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A Concise Approach to 2-Azabicyclo[3.3.1]nonane Derivatives from an Acyclic Precursor

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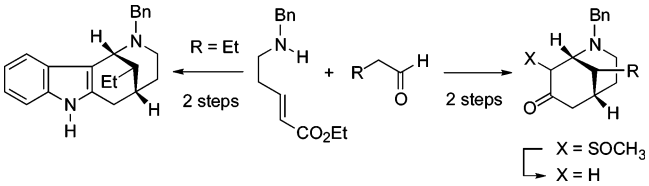

Condensation of a readily available 5-amino-2-alkenoate ester with α-unsubstituted aliphatic aldehydes leads to substituted 1,2,3,4-tetrahydropyridines. Subsequent manipulation of the ester and enamine functions gives a quick access to 2-azabicyclo[3.3.1]nonane-containing compounds.

The synthesis of the 2-azabicyclo[3.3.1]nonane (morphan) skeleton is a topic of current interest due to its occurrence in a number of natural products and other compounds of biological relevance.[1] Some approaches to the morphan framework have utilized cyclic enamines related to tetrahydropyridines **2**−**4** either as synthetic precursors or reaction intermediates.[1a−d,g,o] For example, tetrahydropyridines **2** and **3** are key intermediates in the acid-promoted equilibration of *cis*- and *trans*-iminium ions **6** (Y = Ac or indol-2-yl, R = Et), leading to **7** and **8**, respectively, which are common precursors in the total syntheses of several uleine and *Strychnos* alkaloids.[1b,c,2] Some of these approaches rely on the use of α-aminonitriles **5** to generate iminium ions **6**. However, this presents the drawback of lack of regioselectivity in the formation of **5** from the corresponding 3,4-disubstituted piperidine precursors, thus reducing the efficiency of the overall process.[1b,3] We report here an alternative strategy for the assembly of the 2-azabicyclo[3.3.1]nonane bicyclic system that takes advantage of (i) a direct one-step regioselective synthesis of tetrahydropyridines **4** from a readily available acyclic amine **1** and (ii) the generation of the morphan skeleton in one step from **4** using conventional procedures for manipulation of the ester functionality. The application of this strategy to the preparation of **7** and analogues thereof, as well as an expeditious one-pot synthesis of tetracyclic indole **8** from **4a** (R = Et), will be demonstrated.

We have already reported the simple preparation of bicyclic lactone analogues of enamines **4** by condensation of α-unsubstituted aliphatic aldehydes (RCH_2CHO) with γ,δ-unsaturated secondary amines derived from the vinylogous Mannich reaction between trimethylsilyloxyfuran and iminium ions.[4] The application of this kind of reaction to the preparation of enamine **4a** required the condensation of amine **1**[5] and butyraldehyde (**9a**) (Scheme 2). Thus, heating a mixture of **1** and **9a** in EtOH gave, after chromatographic purification, a good yield (77%) of tetrahydropyridine **4a**, which was fully characterized spectroscopically. The identity of **4a** was further confirmed by its conversion into the known piperidines **10**[6] (Scheme 2).

It was initially envisioned that conversion of **4a** into the corresponding methyl ketone **2**, followed by acid treatment, would yield 7-oxomorphan **7** via an intramolecular Mannich reaction.[1b] Thus, following the reported protocol for transformation of a related ester into the corresponding methyl ketone,[6] **4a** was treated with methylsulfinyl carbanion,[7] and this resulted in the direct formation of morphan derivative **11a** (Scheme 3). This became apparent by the absence of the typical enaminic proton resonance displayed by **4a** at δ ~5.80 and was chemically confirmed by reduction of **11a** with Zn/AcOH, which afforded the desulfinylated product **12a**, identified by comparison of its spectroscopic properties with those reported for the C-9 epimer of 7-oxomorphan **7**.[1b]

It is interesting that presumably related intermediates of type **6** would yield different relative configurations at

(1) Selected representative references: (a) Amat, M.; Sanfeliu, E.; Bonjoch, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 3841−3844. (b) Gracia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939−3951. (c) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765−766. (d) Thomas, J. B.; Zheng, X. L.; Brieaddy, L. E.; Burgess, J. P.; Mascarella, S. W.; Fix, S. E.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *Tetrahedron Lett.* **1998**, *39*, 7001−7004. (e) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968−976. (f) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157−1162. (g) Thomas, J. B.; Gigstad, K. M.; Fix, S. E.; Burgess, J. P.; Cooper, J. B.; Mascarella, S. W.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *Tetrahedron Lett.* **1999**, *40*, 403−406. (h) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225−2228. (i) Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Heterocycles* **2001**, *54*, 747−755. (j) Maeng, J. H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125−1128. (k) Brummond, K. M.; Lu, J. L. *Org. Lett.* **2001**, *3*, 1347−1349. (l) Wardrop, D. J.; Zhang, W. M. *Org. Lett.* **2001**, *3*, 2353−2356. (m) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013−3015. (n) Hashimoto, A.; Jacobson, A. E.; Rothman, R. B.; Dersch, C. M.; George, C.; Flippen-Anderson, J. l.; Rice, K. C. *Bioorg. Med. Chem.* **2002**, *10*, 3319−3329. (o) Kim, I. J.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *Bioorg. Med. Chem.* **2004**, *12*, 4543−4550. (p) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681−8693. (q) Carroll, F. I.; Zhang, L.; Mascarella, S. W.; Navarro, H. A.; Rothman, R. B.; Cantrell, B. E.; Zimmerman, D. M.; Thomas, J. B. *J. Med. Chem.* **2004**, *47*, 281−284. (r) Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907−916.

(2) For enantioselective syntheses of these alkaloids, see references 1c, 1p, and references therein.

(3) See also Díez, A.; Castells, J.; Forns, P.; Rubiralta, M.; Grierson, D. S.; Husson, H.-P.; Solans, X.; Font-Bardía, M. *Tetrahedron* **1994**, *50*, 6585−6602 for a different approach to related α-cyanopiperidines that also suffers from regioselectivity problems.

(4) Aurrecoechea, J. M.; Suero, R. *Tetrahedron Lett.* **2005**, *46*, 4945−4947.

(5) (a) Hirai, Y.; Terada, T.; Hagiwara, A.; Yamazaki, T. *Chem. Pharm. Bull.* **1988**, *36*, 1343−1350. (b) Aurrecoechea, J. M.; Fernández, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, *55*, 7345−7362.

(6) Bonjoch, J.; Linares, A.; Guardià, M.; Bosh, J. *Heterocycles* **1987**, *26*, 2165−2174. For a recent enantioselective synthesis of 3-ethyl-4-piperidineacetates, see ref 1p.

(7) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345−1353.

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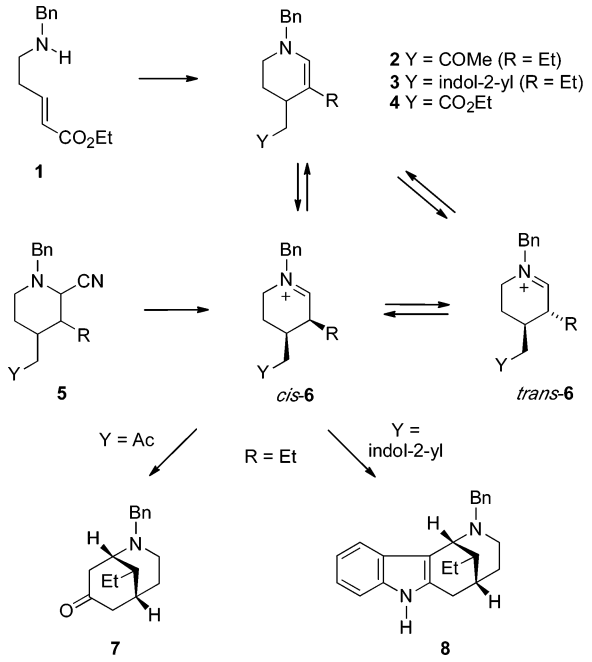
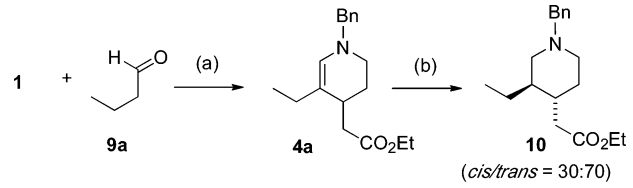
SCHEME 1. Synthetic Approaches to 7-Oxomorphan 7 and Tetracyclic Indole 8

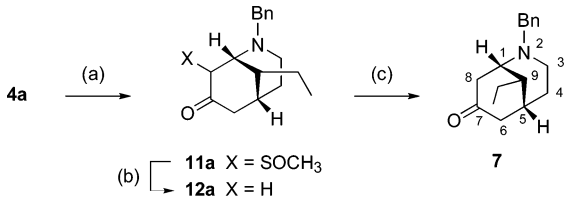


SCHEME 2. Preparation of Piperidine 10 from Amine 1 and Butyraldehyde[a]



[a] Reagents and conditions: (a) EtOH, reflux; (b) $NaBH_3CN/ZnCl_2$, THF, MeOH, rt.

SCHEME 3. Preparation of Morphan Derivatives from Tetrahydropyridine 4a[a]



[a] Reagents and conditions: (a) DMSO/NaH, THF, 0 → 25 °C; (b) Zn/AcOH, EtOH, 65 °C; (c) 12 N HCl, MeOH, reflux.[1b]

C-9 in 3-azabicyclo[3.3.1]nonan-7-ones **7** and **12a** prepared from α-cyanopiperidine **5**[1b] or enamine **4a**, respectively. Isomer **7** was calculated to be more stable than **12a**, and in fact, the complete conversion of **12a** into **7** has been reported under relatively strong acidic conditions, presumably via enamine **2**.[1b] It is apparent that in our case proton transfer takes place at the level of putative intermediate **13** to give **14** with a *trans*-arrangement between the ethyl and ketosulfoxide moieties (Scheme 4). Subsequent cyclization from the diaxial conformer **15** then affords the kinetic product **11**, and the implication is that both **11** and its derived reduced product **12** are configurationally stable under the relatively mildly acidic cyclization and desulfinylation conditions, respectively.

SCHEME 4. Mechanism of Formation of 11 from 4

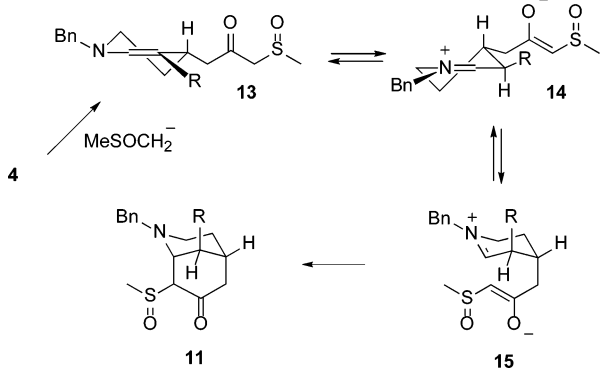
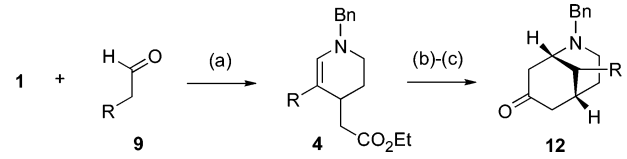


TABLE 1. Preparation of Tetrahydropyridines 4 and Morphans 12 from Amine 1 and Aldehydes 9[a]



	R	yield of **4**[b]	yield of **12**[b]
1[c]	Et	77 (**4a**)	43 (**12a**)
2	CH_2Ph	75 (**4b**)	43 (**12b**)
3	*i*-Pr	67 (**4c**)	45 (**12c**)

[a] Reagents and conditions: (a) EtOH, 4 Å MS, reflux; (b) DMSO/NaH, THF, 0 → 25 °C; (c) Zn/AcOH, EtOH, 65 °C. [b] Yield (%) of isolated purified product. [c] Reaction run without 4 Å MS.

TABLE 2. Comparison of ^{13}C NMR Resonances for Morphans 7, 12a−c[a]

morphan	C-4	C-6	C-8
7[b]	32.7	42.4	35.9
12a	26.4	48.4	40.4
12b	26.3	48.3	40.4
12c	26.4	48.5	40.4

[a] Selected chemical shifts (δ). Assignments were made on the basis of δ values and DEPT data and by comparison with the extensive data collected in ref 8. [b] Data taken from ref 8.

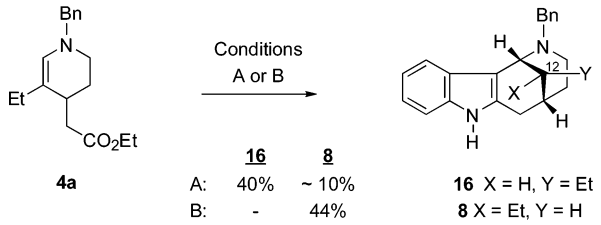
The chemistry described in Schemes 2−4 readily suggests the possibility of preparing 3-azabicyclo[3.3.1]-nonan-3-one derivatives using amine **1** and aldehydes **9** other than butyraldehyde. Thus, following the same protocols, 3-phenylpropanal and isovaleraldehyde also led with similar ease to 7-oxomorphans **12b,c**, as single diastereoisomers, through the corresponding tetrahydropyridines **4b,c** (Table 1).

The relative stereochemistry of **12b,c** at C-9 was initially assigned by analogy with that of the known **12a** and later confirmed by the observation of diagnostic C-4, C-6, and C-8 ^{13}C NMR resonances that had closely similar values within the series **12a−c** but differed substantially from those of the (C-9)-epimer **7** (Table 2).[8]

On the basis of the above results, the preparation of tetracyclic indole derivative **8** (Scheme 1) was readily

(8) Casamitjana, N.; Bonjoch, J.; Gràcia, J.; Bosch, J. *Magn. Reson. Chem.* **1992**, *30*, 183−186.

SCHEME 5. One-Pot Synthesis of Tetracyclic Indoles 8 and 16 from Tetrahydropyridine 4a[a]



[a] Reagents and conditions. Conditions A: *N*-TMS-*o*-toluidine, *n*-BuLi, hexane/THF, −78 → 25 °C. Conditions B: (i) *N*-TMS-*o*-toluidine, *n*-BuLi, hexane/THF, −78 → 25 °C; (ii) 1 M HCl, THF, reflux.

foreseen as arising from the cyclization of a tetrahydropyridine-indole intermediate **3**, which could in principle be directly generated from ester **4a** (R = Et) using a conventional protocol for indole synthesis. Thus, tetrahydropyridine **4a** was treated with the dianion derived from *N*-TMS-*o*-toluidine[9] at low temperature. Not unexpectedly, tetracyclic indole **16**, a C-12 epimer of **8**, was directly formed in moderate yield upon workup, accompanied by a smaller amount of **8** (Scheme 5). As in the preceding discussion with morphans **12**, the preferential formation of isomer **16** is thought to be the result of a faster irreversible cyclization from the *trans*-isomer of an equilibrating mixture of iminium ions **6** (Y = indol-2-yl, R = Et) generated by proton transfer from **3** (Scheme 1).[10] It is then surmised that, under the foregoing nonacidic conditions, indole **16** is stable and does not revert to **6**. However, when the crude **16/8** mixture was directly heated with aqueous HCl in THF, the C-12 epimer **8** was obtained exclusively in a one-pot process starting from **4a**. In this case, protonation at the indole 3-position renders the cyclization step reversible and the more stable isomer **8** is obtained.[1b,11]

In conclusion, this alternative use of readily available amine **1** and tetrahydropyridine **4a** as key intermediates represents a simple, viable, and direct approach to compounds containing a 3-azabicyclo[3.3.1]nonane substructure. This strategy obviates any regioselectivity problem, does not require the separation and handling of mixtures of isomers, and minimizes the number of steps and synthetic manipulations. This is illustrated by the preparation of tetracyclic indole **8** in just two steps and 34% overall yield from amine **1**. The possibility of performing the tetracycle-forming ring-closure step in the absence of added acid gives access to either one of the C-12 epimers depending on the reaction conditions. Finally, the formation of a series of morphan derivatives **12a**−**c** by the simple expedient of employing different starting aldehydes **9** highlights the opportunity for easy structural diversification offered by the use of amine **1** as convenient precursor of tetrahydropyridines **4**.

Experimental Section

Preparation of Tetrahydropyridines 4. In a typical experiment, a mixture of amine **1**[5] (97 mg, 0.42 mmol), an aldehyde **9** (0.42 mmol), 4 Å MS (840 mg), and absolute EtOH (7 mL) was refluxed until consumption of the starting materials and then filtered through Celite. The crude product after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, hexanes/Et_3N mixtures as eluent) to afford tetrahydropyridines **4** as yellowish oils in the yields indicated in Table 1.

Ethyl (1-Benzyl-5-ethyl-1,2,3,4-tetrahydropyridin-4-yl)-acetate (4a). Prepared from butyraldehyde in 5.5 h without 4 Å MS: ^{1}H NMR δ 0.99 (t, J = 7.4 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.60−1.71 (m, 1H), 1.83−2.17 (m, 3H, overlapped with dd at δ 2.07), 2.07 (dd, J = 17.2, 11.2 Hz, 1H), 2.52−2.82 (m, 4H), 3.90 and 3.93 (AB q, J = 14.5 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 5.80 (s, 1H), 7.21−7.37 (m, 5H); ^{13}C NMR δ 13.3, 14.2, 25.5, 27.4, 30.4, 39.7, 43.3, 59.6, 60.1, 112.7, 127.0, 128.1, 128.2, 131.6, 138.5, 173.0; IR (neat) υ 1730 (s, C=O), 1660 (m, C=C) cm^{-1}; LRMS (EI) *m/z* 287 (M, 28), 272 (15), 200 (base), 91 (57); HRMS calcd for $C_{18}H_{25}NO_2$ 287.1885, found 287.1885.

Ethyl (1,5-Dibenzyl-1,2,3,4-tetrahydropyridin-4-yl)acetate (4b). Obtained from 3-phenylpropanal in 3 h, with spectral characteristics identical to those reported in the literature for the same compound.[5b]

Ethyl (1-Benzyl-5-isopropyl-1,2,3,4-tetrahydropyridin-4-yl)acetate (4c). Prepared from isovaleraldehyde in 3 h: ^{1}H NMR δ 1.02 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.61−1.71 (m, 1H), 1.78−1.92 (m, 1H), 2.01 (dd, J = 15.1, 10.7 Hz, 1H), 2.18 (hept, J = 6.8 Hz, 1H), 2.49−2.81 (m, 4H), 3.94 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 5.82 (s, 1H), 7.22−7.36 (m, 5H); ^{13}C NMR δ 14.3, 21.6, 23.7, 27.2, 29.8, 29.9, 40.3, 42.7, 59.8, 60.2, 117.0, 127.0, 128.1, 128.3, 130.6, 138.6, 173.1; IR (neat) υ 1740 (s, C=O), 1660 (m, C=C) cm^{-1}; LRMS (EI) *m/z* 301 (M, 25), 286 (63), 214 (84), 172 (7), 162 (6), 91 (base); HRMS calcd for $C_{19}H_{27}NO_2$ 301.2042, found 301.2038.

Ethyl *cis*- and *trans*-(1-Benzyl-3-ethylpiperidin-4-yl)-acetate (10). $ZnCl_2$ (0.5 M in THF, 4.1 mL, 2.05 mmol) was added to a suspension of $NaBH_3CN$ (0.268 g, 4.20 mmol) in MeOH (2.9 mL) under Ar, and the mixture was stirred at room temperature for 1 h and then added to **4a** (0.581 g, 2.02 mmol) dissolved in MeOH (4.4 mL). The solution was stirred a further 2 h and poured over 1 M NaOH (50 mL), and the whole was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($NaSO_4$), and the residue after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, 99:1 hexanes/Et_3N) to yield in order of elution *cis*-**10** (142 mg, 24%) and *trans*-**10** (326 mg, 55%), whose spectral data coincide with those reported in the literature[6] for the same compounds.

Preparation of Morphans 12. In a typical experiment, under an Ar atmosphere DMSO (2.2 mL) was added to NaH (60% in mineral oil, 0.138 g, 3.46 mmol) at 0 °C, followed by THF (2.7 mL), and to this mixture was added dropwise a solution of a tetrahydropyridine **4** (1.12 mmol) in THF (3 mL). The resulting mixture was allowed to reach room temperature and further stirred for 1 h. Water (8 mL) was added followed by 1 M HCl until pH = 8. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were washed with brine (40 mL) and dried (Na_2SO_4). Evaporation of the solvents afforded a yellow powder that, without further purification, was dissolved in EtOH (7 mL) and AcOH (0.3 mL), and this solution was added to a suspension of activated Zn (0.329 g) in AcOH (0.3 mL) and EtOH (1 mL). The stirred mixture was heated at 65 °C for 1 h, cooled, and filtered. Water (10 mL) was added, and the pH was brought to 8 with solid K_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The crude product after evaporation was purified by flash chromatography (silica gel saturated with Et_3N, hexanes/Et_3N mixtures as eluent) to yield morphans **12** in the yields indicated in Table 1.

(1*R,5*S**,9*S**)-2-Benzyl-9-ethyl-2-azabicyclo[3.3.1]nonan-7-one (12a).** Prepared from **4a**: ^{1}H NMR δ 0.89 (t, J = 7.3 Hz, 3H), 1.34 (dm, J = 17.0 Hz, 1H), 1.61−2.01 (m, 3H), 2.06 (dd, J = 17.2, 4.9 Hz, 1H), 2.12−2.20 (m, 2H), 2.30 (td, J = 13.1, 3.5 Hz, 1H), 2.51 (m, 2H), 2.57 (dd, J = 12.7, 5.2 Hz, 1H), 2.92 (dm, J = 17.0 Hz, 1H), 3.11 (m, 1H), 3.56 (s, 2H), 7.22−7.31 (m, 5H);

(9) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957−2969.

(10) Forns, P.; Díez, A.; Rubiralta, M.; Solans, X.; Font-Bardía, M. *Tetrahedron* **1996**, *52*, 3563−3574.

(11) Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5659−5662.

^{13}C NMR δ 12.1, 23.1, 26.3, 32.0, 40.3, 42.9, 44.6, 48.3, 55.8, 59.4, 126.9, 128.1, 128.5, 139.2, 212.4; IR (neat) υ 1710 (s, C=O) cm^{-1}. These data coincide with those reported in the literature for the same compound.[1b]

(1*R,5*S**,9*S**)-2,9-Dibenzyl-2-azabicyclo[3.3.1]nonan-7-one (12b).** Prepared from **4b**: ^{1}H NMR δ 1.37−1.48 (m, 1H), 2.04 (dd, J = 17.2, 5.0 Hz, 1H), 2.12−2.40 (m, 4H), 2.43−2.80 (m, 3H), 2.90−2.98 (m, 2H), 3.08−3.15 (m, 1H), 3.22 (dd, J = 13.5, 8.3 Hz, 1H), 3.56 and 3.59 (AB q, J = 13.5 Hz, 2H), 7.16−7.40 (m, 10H); ^{13}C NMR δ 26.3, 32.0, 36.8, 40.4, 43.4, 44.3, 48.3, 56.0, 59.5, 125.9, 126.9, 128.3, 128.7, 129.0, 139.0, 141.2, 211.9; IR (neat) υ 1705 (s, C=O) cm^{-1}; LRMS (EI) *m/z* 319 (M, 40), 263 (21), 262 (base), 91 (70); HRMS calcd for $C_{22}H_{25}NO$ 319.1936, found 319.1939.

(1*R,5*S**,9*S**)-2-Benzyl-9-isopropyl-2-azabicyclo[3.3.1]nonan-7-one (12c).** Prepared from **4c**: ^{1}H NMR δ 0.86 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.30−1.38 (m, 2H), 1.95−2.11 (m, 2H), 2.05 (dd, J = 17.1, 5.0 Hz, included in m at 1.95−2.11), 2.24−2.49 (m, 5H), 2.57 (dd, J = 13.0, 5.6 Hz, 1H), 2.94 (d, J = 17.2 Hz, 1H), 3.24−3.30 (m, 1H), 3.53 and 3.59 (AB q, J = 13.3 Hz, 2H), 7.21−7.31 (m, 5H); ^{13}C NMR δ 20.6, 21.3, 25.6, 26.4, 30.0, 40.4, 44.4, 48.3, 48.5, 54.9, 59.6, 126.9, 128.2, 128.7, 139.2, 212.5; IR (KBr) υ 1690 (m, C=O) cm^{-1}; LRMS (EI) *m/z* 271 (M, 37), 256 (30), 214 (base), 91 (30); HRMS calcd for $C_{18}H_{25}NO$ 271.1936, found 271.1939.

Preparation of (1*R,5*R**,12*R**)-2-Benzyl-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (16).** *n*-BuLi (1.5 M in hexane, 0.9 mL, 1.35 mmol) was added to a solution of *N*-trimethylsilyltoluidine (85 mg, 0.47 mmol) in hexane (3 mL) at 0 °C under Ar. The solution was refluxed for 6.5 h and cooled to −78 °C, and a solution of **4a** (106 mg, 0.37 mmol) in THF (3 mL) was added dropwise. The mixture was allowed to reach room temperature, diluted with Et_2O (15 mL), and extracted with brine (6 mL). The aqueous layer was back-extracted with Et_2O (5 × 30 mL). The combined organic layers were washed with brine (15 mL) and dried (Na_2SO_4). The crude product after evaporation was purified by flash chromatography (silica gel, hexanes/EtOAc, 9:1) to yield **16** (49 mg, 40%) as a foam. Further elution with 50:48:2 hexanes/EtOAc/Et_2NH afforded an slightly impure sample of **8** (12 mg). The spectral data for these materials matched those reported in the literature[1b] for the same compounds.

Preparation of (1*R,5*R**,12*S**)-2-Benzyl-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (8).** The procedure described above for the preparation of **16** was followed starting from 0.123 g (0.43 mmol) of **4a**. After the reaction mixture reached room temperature, the solvent was evaporated, and the residue was redissolved in THF (4 mL). Then, 1 M HCl (4 mL) was added, and the mixture was refluxed for 48 h. After cooling, saturated $NaHCO_3$ was added until pH = 8, and the aqueous layer was extracted with Et_2O (5 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). The crude product after evaporation was purified by flash chromatography (silica gel saturated with Et_2NH, 70:26:4 hexanes/EtOAc/Et_2NH) to yield **8**[1b] (62 mg, 44%) as an oil.

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Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **4a**, **4c**, **12b**, and **12c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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