EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Radical Cyclizations in the Synthesis of 3-Methyl-cis-octahydroindol-5-ones

Authors: Sergi Jansana, Guilhem Coussanes, Faïza Diaba, and Josep Bonjoch

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700086

Link to VoR: http://dx.doi.org/10.1002/ejoc.201700086

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201700086

WILEY-VCH

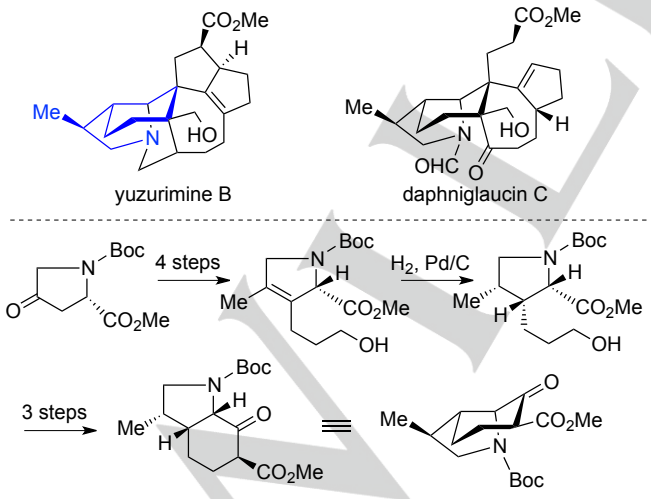
Radical Cyclizations in the Synthesis of 3-Methyl-*cis*-octahydroindol-5-ones

Sergi Jansana,[a] Guilhem Coussanes,[a] Faïza Diaba,[a] and Josep Bonjoch*[a]

Abstract: Three approaches to the stereoselective synthesis of 3-methyl-*cis*-octahydroindoles through a 5-*endo*-*trig* radical cyclization are described, starting from: a) a *N*-vinylic α-chloroacetamide followed by lactam methylenation and hydrogenation; b) an alkyne tether enamide promoted by Bu_3SnH, followed by protonolysis of the vinylstannane and hydrogenation of the exocyclic alkene; and c) a 2,2-dichloropropanamide cyclization onto the alkenyl bond and hydrogenation of the resulting endocyclic double bond, which constitutes the most efficient sequence toward the targeted compounds. 1,5-Enyne cyclizations through a 5-*endo*-*trig* process are reported, in which a remote functional group (ketal or ketone), allowed the diastereoselectivity in the octahydroindole ring formation to be overturned, through steric control in the facial hydrogen radical delivery step.

Introduction

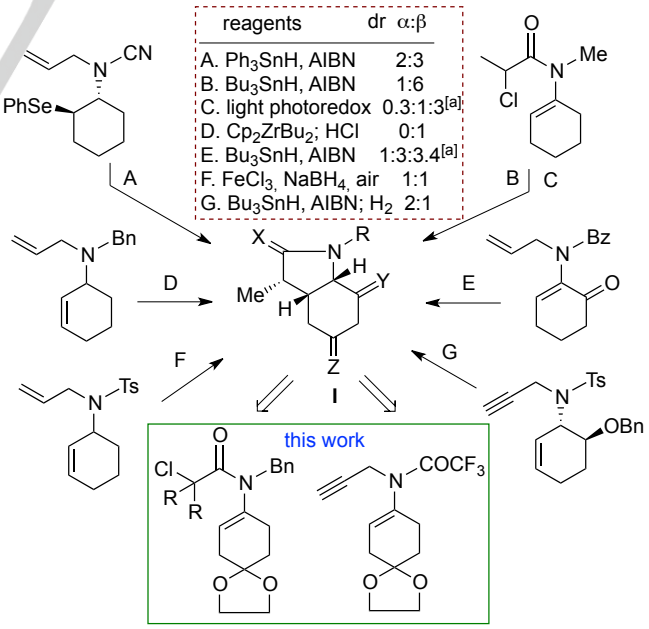
The 3-methyl-*cis*-octahydroindole motif, with a stereochemical pattern as depicted in Scheme 1, is embedded in many *Daphniphyllum* alkaloids belonging to biogenetically different groups (*e.g.* yuzurimine- and daphniglaucine-types,[1] top of Scheme 1). The only stereocontrolled procedure reported so far for to obtain octahydroindoles with the configuration found in *Daphniphyllum* alkaloids (3*S*) was introduced by Hanessian in the synthesis of the tetracyclic core ring of daphniglaucin A.[2] Thus, from a proline derivative and through an eight-step



Scheme 1. a) *Daphniphyllum* alakaloids with a 3-methyloctahydroindole embedded; b) Hanessian's approach to a stereocontrolled access to the AC ring.

sequence, a stereocontrolled synthesis of a 3-methyl-*cis*-octahydroindole was achieved. The hydrogenation of a tetrasubstituted endocyclic alkene was key in the formation of the stereogenic center at C-3 (Scheme 1, bottom).[2,3]

To date, no procedure has been described to diastereoselectively obtain 3-methyloctahydroindoles with the methyl group trans to the ring junction hydrogens (*i.e.* type **I** compounds) starting from aminocyclohexenes or analogs, which would allow a direct entry to this compound type (Scheme 2).[4] In most precedents of hydroindole synthesis using this approach the major diastereomer formed has the methyl substituent in a β-disposition (the epimer of **I**) and cannot be used as a building block in *Daphniphyllum* alkaloid synthesis. Although Hanessian reported a process resulting in a reversed diastereoselection, the dr = 2:1 precludes its synthetic application.[4g] In this context, we explored the radical cyclization of both haloacetamides and enynes to evaluate their usefulness to stereoselectively achieve 3-methyl-*cis*-octahydroindoles starting from functionalized 4-aminocyclohex-3-enes (Scheme 2, bottom).

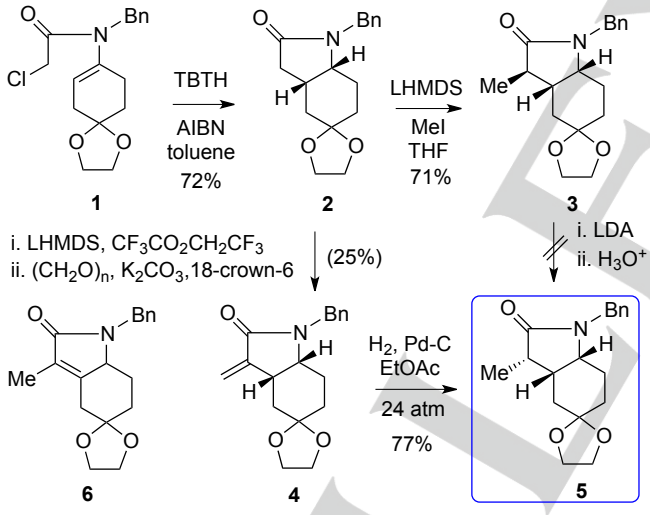


Scheme 2. Synthetic precedents toward *cis*-3-methyloctahydroindoles and the proposed approach. [a] Three diastereomers reported, but not assigned.

Results and Discussion

[a] *Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain*
E-mail: josep.bonjoch@ub.edu
http://www.ub.edu/farmaco/en/quimica/llistat_recerca/
[b] *Supporting information for this article is available on the WWW under http://dx.doi.org/*

We first studied the feasibility of using hydroindolone **2** to achieve the targeted type **I** compound, either by alkylation or methylenation followed by hydrogenation (Scheme 3). Compound **2** was synthesized in a three-step sequence from the monoethylene ketal of the 1,4-cyclohexanedione by formation of the imine with benzylamine, followed by chloroacetylation[5] to give **1**. As expected, when **1** was submitted to a radical cyclization under reductive conditions using tributyltin hydride (TBTH), a *cis*-hydroindole was obtained.[6] The methylation at C-3 occurred via the formation of enolate amide, which reacted with methyl iodide to afford compound **3** with the undesired configuration at C-3. Attempts to induce an epimerization by treatment of **3** with LDA and subsequent reprotonation failed. As an alternative we tried the α-methylenation of **2**, which after some unfruitful attempts was achieved using Colby´s two-step procedure (one-pot reaction),[7] albeit in low yield. Reduction of the exocyclic methylene lactam under 24 bar hydrogen pressure took place diastereoselectively, leading to lactam **5** in 77% yield, with the desired stereochemical arrangement in the octahydroindole ring. The minor compound **6**, generated by an isomerization of **4**, was also observed (13%). After hydrogenation under atmospheric pressure, the overall yield was maintained, although the isomerization increased, compounds **5** and **6** being isolated in a 2:1 ratio. Interestingly, the tetrasubstituted alkene **6** also proved to be a precursor of the targeted octahydroindole **5** (see Scheme 7). Lactam **5** proved to be configurationally stable to treatment with LDA at -78 ºC (5 equiv., THF, 45 min) and quenching with water.



Scheme 3. First-generation synthesis of targeted 3-methyl *cis*-hydroindole.

The stereochemical assignment of the compounds was based on the coupling constants of the methine proton H-3, which appears in **5** as a quintet (J = 7.2 Hz), whereas in lactam **3** it is split into a doublet of quadruplets (J = 8.5, 6.6 Hz), as reported by Ishibashi[4b] for the *N*-methyl analogs of **3** and **5**. ^{13}C NMR data analysis corroborated the structural elucidation, considering the signal at C-4 (δ 31.7) in **5** is upfield with respect to **3** (δ 34.0). This is due to a 1,3-diaxial relationship between the methyl group and H-4ax, which is only possible with the stereochemistry of **5.** Epimeric lactams **3** and **5** are depicted in Figure 1 in their preferred conformation.[8]

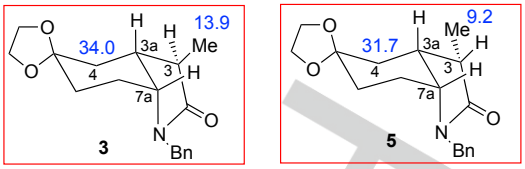
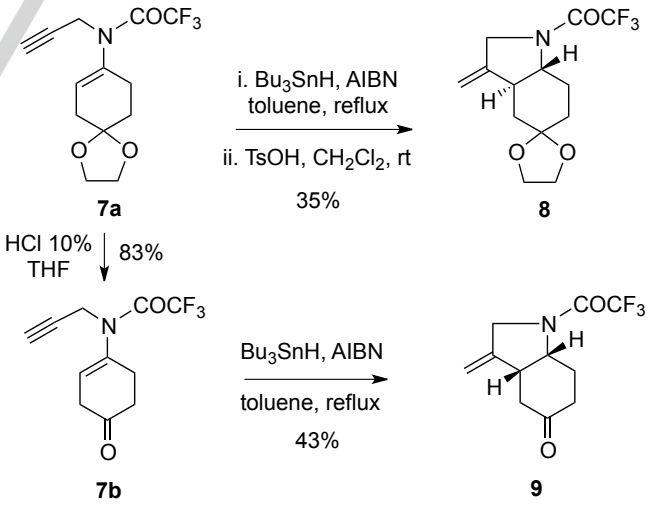


Figure 1. Relative configuration and conformation of lactams **3** and **5**.

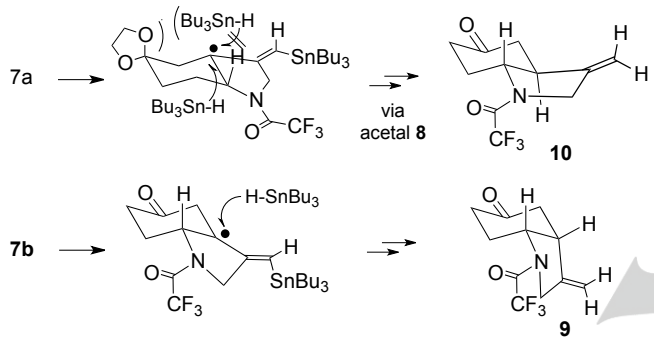
The above approach to an octahydroindole with the desirable stereochemistry was modified to enhance its efficiency. Hence, a radical-mediated enyne cyclization induced by Bu_3SnH [9] was considered from alkyne **7a** [10] (Scheme 4). The latter was prepared via imine formation from 1,4-cyclohexanedione monoethylene ketal with propargyl amine followed by trifluoroacetylation, which gave enamide **7** in 54% overall yield. Initially, the radical cyclization was carried out using slow addition of Bu_3SnH and AIBN to a refluxing benzene solution of **7a**. The radical process gave a vinylstannane (not shown), which by treatment with TsOH was protodestannylated to give ketal **8** in 35% overall yield together with a non-cyclized 1,5-diene compound.[11] Interestingly, a different result was obtained when the cyclization was conducted with freshly prepared tributyltin hydride (from an old sample of tributyltin chloride and sodium cyanoborohydride in *t*-BuOH at reflux temperature). [12] The protonolysis step was conducted as above. In these reaction conditions, ketone **9** was isolated with an overall yield similar to that observed for **8**.[13] At that time the deprotection of ketal **7a** to the corresponding ketone **7b** was carried out and **7b** submitted to the same reaction conditions to promote the radical cyclization used previously from **7a**, cis azabicyclic ketone **9** being isolated in 43% yield.



Scheme 4. Overturning the diastereoselectivity in the radical cyclization of alkyne tether enamides **7**.

A careful examination of the NMR data of **8** revealed the formation of a *trans*-hydroindole. Notably, ketone **9** showed a cis-ring fusion in the hydroindole ring. (For a discussion of the elucidation of the trifluoroacetyl compounds by NMR data, see

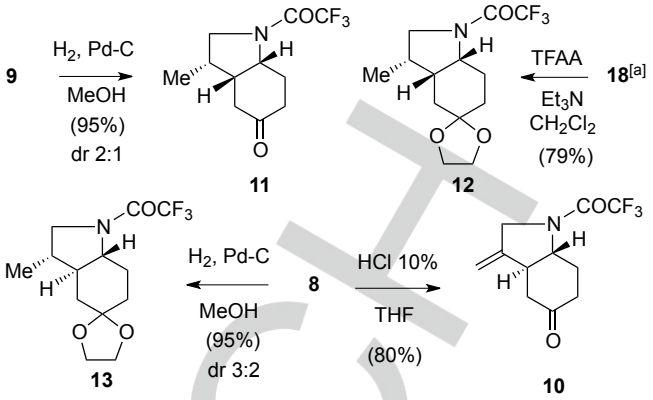
below and Table 1). Thus, changing the ketal group for the deprotected ketone altered the stereochemical course of the radical cyclization. Overturning the diastereoselectivity was crucial to achieve the relative configuration required for the targeted hydroindole-type compounds. The remote stereocontrol of the process was based on the steric hindrance induced by the ketal group, which inhibits the transfer of the hydrogen atom from the top face by the Bu_3SnH to the radical intermediate. Conversely, the reduction in the ketone substrate leading to the most stable *cis*-hydroindole compound **9** was sterically easy (Scheme 5). Additionally, for the comparison of NMR data, ketal hydrolysis in **8** was carried out to obtain ketone **10** (Scheme 6). Although the radical cyclization gave only a moderate overall yield of the targeted hydroindole **9**, compared with that reported by Hanessian using a 5-*exo*-*trig* cyclization,[4g] it should be noted that the transformation from the 1,5-enyne **7b** to **9** took place through an unprecedented 5-*endo*-trig cyclization[14] in the nitrogen-containing heterocycles.[15,16]



Scheme 5. Substrate-controlled diastereoselectivity in the radical cyclization.

At this stage, we performed the hydrogenation of the exocyclic methylene group at C-3 in **9**. Using Pd/C as a catalyst, the methyl derivative **11** with the desired configuration was isolated as an epimeric mixture in a 2:1 ratio (Scheme 6). Ketal **12** was also available from the corresponding secondary amine, synthesized unambiguously, as depicted in Scheme 7. To gain additional spectroscopic data for the 3-methyloctahydroindoles, the trans derivative **8** was also subjected to the methylene reduction process. Its hydrogenation was very slow, requiring up to 3 days, and led to the methyl derivative **13** alongside its epimer in a 3:2 ratio.

The relative stereochemistry of bicyclic trifluoroacetamides **8** and **9** (Z/E rotamers)[17] was elucidated from ^1H and ^{13}C NMR spectral data (Figure 2 and Table 1). The key evidence for the assignment of **8** was found in the coupling pattern for H-3a and H-7a, which appears as a triplet of doublets (J = 11.2, 1.2 Hz) in both cases. This coupling pattern is only compatible with a trans relationship between H-3a and H-7a (both in an axial disposition).



Scheme 6. Transformations of hydroindoles **8** and **9**. [a] See Scheme 7.

The cis-ring fusion in hydroindole **9** was established based on ^{13}C NMR data, which showed a shielding of 6 and 8 ppm in the chemical shift for C3a and C7a, respectively, compared with trans derivative **8**. Moreover the strong deshielding of H-7a (δ 4.72) indicates a *syn*-coplanar disposition with respect to the carbonyl group of the trifluoroacetamide, which is only possible in a *cis*-compound. Regarding the relative configuration of the hydrogenated compound **11**, the NMR spectra showed two set of signals in a 2:1 ratio, which were assigned to a epimeric mixture at C-3. The key configuration at C-3 was established with the pattern of coupling constants of H-2. Thus, a triplet for the signal at δ 3.19 (J = 11.6 Hz) is only compatible with a *cis*-relationship of H-2β with the methine at H-3β.[18] Direct comparison with NMR data for ketal **12** was not possible since each compound has a different preferred conformation (Figure 2). The conformation of ketone **11** was as expected, considering that the amide function induces an axial disposition for the C7-C7a bond with respect to the pyrrolidine ring to avoid the 1,3-allylic strain. However, in ketal **12** this conformation implies a strong 1,3-diaxial interaction between the ketal at C-5 and the C3-C3a bond, hence the preferred *endo*-conformation. Finally, to unambiguously corroborate the structural elucidation of **11**, it was also prepared by hydrolysis of ketal **12**. The NMR data of the sample of **11** obtained from **12** matched those of the major epimer in the hydrogenation procedure from **9**.

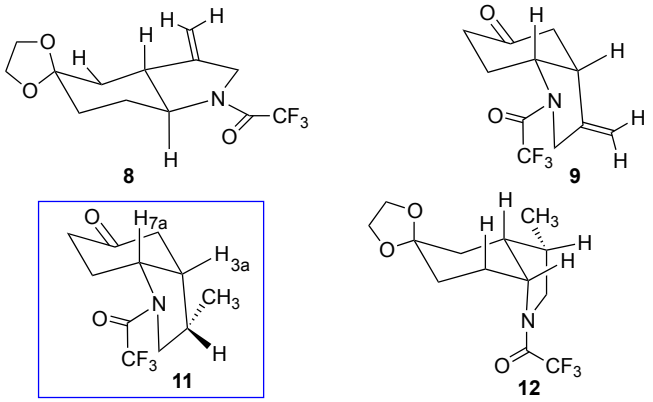


Figure 2. Trifluoroacetamides **8** and **9** in their preferred conformation and stereoview of C-3 methylated compounds **11** and **12**.

Table 1. Key NMR of *cis*- and *trans*-hydroindoles **8-12**[a]

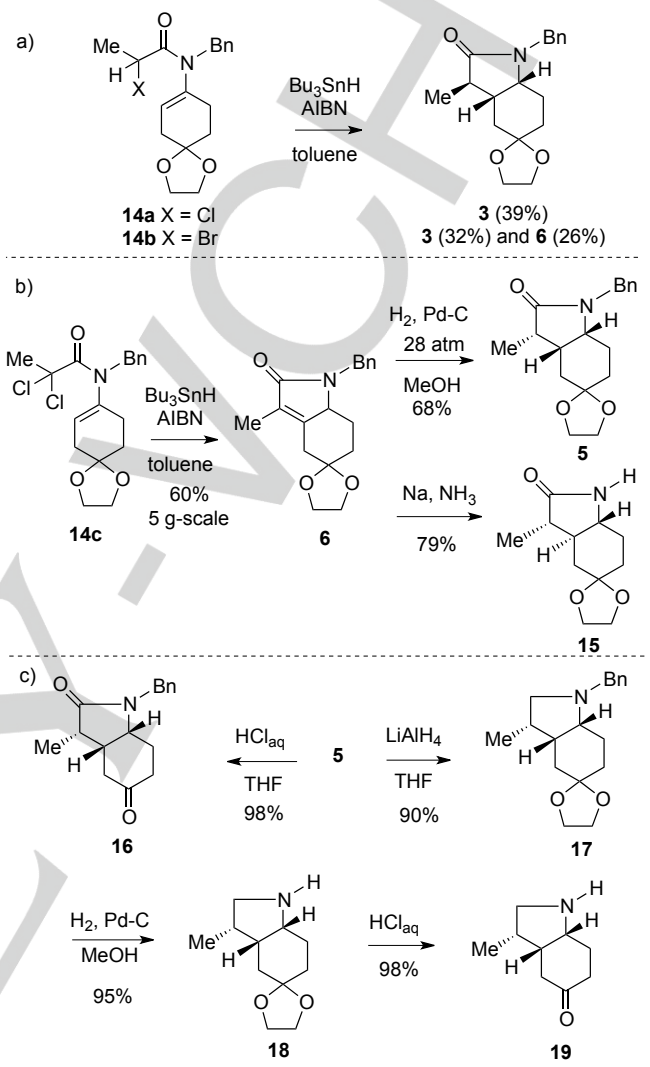
	8	9[b]	11	12	13
H-2	4.39 (d,13.8)[c]	4.44 (d,15.2)	3.91 (t, 11.6)	3.78 (t, 11.1)	3.73 (t,11.0)
	4.22	4.33	3.19	3.26	3.46
C-2	52.8	50.6	51.3	51.8	55.7
H-3	---	---	2.49	2.35	2.26
C-3	143.8	144.6	36.0	35.6	33.6
H-3a	2.54 (t, 11.4)	3.27	2.66	2.35	2.10
C-3a	45.7	39.8	38.1	39.4	45.0
H-4	2.12 (dt,12.4)	2.72	2.34	1.67	1.61
	1.65	2.72	2.34	1.32 (t,13.0)	1.44
C-4	35.3	38.7	36.2	30.8	35.8
H-6	1.89	2.30	2.38	1.55	1.84
	1.61	2.45	2.22	1.45	1.61
C-6	33.7	36.5	35.5	29.4	33.4
H-7	2.98	2.30	2.66	2.70	2.84
	1.65	1.86	1.94	1.93	
C-7	27.2	24.9	24.7	22.8	26.7
H-7a	3.18 (td,11.2)	4.72 (td, 8.0)	4.44 (q,7.5)	4.00 (m)	3.37 (td,11.3)
C-7a	65.1	57.0	58.3	59.7	60.6

[a] Among the ^{1}H NMR data, the only coupling constants shown are those key in determining the configuration. [b] Values for the major *Z* rotamer. [c] Values of coupling constants in Hz.

In summary, although the usefulness of the process involving the 1,5-enyne radical cyclization was compromised by the overall yield, it allowed us to study the remote control of a divergent stereochemical course of a radical process, which hinged on whether a ketal or carbonyl group was embedded in the substrate.

We then decided to revisit the radical cyclization of haloacetamides leading to 3-methyloctahydroindoles via lactams, introduced by Ishibashi some years ago (73%, dr = 6:1 ratio for analogs of **3** and **5**)[4b] and recently studied by Rueping using a photoredox procedure (53%, dr = 3.1).[4c] In both cases the cyclized substrates lacked the oxygenated function at C-5 present in the current work. Starting from enamides **14a**-**c**, the yield and diastereoselectivity obtained after the cyclization depends on the degree of the substitution in the proradical haloacetamide and the presence of the ketal group linked to the cycloxene ring.[19] The cyclization of both chloro- and bromoacetamides **14a-b** afforded a stereochemical result at C-3 similar to that obtained in a related compound by Ishibashi, the undesired epimer **3** being formed. From bromo derivative **14b** the isomerized compound **6** was also isolated in a nearly equimolecular ratio.[20]

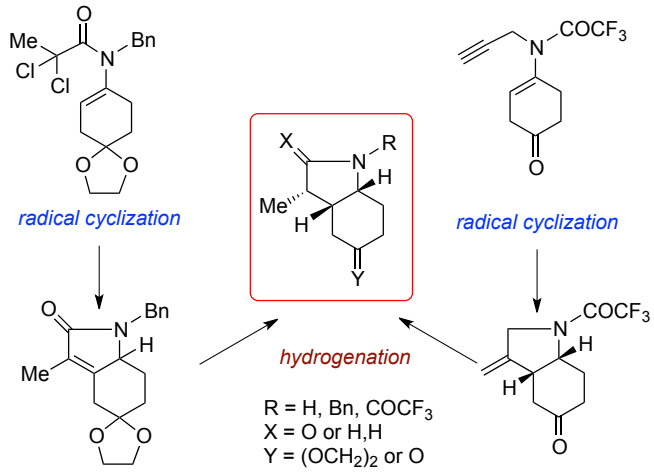
Working with 2,2-dichloropropamide **14c** gave a synthetically interesting result. The major product of the radical cyclization was compound **6**, prepared on a 5 g-scale and with 60% yield. Hydrogenation under pressure of the tetrasubstituted alkene in **6** gave the building block **5** with the targeted configuration. Reduction of **6** using sodium in ammonia led to a concomitant reduction and *N*-debenzylation and the isolation of *trans*-hydroindole **15,** which has a more stable configuration than that of its epimer at C-3.[21] Finally, from cis-octahydroindole **5**, several derivatives were synthesized, namely lactam **16** and the amines **17-19**.



Scheme 7. Third-generation synthesis of targeted 3-methyl *cis*-hydroindoles.

Conclusions

A three-step sequence (enamide formation, radical cyclization, and hydrogenation) either from dichloroacetamides or propargylamines was developed to achieve *cis*-3-methyloctahydroindoles as promising building-blocks for some *Daphniphyllum*-type alkaloids embodying this structural unit. The results obtained here are interesting from the mechanistic point of view, since unexpected reaction pathways were found in the radical cyclization processes (Scheme 8).



Scheme 8. Overview.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si, and ^{13}C NMR spectra are referenced to the deuterated solvent signal ($CDCl_3$: 77.00 ppm). All NMR data assignments are supported by gCOSY and gHSQC experiments. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or on Al_2O_3 (aluminium oxide 60 F254 neutral, Merck). The spots were located by UV light or a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on SiO_2 (Silica Flash P60, Wet & Dry, 200-500 mesh) and when indicated on Al_2O_3 (aluminium oxide 90, Merck). Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4.

4-(*N*-Benzyl-2-chloroacetamido]cyclohex-3-enone ethylene ketal (1): Benzylamine (0.23 mL, 2.1 mmol) and 1,4-cyclohexanedione momoethylene ketal (300 mg, 1.9 mmol) were dissolved in CH_2Cl_2 (6 mL) and molecular sieves 4 Å (375 mg) were added. The reaction mixture was stirred at room temperature for 4 h, filtered through Celite®, washed with CH_2Cl_2 and concentrated to give the corresponding imine: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (dd, J = 10.0, 4.0 Hz, 2 H), 1.92 (dd, J = 10.2, 4.1 Hz, 2 H), 2.55 (t, *J* = 4.6 Hz, 4H), 4.00 (s, 4 H), 4.55 (s, 2H), 7.20-7.30 (m, 5H) ppm. The above imine in toluene (6 mL) was added dropwise to a cooled solution of acetyl chloride (0.167 mL, 2.11 mmol) in toluene (6 mL). The resulting solution was stirred at room temperature for 1 h. After cooling at 0 ºC, a solution of Et_3N (0.8 mL, 5.76 mmol) in toluene (6 mL) was added dropwise and stirred at room temperature for another hour. The reaction mixture was treated with saturated aqueous Na_2CO_3 for 1 h, extracted with Et_2O, washed with brine (3 x 100 mL), and concentrated. Purification by chromatography (hexane/EtOAc, 1:0 to 1:1) afforded enamide **1** (358 mg, 58%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (t, *J* = 6.5 Hz, 2 H), 2.26 (m, 4 H), 3.97 (s, 4 H), 4.14 (s, 2 H), 4.64 (br s, 2 H), 5.35 (br s, 1 H), 7.27-7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.9, 31.0, 35.2, 41.7, 49.9, 64.6, 106.8, 126.7, 127.5, 128.4, 128.8, 137.0, 137.5, 166.0 ppm. HRMS (ESI): *m/z* calcd for $C_{17}H_{21}ClNO_3$ $[M+H]^+$ 322.1204; found 322.1210.

***cis*-1-Benzylhexahydroindole-2,5-dione ethylene ketal (2):** Enamide **1** (6.32 g, 19.6 mmol) was dissolved in toluene (280 mL) and the solution was brought to reflux. A solution of Bu_3SnH (6.34 mL, 23.6 mmol) and AIBN (1.61 g, 9.8 mmol) in toluene (10 mL) was added to the reaction mixture via syringe pump over 4 h. After cooling, the mixture was concentrated and purified by chromatography (hexane/EtOAc; 75:25 to 0:100) to afford **2** as a colorless oil (4.06 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41-1.45 (m, 2 H, H-6), 1.57 (dd, *J* = 13.8, 8.4 Hz, 1 H, H-4ax), 1.73 (dd, *J* = 14.0, 5.2 Hz, 1 H, H-4eq), 1.82-1.89 (m, 2 H, H-7), 2.35 (m, 1 H, H-3a), 2.52-2.45 (m, 2 H, H-3), 3.44 (q, *J* = 5.2 Hz, 1 H, H-7a), 3.93-3.88 (m, 4 H, OCH_2), 4.05 and 4.88 (2d, *J* = 15.1 Hz, 1 H each, CH_2Ph), 7.27-7.32 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC): δ = 23.9 (C-7), 29.7 (C-6), 32.0 (C-3a), 35.7 (C-4), 37.7 (C-3), 44.0 (CH_2Ph), 55.0 (C-7a), 64.2 and 64.3 (OCH_2), 107.9 (C-5), 127.4, 127.9, 128.6 and 136.9 (Ph), 175.5 (C-2) ppm. HRMS (ESI): *m/z* calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$ 288.1594; found 288.1599.

(3*RS*,3a*RS*,7a*RS*)-1-Benzyl-3-Methylhexahydroindol-2,5-dione ethylene ketal (3): To a solution of LiHMDS (1 M in THF, 1.32 mL, 2 equiv.) at -78 °C was added dropwise a solution of **2** (190 mg, 0.66 mmol, 1.0 equiv.) in THF (6.6 mL) over 20 min. MeI (412 µL, 10 equiv.) was then added and the reaction mixture was stirred at -78 °C for 30 min and at room temperature for a further 30 min. The reaction was quenched with a solution of saturated NH_4Cl (10 mL), and extracted with ether (3x10 mL). The combined organic layers were dried, concentrated and purified by chromatography (hexane/EtOAc; 95:5 to 0:100) to afford **3** as a colorless oil (142 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.46 (ddd, *J* = 14.2, 10.8, 4.0 Hz, 1 H, H-6ax), 1.58 (m, 1 H, H-6ax), 1.72–1.76 (m, 2 H, H-4), 1.83-1.91 (m, 2 H, H-7), 2.03-2.10 (m, 1H, H-3a), 2.63 (dq, *J* = 8.5, 6.8 Hz, 1 H, H-3), 3.35 (ddd, *J* = 8.2, 6.2, 6.2 Hz, 1 H, H-7a), 3.88–3.94 (m, 4 H, OCH_2), 4.00 and 4.92 (2d *J* = 15.0 Hz, 1 H each, CH_2Ph), 7.22-7.34 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 24.5 (C-7), 30.7 (C-6), 34.0 (C-4), 40.6 (C-3), 40.8 (C-3a), 44.2 (CH_2Ph), 53.4 (C-7a), 64.0 and 64.4 (OCH_2) 108.0 (C-5), 127.4, 127.9, 128.6 and 137.0 (Ph), 177.3 (C-2) ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$ 302.1751; found 302.1760.

***cis*-1-Benzyl-3-methylenehexahydroindole-2,5-dione ethylene ketal (4):** To a solution of LiHMDS (1.15 mL, 1M in THF, 1.15 mmol, 2 equiv.) was added a solution of compound **2** (165 mg, 0.57 mmol, 1 equiv.) in THF (3 mL). The reaction mixture was allowed to warm to room temperature over 20 min, and then $CF_3CO_2CH_2CF_3$ was added (238 µL, 1.78 mmol, 3.1 equiv.). After an additional 24 h at room temperature, saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The organic extracts were dried and concentrated and the resulting crude mixture was immediately used for the next step. To a solution of the above intermediate in benzene (10 mL) were added K_2CO_3 (246 mg, 1.78 mmol, 3.1 equiv.), 18-crown-6 (40 mg, 0.15 mmol, 0.26 equiv.), and paraformaldehyde (604 mg, 20 mmol, 35 equiv.). The suspension was heated to reflux for 20 h. The mixture was allowed to cool to room temperature, saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The organic extracts were dried, concentrated, and purified by chromatography (hexane: EtOAc, 90:10 to 50:50) to afford **4** as a colorless oil (43 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49-1.57 (m, 2 H, H-6), 1.65-1.74 (m, 2 H, H-4 and H-7), 1.84-1.93 (m, 2 H, H-4 and H-7), 3.03 (dddd, *J* = 12.0, 6.2, 6.0, 2.0 Hz 1 H, H-3a), 3.49 (q, *J* = 6.2 Hz, 1 H, H-7a), 3.90 (s, 4 H, OCH_2), 4.18 and 4.96 (2 d, *J* = 15.0 Hz, 1 H each, CH_2Ph), 5.31 and 6.04 (2 d, *J* = 1.9 Hz, 1 H each, $=CH_2$), 7.24-7.33 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0 (C-7), 30.4 (C-6), 35.8 (C-4), 36.2 (C-3a), 44.6 (CH_2Ph), 53.3 (C-7a), 64.2 (OCH_2), 107.9 (C-5), 115.1 ($=CH_2$), 127.5, 128.0, 128.7 and 136.6 (Ph), 144.0 (C-3), 168.5 (C-2) ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{21}NNaO_3$ $[M+Na]^+$ 322.1414; found 322.1411.

(3*RS*,3a*SR*,7a*SR*)-1-Benzyl-3-Methylhexahydroindol-2,5-dione ethylene ketal (5): Compound **4** (43 mg, 0.14 mmol, 1.0 equiv.) was dissolved in EtOAc (15 mL), and Pd/C (18 mg, 40% w/w) was added. The resulting suspension was stirred at room temperature under 20 atm of H_2. After 24 h, the reaction mixture was filtered twice through Celite® and concentrated to afford **5** together with minor amounts of **6** in an 8:1 ratio, as a colorless oil (38 mg, 87% overall yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 7.2 Hz, 3H, CH_3), 1.25 (m, 1H, H-6ax), 1.32 (t, *J* = 12.8 Hz, 1 H, H-4ax), 1.45 (dq, *J* = 13.2, 3.2 Hz, 1 H, H-6eq), 1.58 (ddd, *J* = 13.6, 5.6, 2.8 Hz, 1 H, H-4eq), 1.80 (tt, *J* = 14.0, 4.2 Hz, 1H, H-7ax), 2.02 (dq *J* = 13.2, 3.0 Hz, 1 H, H-7eq), 2.47 (dddd *J* = 12.6, 7.0, 6.0, 5.0 Hz, 1 H, H-3a), 2.59 (quintuplet, *J* = 7.2 Hz, 1 H, H-3), 3.41 (td, *J* = 4.3, 2.6 Hz, 1 H, H-7a), 3.90-3.94 (m, 4 H, OCH_2), 4.07 and 4.88 (2 d, *J* =

15.1 Hz, 1 H each, CH_2Ph), 7.20-7.36 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.2 (CH_3), 23.1 (C-7), 29.0 (C-6), 31.7 (C-4), 36.8 (C-3a), 42.0 (C-3), 44.0 (CH_2Ph), 53.5 (C-7a), 64.2 and 64.4 (OCH_2), 108.2 (C-5), 127.3, 127.8, 128.6, and 137.0 (Ph), 178.2 (C-2) ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751 found: 302.1760. For analytical data of **6**, see below. When the hydrogenation of **4** was carried out at atmospheric pressure, compounds **5** and **6** were isolated in a 2:1 ratio and 90% overall yield.

[4-(*N*-Trifluoroacetyl-*N*-propargyl)amino]-3-cyclohexenone ethylene ketal (7a): Following the general procedure, cyclohexanedione monoethylene ketal (2.37 g, 15.15 mmol, 1.0 equiv.) and benzylamine were dissolved in CH_2Cl_2 (2 mL). The resulting imine[22] was treated with trifluoroacetic anhydride (2.6 mL, 18.18 mmol, 1.2 equiv.) and Et_3N in toluene (166 mL). Chromatography (hexane/ EtOAc, 90:10 to 0:100) afforded **7** (2.33 g, 54%) as a pale yellow solid: m.p. 87-92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.87 (t, *J* = 6.8 Hz, 2 H), 2.30 (s, 1 H), 2.40 (m, 4 H), 3.98-4.01 (m, 4 H), 4.26 (s, 2 H), 5.74 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5, 30.9, 35.3, 37.5, 64.6, 73.0, 106.4, 127.3, 134.8 ppm. HRMS (ESI): *m/z* calcd for $C_{13}H_{15}F_3NO_3$ $[M+H]^+$ 290.0999; found 290.0989.

[4-(*N*-trifluoroacetyl-*N*-propargyl)amino]-3-cyclohexenone (7b): Ketal **7a** (95 mg, 0.33 mmol, 1.0 equiv.) was dissolved in a THF: HCl (10%) mixture (4:1, 2.5 mL) and stirred at room temperature. After 24 h, the reaction was quenched with a saturated solution of Na_2CO_3 and extracted with CH_2Cl_2. The resulting organic layer was dried, concentrated, and purified by chromatography (hexane/EtOAc, 9:1 to 3:1) to afford ketone **7b** (66 mg, yellow oil, 83%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (t, *J* = 2.4 Hz, 1 H, C≡CH), 2.67 (br s, 4 H, H-6 and H-7), 3.05 (d, *J* = 3.6 Hz, 2 H, H-4), 4.35 (br s, 2 H, CH_2N), 5.96 (t, *J* = 3.6 Hz, 1 H, CHCN) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5 (C-7), 37.4 (CH_2N), 37.8 (C-6), 38.5 (C-4), 73.8 (CH≡C), 76.6 (C≡CH), 116.2 (q, $J_{C\text{-}F}$ = 286 Hz, CF_3), 127.2 (CH-CN), 135.1 (CN), 156.0 (q, $J_{C\text{-}O}$ = 36 Hz, CO), 206.2 (C-5) ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{11}F_3NO_2$ $[M+H]^+$: 246.0736 found: 246.0731.

***trans*-3-Methylene-1-trifluoroacetyloctahydroindol-5-one ethylene ketal (8):** Alkyne **7** (240 mg, 0.83 mmol, 1.0 equiv.) was dissolved in benzene (12 mL) and heated up to reflux. TBTH (268 µL, 1.00 mmol, 1.2 equiv.) and AIBN (68 mg, 0.41 mmol, 0.5 equiv.) were added with a syringe pump over 1.5 h. The reaction was maintained at reflux for 1.5 h. The mixture was cooled to room temperature and concentrated. Then, solid *p*-toluenesulfonic monohydrate (190 mg, 1.00 mmol, 1.2 equiv.) was added in CH_2Cl_2 (25 mL) and the solution stirred for 3 h. The reaction mixture was neutralized and washed with Na_2CO_3, dried, and concentrated. Purification by chromatography (hexane/EtOAc, 95:5 to 50:50) afforded **8** (60 mg, 35%) as a white solid: m.p. 51-56 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.70 (m, 3 H, H-6ax, H-4ax and H-7), 1.89 (dt, *J* = 10.4, 3.2 Hz, 1 H, H-6eq), 2.12 (dt, *J* = 12.4, 2.8 Hz, 1 H, H-4eq), 2.54 (t, *J* = 11.6, 1.2 Hz, 1 H, H-3a), 2.98 (m, 1 H, H-7), 3.18 (td *J* = 11.0, 1.2 Hz, 1 H, H-7a), 3.97-3.99 (m, 4 H, OCH_2), 4.22 and 4.39 (2 br d, *J* = 13.8 Hz, 1 H each, H-2), 4.84 and 4.97 (2d, *J* = 1.2 Hz, 1 H each, =CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (C-7), 33.7 (C-6), 35.3 (C-4), 45.7 (C-3a), 52.8 (C-2), 64.3 (OCH_2), 64.7 (OCH_2), 65.1 (C-7a), 104.3 (=CH_2), 108.5 (C-5), 116.1 (q, $J_{C\text{-}F}$ = 286 Hz, CF_3), 143.8 (C-3) ppm; *masked* (CO). HRMS (ESI): *m/z* calcd for $C_{13}H_{17}F_3NO_3$ $[M+H]^+$ 292.1155; found 292.1157.

***cis*-3-Methylene-1-trifluoroacetyloctahydroindol-5-one (9):** To a solution of alkyne **7b** (153 mg, 0.72 mmol, 1.0 equiv.) in toluene (9 mL) at reflux temperature, TBTH (232 µL, 0.86 mmol, 1.2 equiv.) and AIBN (59 mg, 0.36 mmol, 0.5 equiv.) were added with a syringe pump over 1.5 h. The reaction mixture was maintained at reflux for 1.5 h, cooled to room temperature and concentrated. To the vinylstannane intermediate, solid *p*-toluenesulfonic monohydrate (164 mg, 0.86 mmol, 1.2 equiv.) was added in CH_2Cl_2 (19 mL) and the solution stirred for 3 h. The reaction mixture was washed with Na_2CO_3 solution, dried, and concentrated. Purification by chromatography (hexane/EtOAc, 20:1 to 3:1) afforded 4-(*N*-trifluoroacetyl-*N*-allyl)aminocycloxen-3-enone (18 mg, 12%) and then **9** (66 mg, 43%) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$, 5:2 mixture of *Z*/*E* rotamers) Rotamer *Z*: δ =1.80-1.92 (m, 1 H, H-7), 2.14-2.46 (m, 3 H, H-6 and H-7), 2.72 (m, 2H, H-4), 3.27 (m, 1H, H-3a), 4.33 and 4.44 (2 dd, *J* = 15.2, 0.8 Hz, 1 H each, H-2), 4.72 (td, *J* = 8.0, 4.8 Hz, 1H, H-7a), 5.10 and 5.23 (2 q, *J* = 2.4 Hz, 1H each, =CH_2). Rotamer *E*: δ =1.80-1.92 (m, 1 H, H-7), 2.14-2.46 (m, 3 H, H-6 and H-7), 2.75 (m, 2 H, H-4), 3.35 (m, 1H, H-3a), 4.08 and 4.44 (2 d, *J* = 16.0 Hz, 1 H each, H-2), 4.60 (dt *J* = 10.8, 6.2 Hz, 1 H, H-7a), 5.14 and 5.29 (2 q, *J* = 2.0 Hz, 1 H each, =CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): Rotamer *Z*: δ = 24.9 (C-7), 36.5 (C-6), 38.7 (C-4), 39.8 (C-3a), 50.6 (C-2), 57.0 (C-7a), 109.4 (=CH_2), 116.1 (q, $J_{C\text{-}F}$ = 286 Hz, CF_3), 144.6 (C-3), 155.7 (q, $J_{C\text{-}O}$ = 35.0 Hz, CO), 208.3 (C-5). Rotamer *E*: δ = 28.0 (C-7), 37.4 (C-6), 38.1 (C-4), 43.8 (C-3a), 50.4 (C-2), 56.8 (C-7a), 109.8 (=CH_2), 117.5 (CF_3), 142.0 (C-3), 155.4 (CO), 206.9 (C-5) ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{13}F_3NO_2$ $[M+H]^+$ 248.0893; found 248.0888.

***trans*-3-Methylene-1-trifluoroacetyloctahydroindol-5-one (10):** Ketal **8** (18 mg, 0.06 mmol, 1.0 equiv.) was dissolved in a THF: HCl (10%) mixture (4:1, 1.5 mL) and stirred at room temperature. After 18 h, the reaction was quenched with a saturated solution of Na_2CO_3 and extracted with CH_2Cl_2. The resulting organic layer was dried, concentrated, and purified by chromatography (hexane/EtOAc, 9:1) to afford **10** (12 mg, 80%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.77 (qd, *J* = 12.3, 5.3 Hz, 1 H, H-7ax), 2.36 (m, 1 H, H-4ax), 2.44 (m, 1 H, H-6), 2.61 (m, 2 H, H-6 and H-3a), 2.80 (dq, *J* = 15.0, 3.2 Hz, 1 H, H-4eq), 3.27 (m, 1 H, H-7eq), 3.60 (td, *J* = 11.6, 2.8 Hz, 1 H, H-7a), 4.34 (d, *J* = 14.0 Hz, 1 H, H-2), 4.47 (d, *J* = 14.0 Hz, 1 H, H-2), 4.90 and 5.09 (2 d *J* = 1.2 Hz, 1 H each, =CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0 (C-7), 38.8 (C-6), 41.4 (C-4), 46.9 (C-3a), 52.9 (C-2), 63.8 (C-7a), 106.0 (=CH_2), 116.1 (q, $J_{C\text{-}F}$ = 286 Hz, CF_3), 142.6 (C-3), 155.5 (q, $J_{C\text{-}O}$ = 36 Hz CO), 207.2 (C-5) ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{13}F_3NO_2$ $[M+H]^+$: 248.0893 found: 248.0902.

(3*RS*,3a*SR*,7a*SR*)-1-Trifluoroacetyl-3-Methyloctahydroindol-5-one (11): Ketone **9** (31 mg) in MeOH (2 mL) was hydrogenated overnight, using Pd-C (15 mg). Octahydroindole **11** (as a 2:1 epimeric mixture) was obtained in 95% yield: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.8 Hz 3 H, CH_3), 1.94 (m, 1 H, H-7), 2.22 (m, 1 H, H-6), 2.34 (m, 2 H, H-4), 2.38 (m, 1 H, H-6), 2.49 (m, 1 H, H-3), 2.61 – 2.71 (m, 2 H, H-7 and H-3a), 3.19 (t, *J* = 11.6 Hz, 1 H, H-2), 3.91 (td, *J* = 11.6, 1.6 Hz, 1 H, H-2), 4.44 (q, *J* = 7.5 Hz, 1 H, H-7a) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 (CH_3), 24.7 (C-7), 35.5 (C-6), 36.0 (C-3), 36.2 (C-4), 38.1 (C-3a), 51.3 (C-2), 58.3 (C-7a), 116.1 (q, $J_{C\text{-}F}$ = 286 Hz, CF_3), 155.5 (q, $J_{C\text{-}O}$ = 36 Hz, CO) 211.2 (C-5) ppm. Minor Signals 15.8, 25.1, 28.6, 36.0, 36.9, 38.6, 39.7,43.4, 52.9, 57.5, 65.7, 205.4 ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{15}F_3NO_2$ $[M+H]^+$: 250.1049 found: 250.1049. A pure sample of ketone **11** as a yellow oil was obtained by hydrolysis of ketal **12** using THF-10% HCl (4:1). The NMR data matched those of the major epimer obtained in the above hydrogenation procedure.

(3*RS*,3a*SR*,7a*SR*)-1-Trifluoroacetyl-3-Methyloctahydroindol-5-one ethylene ketal (12): To a cooled solution (0 ºC) of 50 mg (0.25 mmol) of amine **17** (see below) in CH_2Cl_2 (2 mL) were added TFAA (70 µL, 0.50 mmol) and triethylamine (106 µL, 0.76 mmol). After 4 h at room temperature the solution was quenched by a solution of $NaHCO_3$ and extracted with EtOAc. The organic extracts were washed with 1 N HCl, dried, concentrated, and purified by chromatography (hexane/EtOAc, 20:1) to give trifluoroacetamide **12** as a yellow oil (58 mg, 79%): ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.32 (t, *J* = 13.0 Hz, 1 H, H-4ax), 1.45 (dd, *J* = 13.2, 3.9 Hz, 1 H, H-6eq), 1.55 (m, 1 H, H-6ax), 1.67 (ddd, *J* = 13.7, 5.7, 2.4 Hz, 1 H, H-4eq), 1.88 –1.99 (m, 1 H, H-7ax), 2.33 (m, 1 H, H-3a), 2.39 (m, 1 H, H-3), 2.70 (dq, *J* = 15.1, 4.0 Hz, 1 H, H-7eq), 3.26 (t, *J* = 11.1 Hz, 1 H, H-2), 3.78 (td, *J* = 9, 1.2 Hz, 1 H, H-2), 3.94-3.98 (m, 4 H, OCH_2), 4.00 (m, 1 H, H-7a) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5 (CH_3), 22.8 (C-7), 29.4 (C-6), 30.8 (C-4), 35.6 (C-3), 39.4 (C-3a), 51.8 (C-2), 59.7 (C-7a), 64.2 and 64.4 (OCH_2), 108.5 (C-5), 116.0 (q, $J_{C\text{-}F}$ = 286 Hz, CF_3), 143.8 (C-3), 157.0 (q, $J_{C\text{-}O}$ = 35.0 Hz, CO)

ppm. HRMS (ESI): *m/z* calcd for $C_{13}H_{19}F_3NO_3$ $[M+H]^+$: 294.1312 found: 294.1313.

(3*RS*,3a*RS*,7a*RS*)-1-Trifluoro-3-Methyloctahydroindol-5-one ethylene ketal (13): To a stirred solution of alkene **8** (30 mg, 0.13 mmol) in MeOH (2 mL) was added Pd/C (45 mg) at room temperature. The reaction mixture was stirred under a hydrogen atmosphere for 72 h, filtered through Celite®, concentrated and purified by chromatography (Hexane/EtOAc, 90:10) to afford **13** (mixture of epimers, dr 3:2) as a yellow oil (29 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.44 (m, 1 H, H-4), 1.59 – 1.64 (m, 2 H, H-4 and H-6), 1.81 – 1.88 (m, 2 H, H-6 and H-7ax), 2.10 (m, 1 H, H-3a), 2.26 (qdd, *J* = 7.2, 6.0, 4.0, 1.2 Hz, 1 H, H-3), 2.84 (dq, *J* = 12.0, 4.0 Hz, 1 H, H-7eq), 3.37 (td, *J* = 11.4, 3.2 Hz, 1 H, H-7a), 3.46 (dd, *J* = 11.0, 1.5 Hz, 1 H, H-2), 3.73 (dd, *J* = 11.0, 5.8 Hz, 1 H, H-2), 3.96 (s, 4 H, (OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1 (CH_3), 26.7 (C-7), 33.4 (C-6), 33.6 (C-3), 35.8 (C-4), 45.0 (C-3a), 55.7 (C-2), 60.6 (C-7a), 64.6 and (OCH_2), 64.6 (OCH_2), 109.1 (C-5), 116.1 (q, J_{C-F} = 288 Hz, CF_3), 156.9 (q, J_{C-O} = 36.0 Hz, CO). NMR data for the minor epimer at C-3: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.44 (m, 2 H, H-4 and H-7), 1.54 (m, 1 H, H-3a), 1.59–1.64 (m, 1 H, H-6), 1.81–1.88 (m, 2 H, H-3 and H-6), 1.98 (dt, *J* = 12.3, 2.8 Hz, 1 H, H-4), 2.84 (m, 1 H, H-7), 3.17 (t, *J* = 10.7 Hz, 1 H, H-2), 3.24 (m, 1 H, H-7a), 3.91 (m, 1 H, H-2), 3.96 (s, 4 H, OCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 26.6 (C-7), 33.4 (C-6), 36.5 (C-3), 36.8 (C-4), 48.7 (C-3a), 55.4 (C-2), 65.3 (C-7a), 64.3 (OCH_2), 64.4 (OCH_2), 108.6 (C-5), 120.4 (CF_3), 156.5 (CO).

4-[(*N*-Benzyl-N-2-chloropropanoyl)amino]-3-cyclohexenone ethylene ketal (14a): The same imine used above for enamide **1** was prepared on a1.92 mmol scale and treated with 2-chloropropionyl chloride (205 µL, 2.11 mmol, 1.1 equiv.) and TEA in dry toluene (12 mL). Purification by chromatography (hexane/EtOAc, 100:0 to 50:50) afforded **4** (288 mg, 44%) as a yellow solid: m.p. 75-79°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 6.6 Hz, 3 H), 1.80 (dd, *J* = 11.0, 4.4 Hz, 2 H), 2.17-2.34 (m, 4 H), 3.97 (s, 4 H), 4.56 (*masked*, 1 H), 4.74 (br s, 2 H), 5.37 (br s, 1 H), 7.24-7.30 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 27.2, 31.0, 35.2, 50.0, 50.4, 64.5, 106.7, 126.4, 127.4, 128.4, 128.7, 137.2, 169.2 ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{23}ClNO_3$ $[M+H]^+$ 336.1361; found 336.1361.

4-[(*N*-Benzyl-N-2-bromopropanoyl)amino]-3-cyclohexenone ethylene ketal (14b): The same imine used above for enamide **1** was prepared on a 1.93 mmol scale and treated with 2-bromopropionyl chloride (221 µL, 2.13 mmol, 1.1 equiv.) and TEA in dry toluene (6 mL). Chromatography (hexane/EtOAc, 95:5 to 75:25) afforded **5** as a brown oil (343 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 7.1 Hz, 3 H), 2.16 – 2.27 (m, 4 H), 2.35 – 2.43 (m, 2 H), 3.97 (br s, 4 H), 4.52 (br s, 1 H), 4.75 (br s, 2 H), 5.41 (br s, 1 H), 7.25 – 7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.2, 31.0, 35.1, 39.5, 50.0, 64.5, 106.7, 126.4, 127.4, 128.4, 128.7, 137.2, 169.3 ppm; (C-4 not observed). HRMS (ESI): *m/z* calcd for $C_{18}H_{23}BrNO_3$ $[M+H]^+$ 380.0856; found 380.0861.

4-[(*N*-Benzyl-*N*-2,2-dichloropropanoyl)amino]-3-cyclohexenone ethylene ketal (14c): The same imine used above for enamide **1** was prepared on a 22.2 mmol scale and treated with TEA in toluene (130 mL), and 2,2-dichloropropionyl chloride (3.40 mL, 31.10 mmol, 1.4 equiv.) was added slowly in toluene (70 mL). Chromatography (CH_2Cl_2/EtOAc 100:0 to 95:5) afforded **14c** (5.53 g, 68%) as a yellow solid: m.p. 73-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (br s, 2 H), 2.10-2.32 (m, 2 H), 2.35 (s, 3 H), 2.38-2.52 (m, 2 H), 3.95 (s, 4 H), 4.25 and 5.00 (2 br s, 1 H each), 5.53 (br s, 1 H), 7.24-7.31 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (CH_3), 31.0, 35.0, 37.2, 50.3, 64.4, 80.6, 106.8, 127.5, 128.3, 128.7, 136.7, 165.1 ppm, (C-3 and C-4 not observed). HRMS (ESI): *m/z* calcd for $C_{18}H_{22}Cl_2NO_3$ $[M+H]^+$ 370.0971; found 370.0974.

Cyclization of enamides 14

From 14a: Following the general procedure for the cyclization of **1**, haloamide **14a** (140 mg, 0.42 mmol, 1.0 equiv) was dissolved in toluene (6 mL) and heated to reflux. Bu_3SnH (135 µL, 0.50 mmol, 1.2 equiv) and AIBN (14 mg, 0.08 mmol, 0.2 equiv) were added over 4 h with a syringe pump. Purification by chromatography (hexane/EtOAc, 95:5 to 50:50) afforded **3** as a colorless oil (49 mg, 39%). For analytical data when **3** was obtained from **2**, see above.

From 14b: From the bromo derivative **14b** (175 mg, 0.46 mmol) and using the same reaction conditions, lactam **3** (45 mg, 32%) and lactam **6** (36 mg, 26%) were obtained in 58% overall yield.

From 14c. 1-Benzyl-3-methyl-4,6,7,7a-tetrahydro-1*H*-indol-2,5-dione ethylene ketal (6): Following the general procedure for the cyclization of **1**, dichloroamide **14c** (12.5 g, 33.8 mmol, 1.0 equiv) was dissolved in toluene (480 mL) and heated to reflux. Bu_3SnH (20 mL, 74.3 mmol, 2.2 equiv) and AIBN (1.66 g, 10.1 mmol, 0.3 equiv) were added with a syringe pump over 4 h. Chromatography (hexane/EtOAc, 9:1 to 0:1) afforded **6** as a white oil (6.03 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (tdd, *J* = 13.8, 11.2, 4.0, 1 H, H-7ax), 1.64 (td, *J* = 13.8, 3.5 Hz, 1 H, H-6ax), 1.78 (dq, *J* = 13.8, 3.4 Hz, 1 H, H-6eq), 1.84 (t, *J* = 1.6 Hz, 3 H, CH_3), 2.14 (dddd, *J* = 11.6, 6.8, 3.6, 3.2 Hz, 1 H, H-7eq), 2.38 (dd, *J* = 14.2, 1.2 Hz, 1 H, H-4ax), 2.84 (dd, *J* = 14.0, 2.8 Hz, 1 H, H-4eq), 3.57 (dd, *J* = 11.4, 5.0 Hz, 1 H, H-7a), 3.85-4.00 (m, 4 H, OCH_2), 4.23 and 4.98 (2d, *J* = 15.2 Hz, 1 H each, CH_2Ph), 7.22-7.32 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.5 (CH_3), 27.9 (C-7), 32.1 (C-6), 36.0 (C-4), 44.0 (CH_2Ph), 59.1 (C-7a), 64.5 and 64.7 (OCH_2), 64.5 and 64.7 (OCH_2), 109.7 (C-5), 127.2 (C-3), 127.3, 127.9, 128.6, 137.9 (Ph), 149.4 (C-3a), 172.1 (C-2) ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{22}NO_3$ $[M+H]^+$ 300.1594; found 300.1591.

Hydrogenation of 6. Synthesis of Lactam 5: To a solution of alkene **6** (538 mg, 1.80 mmol, 1.0 equiv.) in MeOH (15 mL) was added Pd/C (215 mg, 40% w/w). The resulting suspension was stirred at room temperature under 27 atm of H_2 for 2 days. The reaction mixture was filtered through Celite® and concentrated. Chromatography (hexane/EtOAc, 85:15) afforded **5** (346 mg, 64%). For NMR data of lactam **5**, see above.

(3*RS*,3a*RS*,7a*SR*)-3-Methylhexahydroindol-2,5-dione ethylene ketal (15): NH_3 was condensed in a flask at -78 °C (50 mL) and Na (excess) was added to afford a dark blue solution. A solution of **6** (74 mg, 0.25 mmol, 1.0 equiv.) in THF (12.5mL) was added dropwise. After 20 min, the reaction mixture was quenched with a saturated solution of NH_4Cl. The reaction mixture was gradually warmed to room temperature until the bubbling stopped. It was then extracted with CH_2Cl_2 and the resulting organic layer was washed with brine, dried, and concentrated to afford **15** (41 mg, 79%) as a colorless solid: m.p. 178-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.52 – 1.59 (m, 2 H, H-4ax and H-7ax), 1.64 (td, *J* = 13.2, 4.0 Hz, 1 H, H-6ax), 1.73 (m, 1 H, H-3a), 1.87 (ddd, *J* = 13.2, 4.4, 3.6 Hz, 1 H, H-6eq), 1.93 (dtd, *J* = 12.0, 2.8, 0.8 Hz, 1 H, H-4eq), 2.00 (dq, *J* = 12.0, 3.6 Hz, 1 H, H-7eq), 2.08 (dq, *J* = 12.0, 6.8 Hz, 1 H, H-3), 3.03 (ddd, *J* = 13.2, 9.6, 3.2 Hz, 1 H, H-7a), 3.94 – 3.99 (m, 4 H, (OCH_2), 5.93 (br s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (CH_3), 27.7 (C-7), 33.7 (C-6), 36.9 (C-4), 42.5 (C-3), 48.9 (C-3a), 57.4 (C-7a), 64.4 and (OCH_2), 108.4 (C-5), 180.8 (C-2) ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{18}NO_3$ $[M+H]^+$: 212.1281 found: 212.1288

(3*RS*,3a*SR*,7a*SR*)-1-Benzyl-3-methylhexahydro-2*H*-indole-2,5(3*H*)-dione (16): Ketal **5** (100 mg, 0.33 mmol, 1.0 equiv.) was dissolved in a THF:HCl (10%) mixture (1:5, 6 mL) and stirred at room temperature. After an overnight stirring, the resulting solution was extracted with CH_2Cl_2, dried, and concentrated to afford ketone **16** as a yellow oil (84 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.0 Hz, 3 H, CH_3), 2.01 (m, 1 H, H-7), 2.08 (m, 1 H, H-7), 2.13 (m, 1 H, H-6), 2.19 (m, 1 H, H-6), 2.28 (m, 2 H, H-4), 2.75 (m, 2 H, H-3a, H-3), 3.69 (q, *J* = 5.2 Hz, 1 H, H-7a), 4.06 and 4.99 (2d, *J* = 15.0 Hz, 1 H each, CH_2Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =10.6 (CH_3), 25.0 (C-7), 35.1 (C-6), 35.6 (C-3a), 37.7 (C-4), , 40.3 (C-3), 44.3 (CH_2Ph), 53.3 (C-7a), 127.7, 127.9,

128.7, and 136.4 (Ph), 176.8 (C-2), 210.5 (C-5) ppm. HRMS (ESI): *m/z* calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489; found 258.1490.

(3*RS*,3a*SR*,7a*SR*)-1-Benzyl-3-methyloctahydroindol-5-one ethylene ketal (17): $LiAlH_4$ (26 mg, 2.0 equiv.) was suspended in dry THF (2 mL). A solution of **5** (100 mg, 0.33 mmol, 1.0 equiv.) in THF (6 mL) was added dropwise. The resulting suspension was heated to reflux for 4 h. It was cooled to room temperature and the remaining $LiAlH_4$ was quenched with a 15 % solution of NaOH. The resulting suspension was filtered through Celite® and washed several times with CH_2Cl_2. The resulting filtrate was washed with brine, dried, and concentrated. Chromatography (CH_2Cl_2/MeOH, 100:0 to 98:2) afforded **17** (85 mg, 90%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.44–1.53 (m, 2 H, H-4eq and H-6eq), 1.66 (t, *J* = 12.8 Hz, 1 H, H-4ax), 1.77 (br dt, *J* = 14.0, 3.6 Hz, 1 H, H-7eq), 1.84-1.92 (m, 1 H, H-7ax), 1.98 (td, *J* = 13.6, 4.4, 1 H, H-6ax), 2.11 (dddd, *J* = 12.8, 6.4. 6.4, 3.2 Hz, 1 H, H-3a), 2.26–2.35 (m, 1 H, H-3), 2.47 (t, *J* = 9.6 Hz, 1 H, H-2), 2.65 (t, *J* = 9.6 Hz, 1 H, H-2), 2.79 (q, *J* = 3.2 Hz, 1 H, H-7a), 3.23 (d, *J* = 14 Hz, 1 H, CH_2Ph), 3.95-4.00 (m, 5 H, OCH_2 and CH_2Ph), 7.17–7.32 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 24.1 (C-7), 29.0 (C-6), 31.6 (C-4), 34.2 (C-3), 41.8 (C-3a), 58.0 (CH_2Ph), 59.1 (C-2), 62.7 (C-7a), 64.0 and 64.3 (OCH_2), 110.1 (C-5), 126.5, 128.1, 128.2, and 140.7 (Ph) ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{26}NO_2$ $[M+H]^+$ 288.1958; found 288.1959.

(3*RS*,7*SR*,7a*SR*)-3-Methyloctahydroindol-5-one ethylene ketal (**18**): Amine **17** (73 mg, 0.25 mmol, 1.0 equiv.) was dissolved in MeOH (2.5 mL) and Pd/C (15 mg, 20% w/w) was added. The resulting suspension was stirred under 1 atm of H_2 at room temperature. After 24 h, the reaction mixture was filtered through Celite®, concentrated, and purified by chromatography (CH_2Cl_2/MeOH, 99:1 to 90:10) to afford **18** (50 mg, nearly quantitative) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.35 (t, *J* = 13.0 Hz, 1 H, H-4ax), 1.48–1.54 (m, 2 H, H-4eq and H-6eq), 1.73–1.81 (m, 2 H, H-7), 1.89 (tt, *J* = 14.0, 4.0 Hz, 1 H, H-6ax), 2.06 (dq, *J* = 12.6, 5.2 Hz, 1 H, H-3a), 2.16 (br s, 1 H, NH), 2.32-2.44 (m, 1 H, H-3), 2.62 (t, *J* = 10.4 Hz, 1 H, H-2), 3.14 (t, *J* = 10.4 Hz, 1 H, H-2), 3.28 (q, *J* = 4.0 Hz, 1 H, H-7a), 3.93–3.97 (m, 4 H, OCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1 (CH_3), 25.7 (C-7), 28.6 (C-6), 30.4 (C-4), 37.9 (C-3), 41.1 (C-3a), 51.5 (C-2), 56.8 (C-7a), 64.2 and 64.3 (OCH_2), 109.4 (C-5) ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{20}NO_2$ $[M+H]^+$ 198.1489; found 198.1487.

(3*RS*,3a*SR*,7a*SR*)-3-Methyloctahydro-5*H*-indol-5-one (19): Ketal **18** (40 mg, 0.20 mmol, 1.0 equiv.) was dissolved in HCl (10%) (1 mL) and stirred at room temperature. After an overnight stirring, the resulting solution was extracted with CH_2Cl_2, quenched with a saturated solution of Na_2CO_3 and extracted with $CHCl_3$:*i*PrOH (4:1). The resulting organic layer was dried and concentrated to afford **19** (31 mg, near quantitative) as an amorphous orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.95 (dddd, *J* = 12.8, 6.4, 6.4, 3.2 Hz, 1 H, H-7eq), 2.04 (m, 1 H, H-7), 2.09 (td, *J* = 6.0, 6.0, 1.6 Hz, 1 H, H-6), 2.12 - 2.16 (m, 1 H, H-4), 2.18 (br s, 1H, NH), 2.33 – 2.39 (m, 3 H, H-4, H-3, H-3a), 2.57 – 2.63 (m, 1 H, H-6), 2.68 (t, *J* = 9.2 Hz, 1 H, H-2), 3.19 (dd, *J* = 10.0, 9.2 Hz, 1 H, H-2), 3.52 (br s, 1 H, H-7a). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (CH_3), 28.6 (C-7), 35.9 (C-6), 37.9 (C-4), 38.2 (C-3), 42.1 (C-3a), 51.8 (C-2), 56.9 (C-7a), 213.6 (C-5). HRMS (ESI): *m/z* calcd for $C_9H_{16}NO$ $[M+H]^+$ 154.1226; found 154.1224.

Acknowledgements

Financial support for this research was provided by the Projects CTQ2013-41338-P and CTQ2016-75350-P from the Ministry of Economy and Competitiveness of Spain/ FEDER funds and the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET Network (MCITN-2012–316379).

Keywords: Radical reactions • Nitrogen heterocycles • Lactams • Cyclization • Hydrogenation

[1] a) J. Kobayashi, H. Morita, "The *Daphniphyllum* Alkaloids" in The Alkaloids, Vol 60 (Eds.: G.A. Cordell), Academic Press, New York, **2003**, pp 165-205; b) J. Kobayashi, T. Kubota, *Nat. Prod. Rep.* **2009**, *26*, 936-962. c) A. K. Chattopadhyay, S. Hanessian, *Chem. Rev.* **2017**, DOI: 10.1021/acs.chemrev.6b00412.

[2] S. Hanessian, S. Dorich, H. Menz, *Org. Lett.* **2013**, *15*, 4134-4137.

[3] For other syntheses of penta-, tetra- and tricyclic core structures of *Daphniphyllum* alkaloids with the 3a-methyloctahydroindole scaffold, see respectively: a) S. E. Denmark, R. Y. Baiazitov, S. T. Nguyen, *Tetrahedron* **2009**, *65*, 6535-6548. b) J. Boudreault, F. Lévesque, G. Bélanger, *J. Org. Chem.* **2016**, *81*, 9247-9268. c) I. Coldham, A. J. Burrell, H. D. S. Guerrand, N. Oram, *Org. Lett.* **2011**, *13*, 1267-1269.

[4] a) From tethered phenylseleno alkenes: D. L. J. Clive, A. Y. Mohammed, *Heterocycles* **1989**, *28*, 1157-1167; b) Radical cyclization from 2-chloropropanamides: T. Sato, N. Nakamura, K. Ikeda, M. Okada H. Ishibashi, M. Ikeda, *J. Chem. Soc. Perkin Trans 1*, **1992**, 2399-2407; c) Recently, Rueping has reported this cyclization type by a visible light photoredox process: E. Fava, M. Nakajima, M. B. Tabak, M. Rueping, *Green Chem.* **2016**, *18*, 4531-4535; d) Zr-promoted reductive coupling of dienes: M. Mori, N. Uesaka, M. Shibasaki, *J. Org. Chem.* **1992**, *57*, 3519-3521; N. Uesaka, M. Mori, K. Okamura, T. Date, *J. Org. Chem.* **1994**, *59*, 4542-4547; e) Bu_3SnH-promoted acrylamides tethered alkenes: A. F. Parsons, D. A. J. Williams, *Tetrahedron* **1998**, *54*, 13405-13420; f) For iron-catalyzed redox radical cyclization of 1,6-dienes, see: T. Taniguchi, N. Goto, A. Nishibata, H. Ishibashi, *Org. Lett.* **2010**, *12*, 112-115; g) S. Dorich, J. R. Del Valle, S. Hanessian, *Synlett* **2014**, *25*, 799–804. h) For cyclization of cyclohexene-tethered 2-enynamides using FeX_2, see: M.-C. P. Yeh, Y.-S. Shiue, H.-H. Lin, T.-Y. Yu, T.-C. Hu, J.-J. Hong, *Org. Lett.* **2016**, *18*, 2407-2410.

[5] For synthesis of enamides by acylation of imines with haloacetyl chlorides, see: a) J. Cassayre, B. Quiclet-Sire, J.-B. Saunier, S. Z. Zard *Tetrahedron* **1998**, *54*, 1029-1040; b) A. J. Clark, D. P. Curran, D. J. Fox, F. Ghelfi, C. S. Guy, B. Hay, N. James, J. M. Phillips, F. Roncaglia P. B. Sellars, P. Wilson, H. Zhang, *J. Org. Chem.* **2016**, *81*, 5547-5565.

[6] For radical cyclyzation of analog haloacetamides leading to 3-unsubstituted hydroindoles, see: a) O. Tamura, H. Matsukida, A. Toyao Y. Takeda, H. Ishibashi, *J. Org. Chem.* **2002**, *67*, 5537-5545; b) D. P. Curran, D. B. Guthrie, S. J. Geib, *J. Am. Chem. Soc.* **2008**, *130*, 8437-8445; c) D. B. Guthrie, K. Damodaran, D. P. Curran, P. Wilson, A. J. Clark, *J. Org. Chem.* **2009**, *74*, 4262-4266.

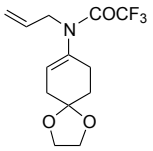
[7] M. V. Riofski, J. P. John, M. M. Zheng, J. Kirshner, D. A. Colby, *J. Org. Chem.* **2011**, *76*, 3676-3683.

[8] For stereochemical elucidation of *cis-trans* octahydroindoles, see: D. Solé, J. Bosch, J. Bonjoch *Tetrahedron* **1996**, *52*, 4013-4028.

[9] G. Stork, R. Mook, *J. Am. Chem. Soc.* **1987**, *109*, 2829-2831.

[10] For radical cyclizations initiated by intermolecular radical addition to alkynes, see: U. Wille, *Chem. Rev*. **2013**, *113*, 813-853.

[11] The non-cyclized allyl derivative depicted below was also isolated in 30% yield.



[12] (a) G. Stork; P. M. Sher; H.-L- Chen, *J. Am. Chem. Soc.* **1986**, 108, 6384-6385. (b) A. Srikrishna; R. Viswajanani, C. V. Yelamaggad, *Tetrahedron* **1997**, *53*, 10479-10488.

[13] We also observed that when using long-stored Bu_3SnH, a mixture of *cis-* and *trans*-hydroindoles **8** and **9** was isolated.

[14] a) 1,5-enynes allows the 5-membered ring formation via gold-catalyzed 5-*endo-dig* cycloisomerizations: R. Dorel, A. M. Echavarren, *Chem. Rev*. **2015**, *115*, 9083-9072. b) For regioselective 6-*endo-dig* cyclizations of *N*-propargyl enamine derivatives using gold- and rhodium-catalyzed reactions, see: G. Abbiati, A. Arcadi, G. Bianchi, S.

Di Giuseppe, F. Marinelli, E. Rossi, *J. Org. Chem.* **2003**, *68*, 6959-6866. c) H. Kim, C. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 6336-6337.

[15] For cyclization of tethered alkyne enamides in a 5-*exo* process, see: a) B. Alcaide, I. M. Rodríguez-Campos, J. Rodríguez-López, A. Rodríguez-Vicente, *J. Org. Chem.* **2004**, *64*, 5377-5387; b) reference 4g.

[16] For tethered alkyne imines, see: J. A. Pigza, J.-S. Han, A. Chandra, D. Mutnick, M. Pink, J. N. Johnston, *J. Org. Chem.* **2013**, *78*, 822-843.

[17] For a discussion about NMR data of Z/E rotamers in nitrogen-containing rings with an exocyclic amide of carbamate function, see: a) N. Valls, V. M. Segarra, J. Bonjoch, *Magn. Reson. Chem.* **1991**, *29*, 985-992; b) N. Valls, M. López-Canet, M. Vallribera, J. Bonjoch, *Chem. Eur. J.* **2001**, *7*, 3446-3460.

[18] For the analysis of coupling constants in ^{1}H NMR in substituted cyclopentanes, see: G. M. Constantino, G. V. J. da Silva, *Tetrahedron* **1988**, *54*, 11363-11374.

[19] Rueping has observed that when starting from 4,4-disubstituted aminocyclohexenes leading to 5,5-disubstituted octahydroindoles, the process took place with lower yields than with other types of substrates in the same reaction conditions. See reference 4c.

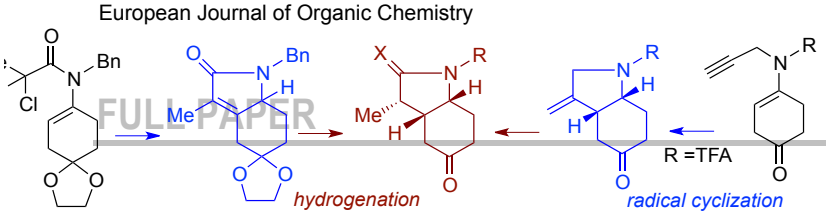
[20] For the influence of the halogen atom in the 5-*endo* radical cyclization of haloacetamides leading to octahydroindoles, see reference 6b.

[21] M. Kojima, T. Tomioka, *Chem. Pharm. Bull.* **1976**, 24, 1613-1620. For 3-methyl *trans*-octahydroindol-2-ones, see also: W. J. Nodes, D. R. Nutt, A. M. Chippindale, A. J. A. Cobb, *J. Am. Chem. Soc.* **2009**, *131*, 16016-16017.

[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (tt, *J* = 6.8, 1.2 Hz, 2 H), 1.90 (tt, *J* = 7.2, 0.8 Hz, 2 H), 2.29 (t, *J* = 2.4 Hz, 1 H), 2.48 (m, 4 H), 4.00 (s, 4 H), 4.26 (d, *J* = 2.4 Hz, 2 H).

10.1002/ejoc.201700086

WILEY-VCH



Stereoselective syntheses of 3-methyl-*cis*-octahydroindoles through a 5-*endo*-*trig* radical cyclization followed by an hydrogenation step were achieved from either an alkyne tether enamide or a *N*-alkenyl-2,2-dichloropropanamide. 1,5-Enyne cyclizations via a 5-*endo*-*trig* process are reported, in which a remote functional group (ketone or ketal) allowed the diastereoselectivity in the octahydroindole ring formation to be overturned.

Radical Cyclizations

*Sergi Jansana, Guilhem Coussanes, Faïza Diaba, Josep Bonjoch**

Page No. – Page No.

Radical cyclizations in the Synthesis of 3-Methyl-cis-octahydroindol-5-ones