Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7981–7984

TETRAHEDRON LETTERS

A general and efficient route to enantioselective synthesis of pumiliotoxin A alkaloids via a common key intermediate

Bing Wang, Kai Fang and Guo-Qiang Lin*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

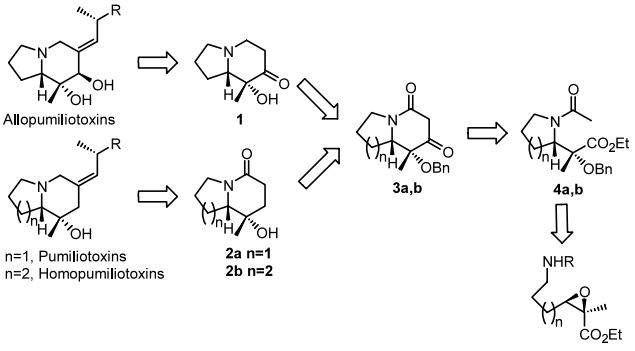
Received 12 May 2003; revised 27 June 2003; accepted 29 August 2003

Abstract—A general and efficient formal synthesis of pumiliotoxins and allopumiliotoxins has been achieved via a common key intermediate **3a**. Our route featured a novel one-pot substitution–ring-opening sequence and an efficient Claisen-type condensation. This method is also applicable to quinolizidine derivative **2b**.

The skin secretion of neotropical frogs of the family *Dendrobatidae* have afforded a wide spectrum of alkaloids, among which pumiliotoxin A[1] class was believed to serve in 'chemical defence' against predators. Because of their structurally unique features and biological significances, pumiliotoxin A alkaloids have aroused numerous synthetic efforts[2] since the synthesis of a relatively simple member, pumiliotoxin 251D, was fulfilled by Overman's group in 1981.[2a] In most previous syntheses, L-proline was the preferred starting material, which provided five-membered ring and the stereogenic center at the ring junction. However, this chiral pool approach undoubtedly has its disadvantage in terms of flexibility and generality. Especially, it limits the synthetic diversity required in modern drug discovery. Only a few attempts have been made to avoid the use of proline in the documents.[3] On the other hand, the general method applicable for both pumiliotoxins and its 7-hydroxy congener allopumiliotoxins has not fully investigated so far.[4] Thus, as our continuing interest in the enantioselective syntheses of polyhydroxyl alkaloids via transformation of epoxides,[5] we focused our attention on the following issues at the very beginning of our research: 1) to construct the chiral azabicyclic core in avoidance of using proline or its homologue and 2) to develop general route and common key intermediate for the whole family of pumiliotoxin A alkaloids.

We envisioned that Overman's intermediate **1**[6] and lactam **2a** could arise from a common key precursor **3a** via proper functional group transformations (Scheme 1). **3a** in turn was derived from acetamide **4a** via a Claisen-type condensation. The pyrrolidine moiety of **4a** could be constructed by intramolecular aminolysis of epoxide. This strategy turned out to be successful. Herein we report a novel, general and efficient synthesis pumiliotoxin A alkaloids.

As shown in Scheme 2, we started from known compound **5a**, which was readily prepared from 1,4-butanediol.[7] At a first glance, Sharpless asymmetric aminohydroxylation[8] seemed to be an apparent option to establish the 2,3-*syn*-aminoalcohol structure in **4a**. However, this method was unsatisfactory for trisubstituted olefins in terms of enantioselectivity.[8b] We envisaged that this issue could be well addressed by a dihydroxylation–double inversion (at C-3) sequence. Sharpless asymmetric dihydroxylation (AD-mix-α)[9] of

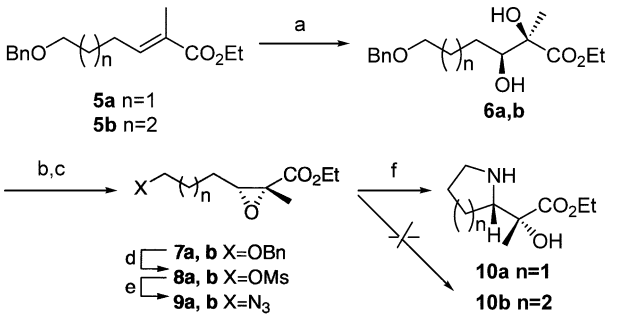


Scheme 1. Retrosynthetic analysis for a general solution.

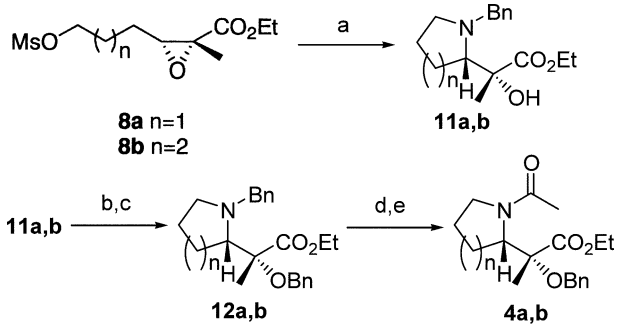
Keywords: pumiliotoxin A alkaloids; pumiliotoxins; allopumiliotoxin; general route.

* Corresponding author. Tel.: +86-021-64163300/83223; fax: +86-021-64166263; e-mail: lingq@mail.sioc.ac.cn

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.08.113



Scheme 2. *Reagents and conditions*: (a) AD-mix-α, ^{t}BuOH, H_2O, $MsNH_2$, 0°C, 98% for **6a** and 96% for **6b**; (b) MsCl, pyridine, CH_2Cl_2, 0°C; (c) K_2CO_3, EtOH, rt, 95% for **7a** and 89% for **7b** (two steps); (d) H_2, 10% Pd/C, EtOH; MsCl, Et_3N, CH_2Cl_2, 95% for **8a** and 92% for **8b**; (e) NaN_3, DMF, 95% for **9a**,**b**; (f) H_2, Pd/C, EtOH, 70% for **10a**.

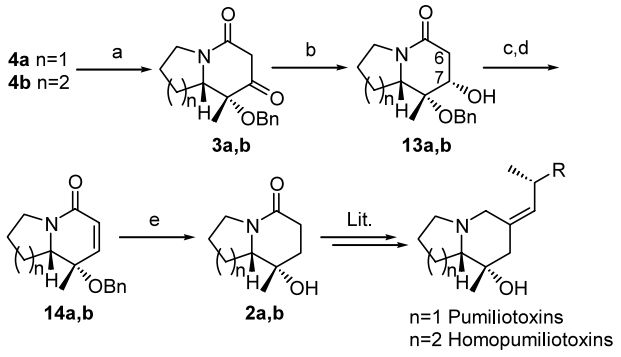


Scheme 3. *Reagents and conditions*: (a) $BnNH_2$, MeCN, reflux 48 h, 97% for **11a**,**b**; (b) BnBr, KH, reflux 30 min, 91% for **12a** and 95% for **12b**; (c) H_2, 10% Pd/C, EtOH, rt; (d) Ac_2O, Et_3N, CH_2Cl_2, 0°C, 83% for **4a** and 80% for **4b** (two steps).

the trisubstituted olefin **5a** afforded chiral diol **6a** in 98% yield and 95% ee. **6a** was mono-mesylated under mild conditions (MsCl, pyridine, CH_2Cl_2, 0°C) without affecting the more sterically hindered tertiary hydroxyl group. Upon subsequent treatment of the crude mesylate with K_2CO_3, epoxide **7a** was obtained with inversion of configuration at C-3 of **6a**. Catalytic hydrogenolysis followed by conversion to mesylate furnished **8a** smoothly. With **8a** in hand, we first explored the construction of the pyrrolidine ring. Azide **9a** was prepared in 95% yield, which was subject to catalytic hydrogenation under atmospheric pressure. We were pleased to find that proline derivative **10a** was formed in 70% yield resulting from the anticipated one-pot azide reduction and intramolecular aminolysis of the epoxide of **9a**. The rate of the ring-opening process is far greater than that of the reduction of azide as no intermediate was detected. However, with **9b** as substrate, which was prepared along the same line as its homologue **9a**, the reaction was very complex.[10] We assumed that the failure to give the piperidine derivative **10b** was due to the much lower reaction rate in six-membered ring formation as compared to five-membered ring formation,[11] hence side reactions such as intermolecular condensation, which was negligible in the case of **9a**, predominated in the reaction of **9b**.

To solve the problem associated with the intrinsic kinetic difference, another approach was examined. We reasoned that if the terminal primary amine produced by the reduction of **9b** could be properly protected, lowering its nucleophilicity and increasing the steric hindrance simultaneously, the undesired intermolecular condensation could thus be suppressed. Benzyl group was ideal for this purpose due to its easy and mild removal at later stages in our synthesis. However, as no intermediate could be isolated in the hydrogenation of **9a** or **9b**, this protection must be incorporated into the substrate beforehand. Thus **8a**,**b** were reacted with benzylamine (MeCN, reflux 48 h), in the hope that a stepwise substitution–ring-opening sequence would afford the desired product **11a**,**b** (Scheme 3). To our delight, both pyrrolidine and piperidine derivatives were obtained in one pot in excellent yields (>95%). Moreover, this reaction showed remarkably high regioselectivity, no regioisomer (C-2 opening product) was found. This observation was in agreement with Baldwin's rule as 5/6-*exo*-tet cyclization being favored over 6/7-*endo*-tet process,[12] since nucleophilic opening of epoxide was not always regioselective and not solely dependent on steric factors.[13] Our strategy compared favorably with other methods such as azidolysis of epoxide[14] in simplicity and efficiency. The tertiary hydroxyl of **11** was protected with benzyl in high yield under the reported conditions.[15] Selective removal of *N*-benzyl (10% Pd/C, EtOH) followed by acetylation (Et_3N, Ac_2O, CH_2Cl_2) furnished acetamide **4** in good yield.

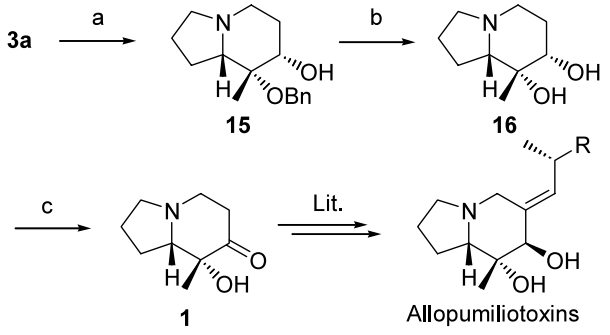
Taking advantage of the structural feature that the α,α-disubstituted ester was non-enolizable and non-epimerizable, we adopted an acetamide[16] version of the Claisen condensation for the construction of the indolizidine/quinolizidine core. In the screening of bases for this purpose, we found that while the previously reported DBU and sodium ethoxide[16] were ineffective, the use of LDA did afford the desired product, however, in low conversion. With this in mind, KH was then tried, which effected irreversible deprotonation of **4a**, and it was found that the cyclization was complete within 60 minutes. HPLC showed that the ee of **3a** is equal to that of **6a**, confirming the stereo-integrity of the above reaction sequences. A single recrystallization afforded optically pure **3a** in 87% recovery. We then set out to reduce the ketonic carbonyl in **3a** to methylene. Reduction with sodium borohydride furnished **13a** in quantitative yield, the configuration of the 7-hydroxyl was assigned to be *S* on the basis of ^{1}H NMR coupling constants (J_{H7-6} = 10.7, 6.6 Hz). **13a** was converted to mesylate, which was subject to elimination under basic conditions (DBU, toluene, reflux) to provide **14a** in 90% yield. Saturation of the double bond and debenzylation were carried out in one pot to give **2a** in 100% yield. Since **2a** has been employed as the key intermediate in several syntheses of pumiliotoxins,[17a–f] our route constituted a formal synthesis of this subclass of alkaloid in good overall yield. Moreover, all reactions in Scheme 4 worked equally well with **4b**, providing quinolizidine derivative **2b** as intermediate for homopumiliotoxin synthesis.[17g]



Scheme 4. *Reagents and conditions*: (a) KH, THF, rt, 87% for **3a** and 90% for **3b**; (b) $NaBH_4$, MeOH, 0°C, 100% for **13a**, **b**; (c) MsCl, Et_3N, CH_2Cl_2, 0°C; (d) DBU, toluene, reflux, 90% for **14a** and 97%for **14b** (two steps); (e) H_2, 10% Pd/C, EtOH, 100% for **2a** and 90% for **2b**.

For the synthesis of Overman's intermediate,[6] lactam **3a** was reduced with $LiAlH_4$ to afford tertiary amine **15** (Scheme 5). Then the benzyl protection was removed cleanly (Li^0/4,4-di-*tert*-butylbiphenyl, THF, −78°C)[18] to give crystalline **16**, the spectroscopic data of which were in agreement with those reported.[3a] This also confirmed our assignment of the structure of **12a**.[19] Finally, **16** was oxidized to ketone **1** in 75% yield with Swern's protocol, while Dess–Martin oxidation resulted in ring cleavage. Thus, an efficient formal synthesis of allopumiliotoxin 267A (when R = *n*-Bu in Scheme 5) was achieved in 12 steps starting from **5a** with an estimated overall yield of 12% according to the literature.[6]

In summary, a general and efficient synthesis of all three known subclasses of pumiliotoxin A alkaloids has been developed. This route featured a one-pot substitution–ring-opening sequence and an efficient Claisen-type condensation. With simple linear 1,ω-diol compounds as the starting material, the synthesis can be carried out in multigram scale under mild conditions. Our work provides a novel and practical access to natural and unnatural products possessing indolizidine and quinolizidine skeletons, thus compliments earlier work in this field.[2,17] Efforts toward the total synthesis of homopumiliotoxins are underway and will be reported in due course.



Scheme 5. *Reagents and conditions*: (a) $LiAlH_4$, THF, reflux, 75%; (b) Li-DBB, THF, −78°C, 85%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; Et_3N, −78°C, then rt, 75%.

Acknowledgements

We thank the National Natural Sciences Foundation (No. 297912045) and the Major Basic Research Development Program (G 2000 077506) for financial aid.

References

1. For reviews, see: (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999, Vol. 13, Chapter 1; (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids* **1993**, *43*, 185; (c) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1984**, *40*, 1183; (d) Daly, J. W.; Garraffo, H. M.; Jain, P.; Spande, T. F.; Snelling, R. R.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **2000**, *26*, 73.
2. For some selected reports on chemical synthesis, see: (a) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851; (b) Franklin, A. S.; Overman, L. E.; *Chem. Rev.* **1996**, *96*, 505 and references cited therein; (c) Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984; (d) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950; (e) Aoyagi, S.; Hirashima, S.; Saito, K.; Kibayashi, C. *J. Org. Chem.* **2002**, *67*, 5517.
3. (a) Comins, D. L.; Huang, S. L.; McArdle, C. L.; Ingalls, C. *Org. Lett.* **2001**, *3*, 469; (b) Tan, C.-H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1397.
4. It seems that only reported general method compatible for the syntheses of both subclasses is the iminum ion–alkyne cyclization developed by Overman's group, see: (a) Arnold, H.; Overman, L. E.; Sharp, M. J.; Witschel, M. C. *Org. Synth.* **1991**, *70*, 111; (b) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073.
5. (a) Shi, Z.-C.; Lin, G.-Q. *Tetrahedron: Asymmetry* **1995**, *6*, 2907; (b) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2000**, *65*, 9114; (c) Wang, B.; Yu, X.-M.; Lin, G.-Q. *Synlett* **2001**, 904.
6. Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179.
7. Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1987**, *52*, 4369.
8. (a) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2810; (b) Sharpless, K. B.; Nicolaou, K. C.; Li, G.; Guy, R. WO 982751A2.
9. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
10. Side products of low polarity and higher molecular weight were isolated which suggested formation of side products resulting from intermolecular condensation of the reduction product of **9b**.
11. (a) Mandolini, L. *J. Am. Chem. Soc.* **1978**, *100*, 550; (b) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.
12. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
13. Schneider, C. *Synlett* **2000**, 1840.

14. (a) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synlett* **2000**, 311; (b) Azzena, F.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron* **1995**, *48*, 13409.
15. Lett, R. M.; Overman, L. E.; Zablocki, J. *Tetrahedron Lett*. **1988**, *29*, 6541.
16. (a) Schneider, M. J.; Harris, T. M. *J. Org. Chem*. **1984**, *49*, 3681; (b) Akiba, K.; Nakatani, M.; Wada, M.; Yamamoto, Y. *J. Org. Chem*. **1985**, *50*, 63; (c) Vercauteren, J.; Bideau, A.; Massiot, G. *Tetrahedron Lett*. **1987**, *28*, 1267.
17. (a) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc*. **1991**, *113*, 2652; (b) Barrett, A. G. M.; Damiani, F. *J. Org. Chem*. **1999**, *64*, 1410; (c) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905; (d) Sudau, A.; Muech, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem*. **2002**, 3315; (e) Cossy, J.; Cases, M.; Gomez-Pardo, D. *Synlett* **1996**, 909; (f) Ni, Y.; Zhao, G.; Ding, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3264; (g) Santos, L. S.; Pilli, R. A. *Tetrahedron Lett*. **2001**, *42*, 6999.
18. (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem*. **1980**, *45*, 1924; (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc*. **1988**, *110*, 854.
19. All novel compounds were fully characterized by IR, MS, ^{1}H and C NMR spectra and satisfactory elemental analysis or high-resolution MS. Some selected examples are as follows.

Compound **3a**: mp 109–110°C; $[\alpha]_D^{20}=-11.3°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50–7.20 (m, 5H), 4.60–4.20 (AB, $J_{AB}=11.7$ Hz, 2H), 3.75–3.55 (m, 3H), 3.40–3.25 (AB, $J_{AB}=10.4$ Hz, 2H), 2.40–1.80 (m, 4H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.10, 164.82, 137.39, 128.49, 127.77, 126.93, 78.29, 66.44, 63.66, 46.17, 44.31, 25.58, 22.69, 14.25; IR (*v*, KBr): 2925, 2864, 1731, 1645, 1605, 1558, 1457 cm^{-1}; EI-MS (*m*/*z*, %): 274 (12), 70 (100), 91 (64), 182 (35.0), 42 (25), 41 (15), 96 (15), 65 (13); HR-MS calcd for $C_9H_{12}NO_3$ (M−Bn): 182.0862. Found: 182.0907.

Compound **3b**: mp 138–139.5°C; $[\alpha]_D^{20}=+15.9°$ (*c* 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.50–7.20 (m, 5H), 4.80–4.60 (d-like, 1H), 4.60–4.30 (AB, $J_{AB}=11.4$ Hz, 2H), 3.80–3.20 (AB, $J_{AB}=18.5$ Hz, 2H), 3.25–3.10 (dd, $J=12.5$, 2.4 Hz, 1H), 2.70–2.40 (td, $J=12.4$, 2.7 Hz, 1H), 2.10–1.40 (m, 6H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 203.80, 165.16, 137.68, 128.45, 127.73, 127.05, 80.38, 66.53, 64.36, 45.64, 44.04, 26.16, 24.66, 24.49, 16.62; IR (*v*, KBr): 3065, 3027, 2953, 2860, 2511, 1890, 1616, 1575, 1542, 1499, 1451, 1329, 1298, 1232, 1194 cm^{-1}; EI-MS (*m*/*z*, %): 288 (0.4), 84 (100), 91 (32), 86 (23), 196 (22); HR-MS calcd for $C_{16}H_{19}NO_3$: 287.1517. Found: 287.1512.

Compound **12a**: $[\alpha]_D^{20}=+5.8°$ (*c* 1.60, $CHCl_3$).; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.40–7.20 (m, 10H), 4.65–4.30 (AB, $J_{AB}=11.4$ Hz, 2H), 4.55–3.35 (AB, $J_{AB}=13.3$ Hz, 2H), 4.46 (q, $J=7.1$ Hz, 2H), 3.30–3.20 (m, 1H), 3.05–2.85 (m, 1H), 2.30–2.15 (m, 1H), 1.95–1.50 (m, 4H), 1.75 (s, 3H), 1.28 (t, $J=7.1$ Hz, 3H); IR (*v*, film): 3064, 3030, 1731, 1605, 1496, 1454, 1382, 1263, 1243, 1109 cm^{-1}; EI-MS (*m*/*z*, %): 367 (0.1), 294 (2.3), 160 (100), 91 (59), 161 (15). Anal. calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.98; H, 7.96; N, 3.59.

Compound **13a**: mp 164.5–165.5°C; $[\alpha]_D^{20}=-70.5°$ (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.40–7.20 (m, 5H), 4.95–4.70 (AB, $J_{AB}=12.2$ Hz, 2H), 3.91 (dd, $J=10.3$, 7.0 Hz, 1H), 3.65–3.40 (m, 3H), 3.40–3.20 (dd, $J=9.9$, 5.4 Hz, 1H), 2.85–2.65 (dd, $J=17.2$, 6.7 Hz, 1H), 2.65–2.50 (dd, $J=17.2$, 10.7 Hz, 1H), 2.20–1.60 (m, 4H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.18, 139.71, 128.30, 127.10, 126.70, 74.30, 73.31, 66.75, 65.82, 45.59, 37.76, 26.04, 22.39, 16.98; IR (*v*, KBr): 3201, 2977, 2854, 1617, 1450 cm^{-1}; EI-MS (*m*/*z*, %): 276 (8.2), 70 (100), 91 (39), 184 (15), 97 (13), 43 (11), 96 (10); HR-MS calcd for $C_{16}H_{21}NO_3$: 275.1531. Found: 275.1541.

Compound **13b**: mp 151–151.5°C; $[\alpha]_D^{20}=+3.9°$ (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.40–7.20 (m, 5H), 4.80–4.70 (m, 1H), 4.76–4.61 (AB, $J_{AB}=11.7$ Hz, 2H), 3.91 (m, 1H), 3.20–3.10 (m, 2H), 2.77 (part of AB-d, $J_{AB}=17.4$ Hz, $J=7.5$ Hz, 1H), 2.58 (part of AB-d, $J_{AB}=17.1$ Hz, $J=4.8$ Hz, 1H), 2.38 (t-like, 1H), 2.00–1.70 (m, 3H), 1.70–1.55 (m, 1H), 1.46 (s, 3H), 1.50–1.30 (m, 2H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.06, 138.81, 128.33, 127.34, 126.87, 74.88, 71.12, 65.51, 65.25, 43.76, 36.71, 26.94, 25.04, 25.01, 19.10; IR (*v*, KBr): 3243, 2955, 2860, 1616, 1450 cm^{-1}; EI-MS (*m*/*z*, %): 289 (2.5), 198 (9.8), 91 (36.4), 84 (100); HR-MS calcd for $C_{17}H_{23}NO_3$: 289.1698. Found: 289.1718.