Pergamon

Tetrahedron Letters 42 (2001) 7823–7827

TETRAHEDRON LETTERS

A straightforward approach to the galanthan ring system using the imine Michael reaction followed by a radical cyclization

Ivan Jabin* and Pierre Netchitaïlo

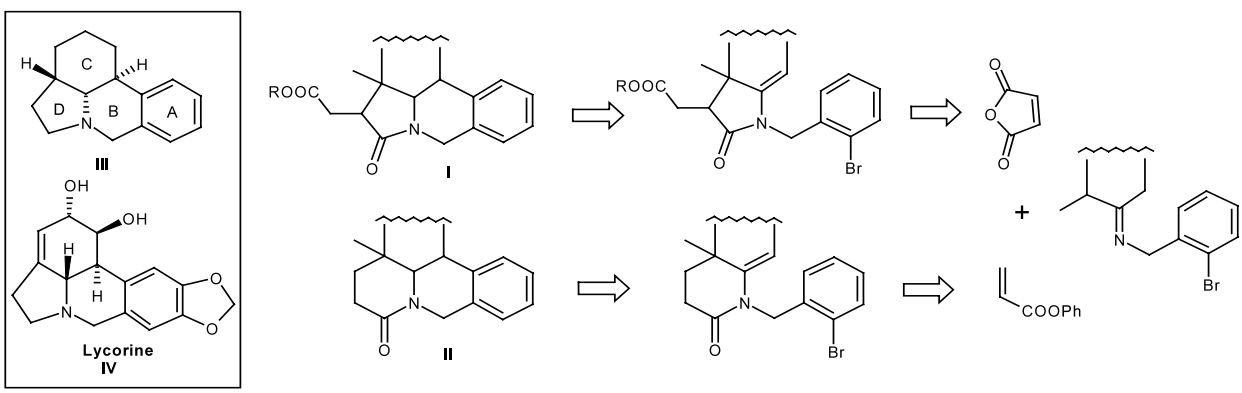
URCOM, Université du Havre, Faculté des Sciences et Techniques, 25 rue Philippe Lebon, BP 540, 76058 Le Havre Cedex, France

Received 25 June 2001; accepted 7 September 2001

Abstract—A two-step procedure based on the Michael reaction of imines followed by a radical cyclization has proved to be a regioselective and stereoselective method for the construction of the skeleton of galanthan-type alkaloids.

The Michael type reaction of imines with electrophilic olefins can afford stereoselectively polycyclic functionalized enamides.[1] Since numerous alkaloids possess polycyclic aza-heterocycles structures, our aim was to develop a simple procedure based on the Michael type reaction of imines for the stereoselective approach to the skeleton of biologically important alkaloids. Our synthetic strategy was directed toward the preparation of type **I** and **II** polycyclic structures (Scheme 1). A straightforward construction of type **I** skeleton would constitute an interesting approach of the galanthan ring system **III**, common to many Amaryllidacae alkaloids. Most natural substances of this family possess important biological activities, as for instance lycorine **IV**.[2] In the literature, the C-ring of the galanthan ring system is generally prepared through an intramolecular Diels–Alder reaction and a subsequent radical cyclization usually affords the B-ring.[3] In the present paper, we describe a new synthetic route for the elaboration of type **I** and **II** structures based on a Michael type reaction of easily available imines followed by a radical cyclization. The electrophilic olefins used for the Michael reactions were maleic anhydride and phenyl acrylate[4] since these olefins are known[5] to lead in situ to 5- or 6-ring enamides, respectively (Scheme 1). Control of the stereochemistry of the B/C-ring junction is an important aspect of this approach; therefore, stereoselectivity of the two key steps will be discussed.

In order to study the feasibility of our synthetic approach and in particular the regioselectivity of the radical cyclization (5-*exo* versus 6-*endo* cyclization), we



Scheme 1.

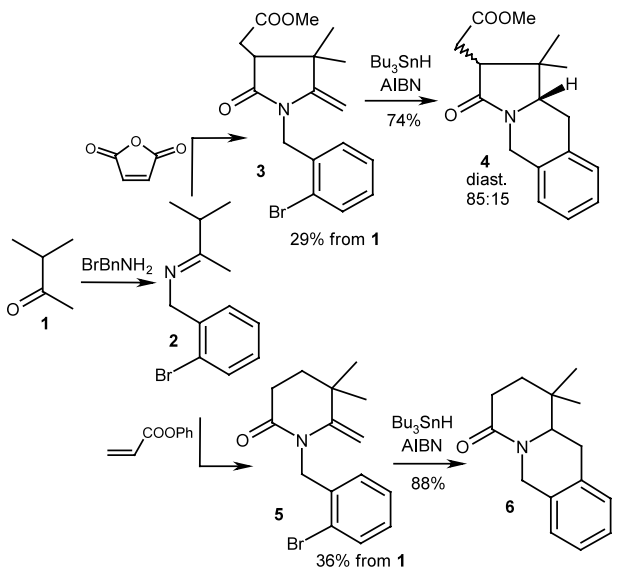
Keywords: imines; Michael reaction; radical cyclization; stereoselectivity; galanthan.

* Corresponding author. Tel.: +332 32 74 43 94; fax: +332 32 74 43 91; e-mail: ivan.jabin@univ-lehavre.fr

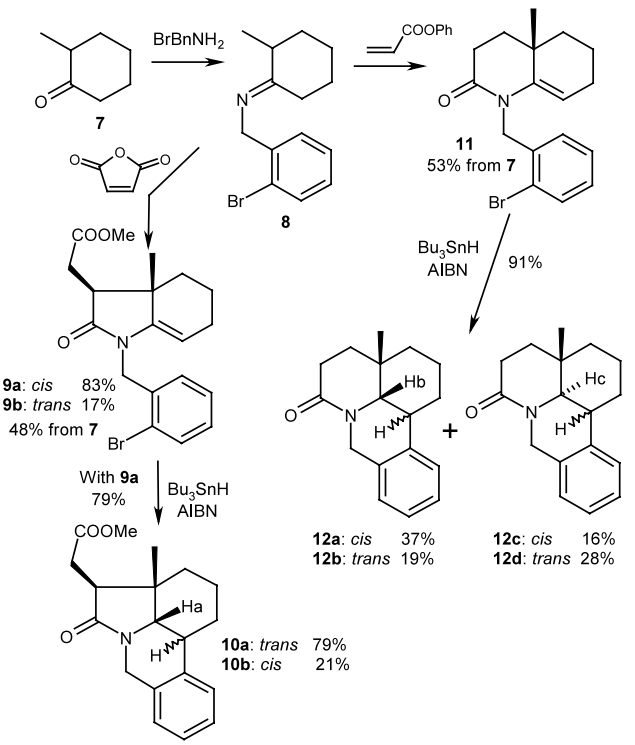
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01679-3

first performed the Michael reaction with a model, i.e. an acyclic imine. Thus, crude imine **2**[6] was reacted on one hand with maleic anhydride (1.1 equiv., THF, rt, 15 h) and on the other hand with phenyl acrylate (1.1 equiv., neat, rt, 15 h). The resulting cyclized Michael adducts **3**[7] (produced after esterification of the intermediate lactam acid: 1.1 equiv. of DCC, trace of DMAP, $MeOH/CH_2Cl_2$, rt, 1 h) and **5**[7] were obtained, respectively, in 29 and 36% overall yields from **1**. Both radical cyclizations[8] proceeded regioselectively giving tricyclic lactams **4**[7] and **6**[7] in 74 and 88% yields, respectively (Scheme 2). It is known that radical cyclizations with cyclic enamides generally produce an important amount of the uncyclized product of reduction.[3,9] To our delight, with starting enamides **3** and **5** these undesired reduced products were not formed in both cases. A similar result was reported previously on very closely related compounds.[10] Radical cyclization of **3** proceeded with a good diastereoselectivity (85:15, determined by ^{1}H NMR analysis of crude **4**) but *cis* and *trans* diastereomers were not separable by FC[11] and therefore the stereochemistry of the major diastereomer was not determined.

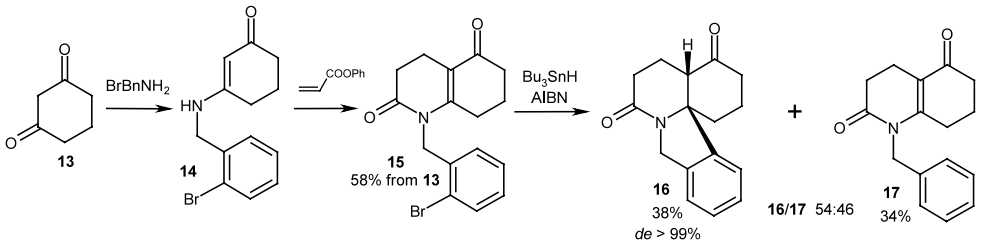
We have then tested our approach with the cyclic imine **8**.[6] Thus, Michael reactions with maleic anhydride (1.1 equiv., THF, rt, 15 h, then esterification of the intermediate lactam acid: 1.1 equiv. of DCC, trace of DMAP, $MeOH/CH_2Cl_2$, rt, 1 h) and with phenyl acrylate (1.1 equiv., neat, rt, 15 h) led, respectively, to lactams **9** and **11**[7] in 48 and 53% overall yields from **7**. Lactam **9** was obtained as a 83:17[12] mixture of *cis*/*trans* diastereomers (**9a**[7] and **9b**[7]), which were separated by FC. The diastereoselectivity of the Michael reaction is in accordance with theoretical studies[1g,h] and with previous results on closely related compounds.[1a] The relative configuration of the major diastereomer (i.e. *cis*) is given by analogy with these earlier results and has been confirmed with the stereochemical assignment for compound **10a**.[7] Radical cyclizations[8] of enamides **9a** and **11** gave the expected cyclized compounds **10** and **12** in good yields (79 and 91%, respectively) without any significant amount of reduced compounds. Cyclization of lactam **9a** proceeded stereoselectively since a 79:21[12] mixture of only two diastereomers (**10a**[7] and **10b**[7]) was obtained. These compounds were separated by FC and their stereochemistry was determined by ^{1}H NMR and NOEDIFF experiments. For instance, **10a** and **10b** exhibit coupling constants for Ha of 11.7 and 3.9 Hz, which are compatible for *trans* and *cis* ring junctions, respectively. The presence of the *trans*-B/C ring fusion in the major diastereomer **10a**, which was a requisite for a stereoselective approach of lycoryne-type alkaloids, is in agreement with earlier literature reports.[3,9a,9b,10] This result is consistent with studies on closely related enamides dealing with facial selectivity during radical cyclization.[9a] First, it was suggested that the β face of the enamide double bond is sterically more accessible and secondly that the stereoselectivity of the reduction with Bu_3SnH correlates with product stability. On the other hand cyclization of lactam **11** proceeded with a poor stereoselectivity since the four possible diastereomers (**12a**,[7] **12b**,[7] **12c**[7] and **12d**[7]) were formed in close relative proportions. Compared to the cyclization of **9a**, the loss of stereoselectivity for reduction of the intermediate tertiary radical presumably results from the loss of large ring strain difference between the diastereomers of **12**. These diastereomers were separated by FC and their stereochemistry was determined by ^{1}H NMR and NOEDIFF experiments.[13] In particular, the major isomer **12a** exhibits a coupling constant of 7.0 Hz for Hb (*cis*-B/C ring fusion) and isomer **12d** a coupling constant of 11.7 Hz for Hc (*trans*-B/C ring fusion) (Scheme 3).



Scheme 2.



Scheme 3.



Scheme 4.

Finally, a study on the regioselectivity of the radical cyclization has been undertaken in order to see if 5-*exo* cyclization can take place with our enamide system. Thus, an enamide (i.e. lactam **15**) which can cyclize only through a 5-*exo* way was prepared. The Michael reaction of crude enaminone **14**[6] with phenyl acrylate (1.3 equiv., 1,4-dioxane, 110°C, 3 days) yielded lactam **15**[7] (58% overall yield from **13**) and its radical cyclization led to a 54:46[12] mixture of spirocyclic lactam **16**[7] (38% yield) and reduced compound **17**[7] (34% yield) (Scheme 4). This result suggests that 5-*exo* cyclization of enamides **3**, **5**, **9a** and **11** could have taken place, but it is less favorable than the 6-*endo* one. It is noteworthy that the lactam **16** was obtained as a single diastereomer. This result can be rationalized if we suppose that the diastereomer of **16**, which would have been produced by α-facial attack of the double bond, has important ring strain and is thus not formed. Moreover, the reaction was also performed under the same conditions but with Bu_3SnD. In this case, the ^1H NMR analysis of the deuterated compound **17** revealed the presence of the deuterium atom at the allylic position instead of the expected aromatic one. This result shows that formation of **17** does not result from direct reduction of the aryl radical, but that intramolecular allylic to aryl 1,6-hydrogen atom transfer followed by reduction takes place.

In conclusion, we have reported a two-step procedure based on the Michael reaction of imines followed by a radical cyclization, which can lead regioselectively to polycyclic lactams. The stereoselectively of the radical cyclization depends on the nature of the starting bicyclic enamide. Moreover, we have shown the synthetic utility of this procedure with a stereoselective approach of lycoryne-type alkaloids. The application of this study to chiral imines and other electrophilic olefins is under investigation in our Laboratory in order to develop straightforward enantioselective syntheses of galanthan alkaloids.

Acknowledgements

We thank the students of the MST CIC RSA1 2001 class for the preliminary study made during their practical work and Dr. G. Revial and Dr. M. Pfau for their help.

References

1. (a) Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.* **1995**, *60*, 1143–1147; (b) Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795–1812; (c) Jabin, I.; Revial, G.; Pfau, M.; Decroix, B.; Netchitaïlo, P. *Org. Lett.* **1999**, *1*, 1901–1904; (d) Revial, G.; Jabin, I.; Pfau, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4975–4983; (e) Jabin, I.; Revial, G.; Monnier-Benoit, N.; Netchitaïlo, P. *J. Org. Chem.* **2001**, *66*, 256–261; (f) Revial, G.; Jabin, I.; Redolfi, M.; Pfau, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1683–1688; (g) Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* **1986**, *51*, 2671–2675; (h) Sevin, A.; Masure, D.; Giessner-Prettre, C.; Pfau, M. *Helv. Chim. Acta* **1990**, *73*, 552–573.
2. (a) Cook, J. W.; Loudon, J. D. In *The Alkaloids*; Manske, R. H. F.; Holmes, H. L., Eds.; Academic Press: New York, 1952; Vol. 2, p. 331; (b) Ghosal, S.; Saini, K. S.; Razdan, S. *Phytochemistry* **1985**, *24*, 2141.
3. Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716–1724 and references cited therein.
4. Phenyl acrylate was prepared according to the literature: Ahlbretch, A.; Codding, D. W. *J. Am. Chem. Soc.* **1953**, *75*, 984.
5. See Ref. 1c.
6. Imines **2**, **8** and enaminone **14** were obtained from the corresponding ketones and 2-bromobenzylamine (1 equiv.) in refluxing toluene in a Dean–Stark water separator for 24 h.
7. **3**: oil, EIMS *m*/*z* (rel. int.) 367 (M^+, <1), 286 (base), 254 (74), 226 (42), 169 (32), 90 (32). IR (neat) 1721, 1654 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.31 (s, 3H), 2.47 (dd, $J_1=8.6$ Hz, $J_2=16.4$ Hz, 1H), 2.83 (dd, $J_1=6.3$ Hz, $J_2=16.4$ Hz, 1H), 3.02 (dd, $J_1=6.3$ Hz, $J_2=7.8$ Hz, 1H), 3.73 (s, 3H), 4.08 (d, $J=2.3$ Hz, 1H), 4.15 (d, $J=2.3$ Hz, 1H), 4.74 (s, 2H), 6.95 (dd, $J_1=1.6$ Hz, $J_2=7.8$ Hz, 1H), 7.09 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.22 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.53 (dd, $J_1=1.6$ Hz, $J_2=7.8$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.38, 27.49, 31.03, 40.43, 44.30, 48.60, 52.40, 84.97, 123.1, 127.6, 128.0, 129.1, 133.2, 134.8, 155.6, 173.0, 175.3.
4 (major diastereomer): oil, EIMS *m*/*z* (rel. int.) 287 (M^+, 92), 272 (31), 256 (24), 227 (25), 132 (58), 130 (49), 104 (base). IR (neat) 1738, 1682 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.17 (s, 3H), 2.31 (dd, $J_1=7.8$ Hz, $J_2=15.7$ Hz, 1H), 2.62–2.92 (m, 4H), 3.39 (dd, $J_1=4.1$ Hz, $J_2=10.3$ Hz, 1H), 3.70 (s, 3H), 4.42 (d, $J=17.2$ Hz, 1H), 4.59 (d, $J=17.2$ Hz, 1H), 7.06–7.30 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.70, 25.52, 30.03, 30.20, 41.01, 43.48, 50.75, 52.16, 62.83, 127.1, 127.2, 128.9, 132.1, 134.4, 173.4, 174.4.

5: white solid, mp 65°C (hexane), EIMS *m/z* (rel. int.) 309 (M^++1, <1), 307 (M^+−1, <1), 228 (base), 171 (20), 90 (25). IR ($CHCl_3$) 1666, 1620 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.72 (t, $J=7.0$ Hz, 2H), 2.69 (t, $J=7.0$ Hz, 2H), 4.10 (d, $J=2.3$ Hz, 1H), 4.27 (d, $J=2.3$ Hz, 1H), 4.96 (s, 2H), 6.88 (d, $J=7.8$ Hz, 1H), 7.06 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.20 (t, $J=7.8$ Hz, 1H), 7.52 (dd, $J_1=1.6$ Hz, $J_2=7.8$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.96, 29.80, 33.47, 34.42, 48.60, 92.13, 122.8, 127.0, 127.8, 128.6, 133.0, 135.9, 152.7, 169.8. Anal. calcd for $C_{15}H_{18}BrNO$: C, 58.45; H, 5.89; N, 4.54. Found: C, 58.37; H, 5.91; N, 4.63.

6: white solid, mp 104°C (hexane:EtOAc, 10:1), EIMS *m/z* (rel. int.) 229 (M^+, 81), 173 (21), 145 (base), 104 (94). IR ($CHCl_3$) 1634 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.12 (s, 3H), 1.53 (ddd, $J_1\approx J_2\approx 6$ Hz, $J_3=13$ Hz, 1H), 1.76 (ddd, $J_1\approx J_2\approx 7$ Hz, $J_3=14$ Hz, 1H), 2.58 (t, $J=6.3$ Hz, 2H), 2.68–2.92 (m, 2H), 3.27 (dd, $J_1=3.9$ Hz, $J_2=11.0$ Hz, 1H), 4.36 (d, $J=17.2$ Hz, 1H), 5.18 (d, $J=16.4$ Hz, 1H), 7.03–7.20 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.75, 27.03, 28.76, 31.77, 31.91, 31.96, 46.48, 63.86, 126.7, 127.0, 127.1, 128.6, 132.8, 134.5, 170.2. Anal. calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.48; H, 8.43; N, 6.21.

9a: oil, EIMS *m/z* (rel. int.) 393 (M^++1, 3), 391 (M^+−1, 3), 313 (21), 312 (base), 252 (56), 171 (28), 169 (30). IR (neat) 1754–1654 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.50–2.15 (m, 6H), 2.45 (dd, $J_1=10.1$ Hz, $J_2=18.0$ Hz, 1H), 2.83–2.98 (m, 2H), 3.71 (s, 3H), 4.61 (d, $J=16.4$ Hz, 1H), 4.71 (t, $J=3.9$ Hz, 1H), 4.77 (d, $J=16.4$ Hz, 1H), 7.00 (dd, $J_1=1.6$ Hz, $J_2=7.8$ Hz, 1H), 7.08 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.22 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.51 (dd, $J_1=1.6$ Hz, $J_2=7.8$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.47, 21.22, 23.02, 29.91, 34.17, 39.93, 43.97, 50.92, 52.26, 99.58, 123.1, 127.9, 128.1, 129.1, 133.1, 135.5, 144.1, 173.2, 174.9.

9b: oil, EIMS *m/z* (rel. int.) 393 (M^++1, 5), 391 (M^+−1, 5), 312 (base), 280 (33), 252 (64), 171 (31), 169 (34). IR (neat) 1738–1681 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.13–2.20 (m, 6H), 1.29 (s, 3H), 2.38–2.58 (m, 2H), 2.81–3.00 (m, 1H), 3.70 (s, 3H), 4.59 (d, $J=16.4$ Hz, 1H), 4.68–4.79 (m, 2H), 7.00 (d, $J=7.0$ Hz, 1H), 7.10 (dd, $J_1\approx J_2\approx 8$ Hz, 1H), 7.24 (dd, $J_1\approx J_2\approx 7$ Hz, 1H), 7.53 (d, $J=7.5$ Hz, 1H).

10a: white solid, mp 144–145°C (hexane:EtOAc, 1:2), EIMS *m/z* (rel. int.) 313 (M^+, base), 238 (34), 212 (39), 210 (82), 130 (28). IR ($CHCl_3$) 1734, 1682 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.10–1.93 (m, 5H), 2.28–2.41 (m, 1H), 2.37 (dd, $J_1=8.6$ Hz, $J_2=15.6$ Hz, 1H), 2.54 (ddd, $J_1=3.1$ Hz, $J_2\approx J_3\approx 11$ Hz, 1H), 2.78 (d, $J=11.7$ Hz, 1H), 2.84 (dd, $J_1=5.5$ Hz, $J_2=16.4$ Hz, 1H), 3.03 (dd, $J_1=6.5$ Hz, $J_2=8.6$ Hz, 1H), 3.71 (s, 3H), 4.31 (d, $J=17.2$ Hz, 1H), 5.07 (d, $J=17.2$ Hz, 1H), 7.05–7.28 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.75, 24.82, 24.95, 29.97, 33.59, 38.06, 39.49, 44.06, 45.01, 52.22, 65.69, 124.7, 126.7, 126.8, 126.9, 132.6, 139.1, 173.6, 175.0. Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.84; H, 7.45; N, 4.32.

10b: oil, EIMS *m/z* (rel. int.) 313 (M^+, base), 270 (80), 240 (64), 210 (36). ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.12–1.78 (m, 6H), 2.49–2.66 (m, 3H), 2.86 (ddd, $J_1=3.9$ Hz, $J_2\approx J_3\approx 9$ Hz, 1H), 3.46 (d, $J=3.9$ Hz, 1H), 3.67 (s, 3H), 4.44 (d, $J=18.0$ Hz, 1H), 4.61 (d, $J=18.0$ Hz, 1H), 7.08–7.25 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.38, 21.46, 30.15, 31.80, 35.30, 38.31, 39.11, 43.15, 51.84, 52.31, 60.03, 127.2, 127.3, 127.4, 129.0, 130.7, 138.9, 172.7, 176.6.

11: white solid, mp 73°C (hexane:EtOAc, 7:3), EIMS *m/z* (rel. int.) 335 (M^++1, 3), 333 (M^+−1, 3), 254 (base). IR (neat) 1670, 1644 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.35–2.15 (m, 8H), 2.68 (dd, $J_1=7.0$ Hz, $J_2=10.7$ Hz, 1H), 4.49 (d, $J=16.7$ Hz, 1H), 4.72 (dd, $J_1=2.7$ Hz, $J_2=4.8$ Hz, 1H), 5.23 (d, $J=16.7$ Hz, 1H), 6.87 (d, $J=7.5$ Hz, 1H), 7.04 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.19 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.49 (dd, $J_1=1.6$ Hz, $J_2=8.1$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.80, 23.01, 24.65, 29.34, 32.60, 34.36, 38.16, 48.58, 106.1, 122.5, 127.0, 127.6, 128.3, 132.7, 136.2, 142.2, 169.0. Anal. calcd for $C_{17}H_{20}BrNO$: C, 61.09; H, 6.03; N, 4.19. Found: C, 60.73; H, 6.02; N, 4.21.

12a: white solid, mp 138–140°C (hexane:EtOAc, 3:2), EIMS *m/z* (rel. int.) 255 (M^+, base), 254 (58), 130 (46). IR ($CHCl_3$) 1622 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.15 (s, 3H), 1.11–1.90 (m, 7H), 2.25–2.70 (m, 3H), 3.17 (s_l, 1H), 3.68 (d, $J=7.0$ Hz, 1H), 3.81 (d, $J=14.9$ Hz, 1H), 5.50 (d, $J=14.9$ Hz, 1H), 7.10–7.50 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.31, 17.72, 25.03, 29.04, 34.78, 34.94, 37.38, 38.89, 42.32, 60.86, 123.4, 126.4, 126.5, 128.0, 135.9, 138.5, 170.3. Anal. calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.52; H, 8.68; N, 5.58.

12b: oil, EIMS *m/z* (rel. int.) 255 (M^+, base), 254 (47) ^1H NMR (200 MHz, $CDCl_3$) δ 1.09–1.87 (m, 7H), 1.14 (s, 3H), 2.17–2.91 (m, 4H), 2.95 (d, $J=12.1$ Hz, 1H), 4.08 (d, $J=16.8$ Hz, 1H), 5.67 (d, $J=16.8$ Hz, 1H), 7.00–7.30 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.16, 26.70, 26.75, 28.90, 29.78, 32.19, 39.42, 40.46, 46.33, 66.00, 125.9, 126.6, 126.7, 126.8, 133.4, 138.5, 168.1.

12c: EIMS *m/z* (rel. int.) 255 (M^+, base), 254 (43), 130 (30).

12d: oil, EIMS *m/z* (rel. int.) 255 (M^+, 88), 254 (base). IR (neat) 1633 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.10–1.90 (m, 8H), 2.40–2.78 (m, 3H), 2.86 (d, $J=11.7$ Hz, 1H), 4.09 (d, $J=16.4$ Hz, 1H), 5.21 (d, $J=16.4$ Hz, 1H), 7.07–7.40 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.92, 20.53, 28.54, 29.46, 34.58, 35.59, 36.21, 38.35, 44.58, 64.70, 123.9, 126.8, 126.9, 127.6, 133.6, 139.4, 170.4.

15: yellow solid, mp 127–129°C (hexane:EtOAc, 3:7), EIMS *m/z* (rel. int.) 335 (M^++1, 8), 333 (M^+−1, 8), 254 (base), 171 (25), 169 (26). IR ($CHCl_3$) 1694, 1644, 1614 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.86–2.01 (m, 2H), 2.30–2.43 (m, 4H), 2.66 (s, 4H), 5.00 (s, 2H), 6.85 (d, $J=7.8$ Hz, 1H), 7.12 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.25 (ddd, $J_1=1.6$ Hz, $J_2\approx J_3\approx 8$ Hz, 1H), 7.55 (dd, $J_1=1.6$ Hz, $J_2=7.8$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.42, 22.06, 26.49, 31.33, 36.28, 45.73, 117.0, 122.3, 126.5, 128.3, 129.2, 133.4, 135.9, 155.0, 171.3, 196.6. Anal. calcd for $C_{16}H_{16}BrNO_2$: C, 57.50; H, 4.83; N, 4.19. Found: C, 57.49; H, 4.92; N, 4.28.

16: white solid, mp 149–150°C (hexane:EtOAc, 1:2), EIMS *m/z* (rel. int.) 255 (M^+, 47), 212 (base), 185 (97), 184 (47), 156 (35). IR ($CHCl_3$) 1713, 1640 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.50–2.70 (m, 11H), 4.43 (d, $J=15.6$ Hz, 1H), 5.11 (d, $J=15.6$ Hz, 1H), 6.90 (d, $J=7.1$ Hz,

1H), 7.10–7.32 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.38, 23.70, 30.06, 32.28, 37.17, 49.10, 53.91, 69.91, 122.3, 123.4, 127.3, 128.5, 136.3, 144.4, 167.4, 205.9. Anal. calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.22; H, 6.72; N, 5.36.

17: oil, EIMS m/z (rel. int.) 255 (M^+, 49), 164 (43), 91 (base). IR (neat) 1682, 1634 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.89 (dddd, $J_1 \approx J_2 \approx J_3 \approx J_4 \approx 6$ Hz, 2H), 2.18 (dd, $J_1 \approx J_2 \approx 7$ Hz, 2H), 2.42 (dd, $J_1 \approx J_2 \approx 6$ Hz, 2H), 2.58 (s, 4H), 4.95 (s, 2H), 7.00–7.33 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.28, 21.93, 26.66, 31.24, 36.12, 45.05, 116.7, 126.1 (2C), 127.6, 129.1 (2C), 137.2, 155.3, 171.2, 196.4.

8. All the radical cyclizations were performed according to the following procedure: 1.2 equiv. of Bu_3SnH, 0.1 equiv. of AIBN, refluxing benzene, 2 h.
9. (a) Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem.* **1995**, *60*, 8044–8050; (b) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210–6219.
10. Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569–10582.
11. Flash chromatographies (FC) were performed with silica gel 230–400 Mesh.
12. The relative% values were determined by a GC–MS analysis of the reaction medium.
13. Except for isomer **12c** which has not been separated by FC and whose stereochemistry has been deduced after assignment of the three other isomers.