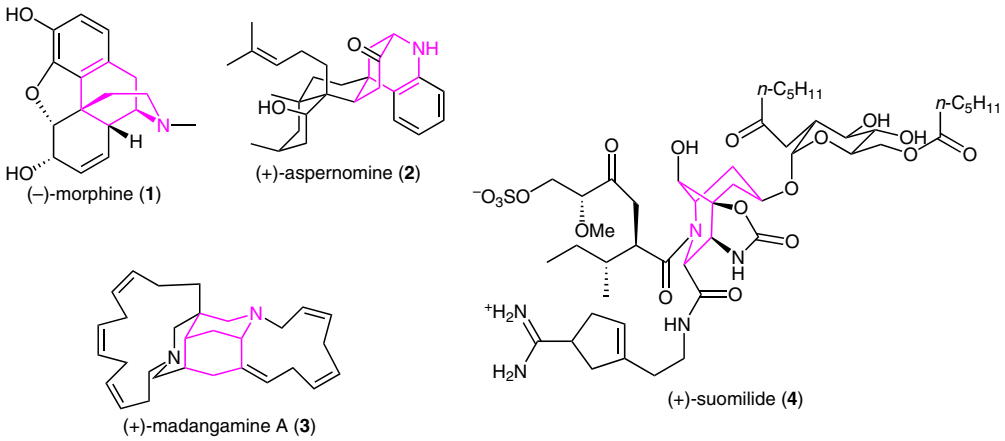

Figure 1 Structures with a morphan core

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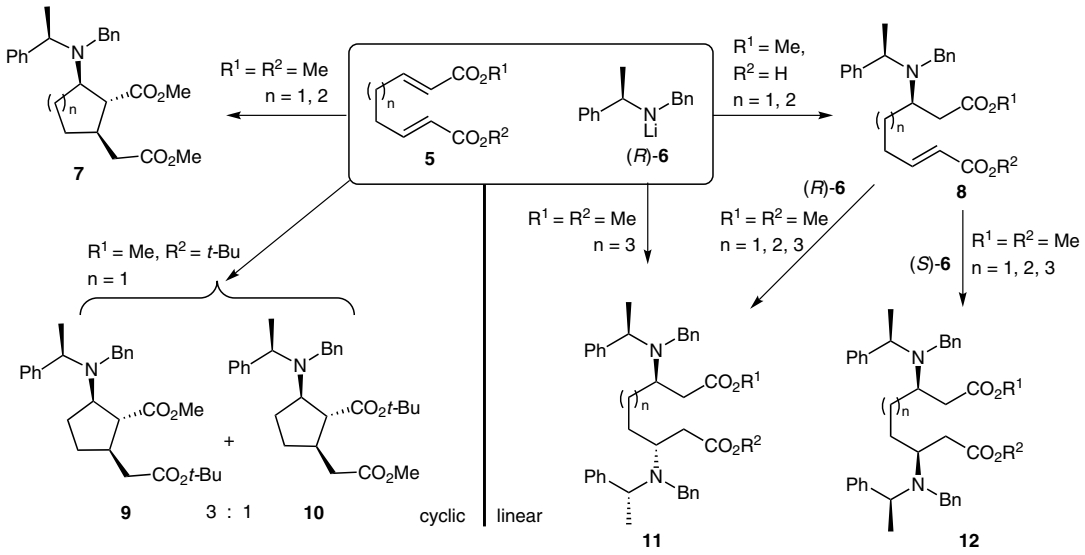


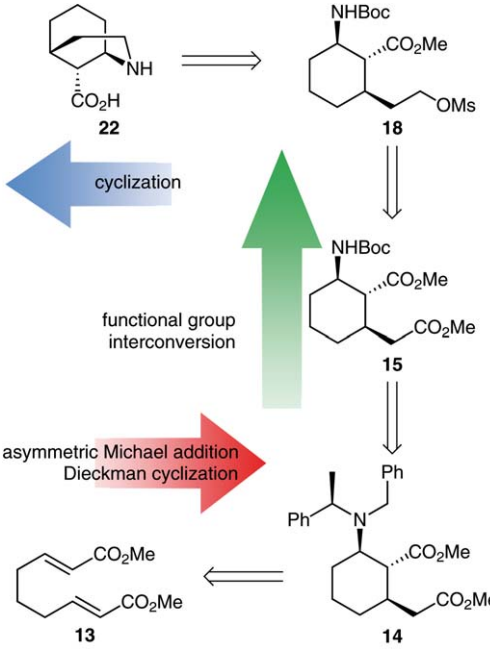
Scheme 1 Spectrum of the adducts of (*R*)-**6** and (*S*)-**6** over binary Michael acceptors

E,*Z* counterpart or the acid ester (**5**, R^1 =Me, R^2 =H) was used, the monoaddition adduct was obtained.[10a,g] Interestingly, these monoaddition products can be used to give the diaddition derivatives by a second addition of the suitable chiral *R*- or *S*-amide (Scheme 1), increasing the stereochemical range of the method.[10g]

Herein we report the enantioselective synthesis of several β-amino acids and esters containing a 2-azabicyclo[3.3.1]nonane (morphan) motif embedded in their structures. Scheme 2 shows the retrosynthetic route from the morphan backbone to the starting material, (2*E*,7*E*)-dimethyl nonadienedioate, which is readily available from azelaic acid in two steps.[11] In essence, the procedure has three keys stages: 1) asymmetric conjugate addition of the chiral amine[12] (*R*)-**6** to the binary Michael acceptor (2*E*,7*E*)-dimethyl nonadienedioate, achieving the assembly of the cyclohexane ring with the desired absolute and relative stereochemistry; 2) protecting-group exchange from the dibenzyl amine to the Boc amine, which leads to better yields in subsequent functional-group transformations, and 3) cyclization to the final morphan structure. The generation of the morphan framework late in the sequence was dictated by the reluctance of the centers involved in the morphan core to undergo forward transformations.[13]

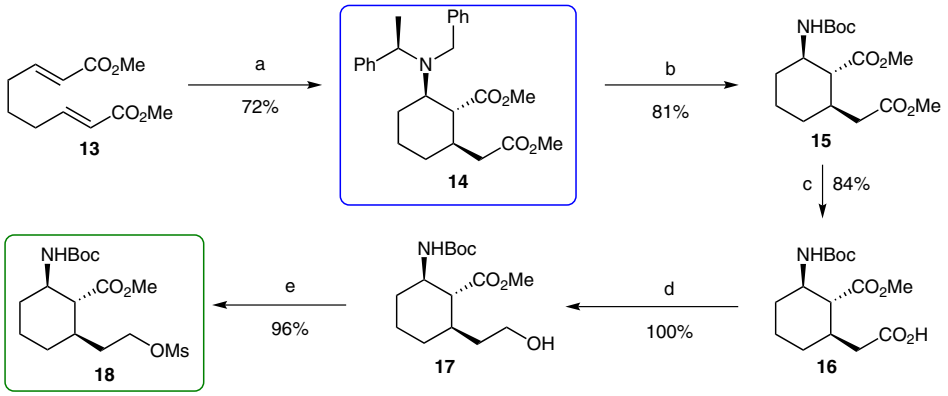
The route starts with the previously discussed reaction between the lithium (α-methylbenzyl)benzylamide (*R*)-**6** and substrate **13** that furnished **14** in 72% yield (de > 95%)[10c,d,g] via a domino sequence comprising an asymmetric Michael addition and a 6-*exo*-*trig* cyclization that generated one ring and three contiguous stereocenters in a fully controlled fashion (Scheme 3).[14]

The next stage, aiming at protecting-group interconversion, involved releasing the free primary amine by hydrogenation in the presence of $Pd(OH)_2/C$ at 3.5 bar and reprotecting it as a Boc carbamate with Boc_2O in one pot. In our experience, the presence of the tertiary amine in **14** complicates the reaction steps towards the cyclization to the morphan core.[13] In the next step, we transformed selectively the ester group in the C-6 side chain of **15** into a mesylate.



Scheme 2 Retrosynthetic scheme of the 9-substituted morphan core

Selective hydrolysis of the desired ester using $LiOH·H_2O$ in MeOH–THF–H_2O (3:1:1) was possible, presumably as a consequence of the shielding of the ester in position 1 by the carbamate group. BH_3·THF reduction[10a,15] of the resulting acid led to the corresponding alcohol in quantitative yield. A final esterification of **17** with MsCl/pyridine catalyzed by DMAP in CH_2Cl_2 afforded mesylate **18** in high yield.

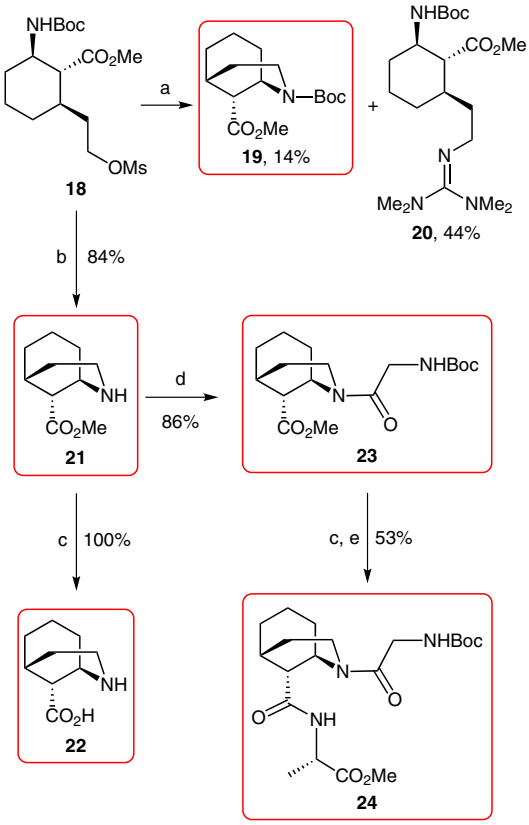


Scheme 3 *Reagents and conditions*: (a) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide [(*R*)-**6**; 1.6 equiv], THF, –78 °C; (b) $Pd(OH)_2/C$, H_2 (3.5 bar), Boc_2O, EtOAc, 3 d; (c) $LiOH·H_2O$, MeOH–THF–H_2O (3:1:1), 4 h; (d) BH_3·THF, THF, 20 °C, 60 min; (e) MsCl, pyridine, DMAP, CH_2Cl_2, 2 h.

Finally, we undertook the cyclization of **18** to generate the morphan core. Taking into account the presence of the Boc carbamate, two approaches were conceived (Scheme 4). First, we carried out the cyclization on the Boc carbamate under basic conditions with 1,1,3,3-tetramethylguanidine (TMG) in toluene.[16] However, competition between the nucleophilic and base nature of TMG led to 14% yield of the morphan-derived protected amino acid **19** and the TMG substitution product of the mesylate **20** in a 44% yield. Alternatively, deprotection of the carbamate **18** under acidic conditions with TFA followed by treatment with Et_3N to promote cyclization[17] of the free amine gave amino ester **21** in 84% yield.[18] Hydrolysis of the ester with $LiOH·H_2O$ quantitatively afforded the corresponding amino acid **22**, isolated in its neutral form by ion-exchange chromatography followed by freeze-drying.

In order to examine the application of these compounds in peptide chemistry, the synthesis of tripeptide **24** was envisaged (Scheme 4). Homogeneous-phase coupling of **21** with *N*-(*tert*-butoxycarbonyl)glycine in the presence of EDCI and 1-hydroxybenzotriazole led to dipeptide **23** in 86% yield {$[\alpha]_D^{20}$ –32.4 (*c* 1.54, $CHCl_3$)}. Hydrolysis of the ester with $LiOH·H_2O$ and subsequent coupling with L-alanine methyl ester hydrochloride in the same conditions afforded tripeptide **24** {$[\alpha]_D^{20}$ –7.6 (*c* 0.41, $CHCl_3$)}.[19]

In conclusion, we have developed a methodology that allows the easy preparation in seven steps of **22**, an enantiomerically enriched 9-substituted morphan-type amino acid, with a global yield of 40%. All three stereocenters are defined in a tandem asymmetric Michael addition–Dieckman cyclization, and hence use of the *S*-amine would make the other enantiomer accessible. Moreover, the versatility of this amino acid was demonstrated coupling it with two common amino acids, evidencing the accessibility of the amino and carboxylic acid functions. These amino acids may be valuable products in the search of bridged constrained amino acids, in the development of new turns and hairpins in peptide structures. Their resemblance to morphine make them suitable to explore their potential as narcotic analgesics, and their similarity with guvacine or isoguvacine may make them interesting in the study of GABA uptake inhibition processes.[20]



Scheme 4 *Reagents and conditions*: (a) tetramethylguanidine, toluene, 100 °C, 12 h; (b) TFA, CH_2Cl_2, 2 h, then Et_3N, EtOH, 12 h; (c) $LiOH·H_2O$, MeOH–THF–H_2O (3:1:1), 2 h; (d) *N*-(*tert*-butoxycarbonyl)glycine, EDCI, 1-hydroxybenzotriazole, DMF, r.t., 12 h; (e) L-alanine methyl ester hydrochloride, EDCI, 1-hydroxybenzotriazole, DIPEA, DMF, r.t., 12 h.

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(18) **Typical Procedure**
Mesylate **18** (18 mg, 0.047 mmol) was dissolved in CH_2Cl_2–TFA 1:1 (5 mL) and stirred 2 h at r.t. Solvent was evaporated, and the crude was further dissolved in EtOH–Et_3N 1:1 (5 mL). The mixture was refluxed at 80 °C for 20 h. The solvent was again evaporated and the crude dissolved in EtOAc (30 mL) and extracted with HCl (0.5 M, 30 mL). The aqueous phase was basified to pH 8 with NaOH (1 M) and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed at reduced pressure. Purification of the crude product by flash chromatography ($CHCl_3$–MeOH, 9:1) provided **21** (7.1 mg, 84%) as an oil. $[\alpha]_D^{20} = -4.01$ (*c* 0.71, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65–2.24 (m, 8 H, H-4, H-6, H-7, H-8), 2.52 (s, 1 H, H-5), 3.06 (s, 1 H, H-9), 3.27 (dd, *J* = 13.5, 7.3 Hz, 1 H, H-3$_{eq}$), 3.44 (dt, *J* = 13.5, 8.0 Hz, 1 H, H-3$_{ax}$), 3.73 (s, 3 H, OCH_3), 3.91 (br s, 1 H, H-1), 5.51 (br s, 1 H, NH). IR (neat): 3396, 2931, 2858, 1733, 1426, 1384, 1287, 1203, 1124, 1405, 1023 cm^{-1}. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.8, 23.4, 25.5, 26.9, 28.9, 40.1, 43.6, 47.7, 52.7, 171.3. HRMS: *m*/*z* calcd for $C_{10}H_{18}NO_2$ [M + H]: 184.1332; found: 184.1313.

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