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Expedious and practical synthesis of the bioactive alkaloids rutaecarpine, euxylophoricine A, deoxyvasicinone and their heterocyclic homologues

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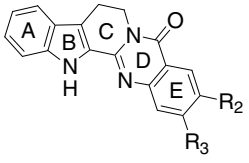
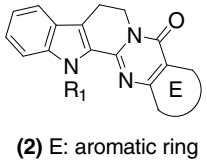
Abstract—Efficient assembly of pyrimido-β-carbolines **1** and **2**, including the bioactive alkaloids rutaecarpine, euxylophoricine A, and deoxyvasicinone (**3**), is reported from suitable aromatic amino acids **7** or corresponding aromatic amino esters **8** and imino-thioethers **5** or **6** in a one-step sequence in moderate to good yields. The key step of this methodology is based on an intramolecular aza-displacement of a methylthio group followed by spontaneous cyclodehydration. Furthermore, when aromatic amino esters **8** were used instead of amino acids, a tandem amino-methylthio displacement/amino ester cyclization takes place.

1. Introduction

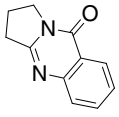
The indolopyridoquinazolinone framework constitutes an important class of heterocycles belonging to quinazoline-type alkaloids isolated from both the heartwood and the fruit of rutaceous plants and rutaceae trees as well as animals and microorganisms.[1] Their extracts have long been used as important remedies in Chinese traditional medicine for the treatment of various diseases.[2]



(1a) R_2=H, R_3=H
Rutaecarpine
(1b) R_2=MeO, R_3=MeO
Euxylophoricine A
(1c) R_2=Cl, R_2=H



(2) E: aromatic ring



(3) Deoxyvasicinone

Among the products isolated and structurally identified from these extracts, rutaecarpine (**1a**) isolated from the dried fruit of *Evodia rutaecarpa*[3] showed remarkable activities against headache, cholera, dysentery, worm infestations and post partum disturbances.[2,4] Recent investigations have shown that rutaecarpine (**1a**) and/or the quinazoline–carboline alkaloids are present in numerous plants,[5–9] all members of the Rutaceae family. Besides, further biological investigations revealed that, in addition to its strong anti-inflammatory activity,[10] rutaecarpine (**1a**) possess numerous other interesting medicinal profiles such as analgesic,[11] astringent, anti-emetic, anti-hypertensive,[11b,c] uterotonic,[12] anti-platelet aggregation,[13] and vasorelaxing[14] activities. Moreover, rutaecarpine (**1a**) and/or its derivatives possess a strong and selective inhibitory activity on cyclooxygenase-2 (COX-2),[10b,11c] on human CYP1A1, CYP1A2, and CYP1B1.[15]

Their anti-tumor activity[16] is less important than the one exhibited by luotonins A and B[17] and camptothecin.[18] In these cases, 10-bromo-, 11-methoxy-, and 10,11-methylenedioxyrutaecarpines are the most active derivatives in the series. More recently, numerous thiophene analogues of rutaecarpine (**1a**) have shown good anti-cancer activity in vitro but no activity in vivo.[16c]

Keywords: Bioactive product; Alkaloid; Thioether; Imino-thioether; Heterocycle; Peptedic coupling; Lawesson's; Thionation; One-pot procedure.
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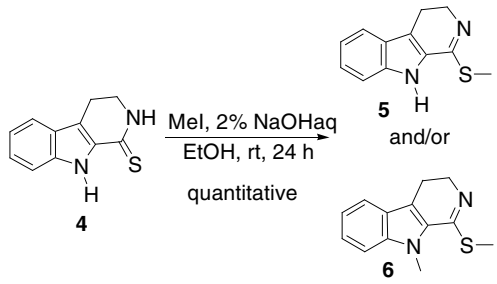
Due to their interesting biological profile, a number of reliable preparative methods are known in the literature. Thus, Fischer indole synthesis under harsh conditions of temperature can yield the quinazolinocarboline systems in several forms.[17] Also, treatment of aromatic amino acids or the corresponding amino esters with lactam derivatives such as chloro-imine[18] and amino-imine[19] has been applied successfully and resulted in the formation of **D** ring. The iminoketenes, derived from the latter amino acids, with amides or the corresponding imino-ethers under cycloaddition conditions, furnished the suitable quinazolone systems via the formation of **C** ring.[20] Furthermore, other ring-closure protocols which consist in the protonation of the 4(3*H*)-quinazolinone moiety followed by electrophilic attack on the indole ring,[21] or the simple condensation of Appel's salt with amino esters followed by successive treatment with tryptamine derivatives and TFAA/HCl(g) combination on heating,[22] and finally the aryl–aryl coupling reaction of 2-bromoaromatic derivatives with the quinazolinone heterocycle with Pd reagents, have also been explored.[23] In all these methods, the synthetic strategy is to construct the **D** ring and/or to build the connection between the **D** and **B** rings starting from tryptamine derivatives.

2. Results and discussion

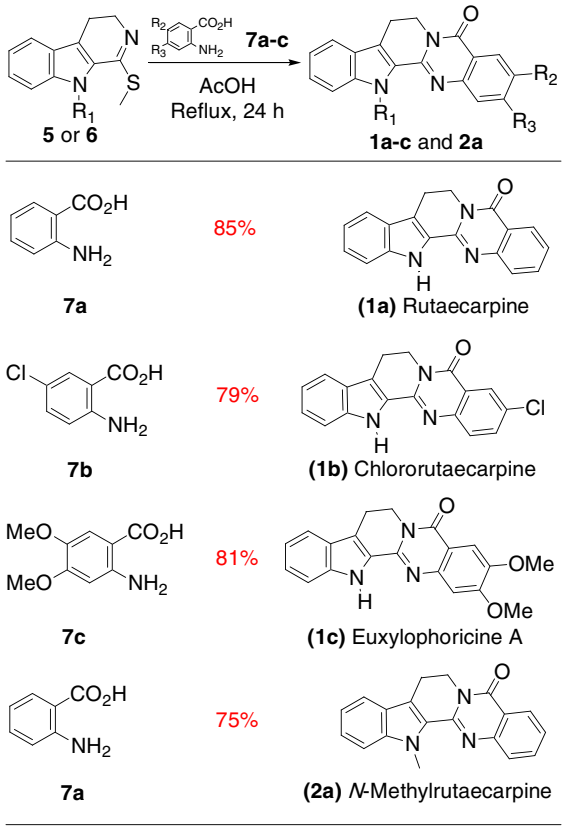
As part of a long-term project dealing with the search for a simple synthetic route to rutaecarpine (**1a**) as well as its homologues, we report herein a concise and facile synthesis of these derivatives. Our synthetic strategy is based on the simple condensation of amino acids or the corresponding amino esters with the more accessible imino-thioether function in a one-pot fashion using two procedures.

As the starting point of our study, the requisite triheterocyclic imino-thioether **5** (Scheme 1) was obtained in one step in quantitative yield by S-alkylation of 2,3,4,9-tetrahydro-β-carboline-1-thione (**4**)[24] with 1 equiv of methyl iodide in ethanol at room temperature for 24 h in the presence of 2% aqueous NaOH. In a similar manner, but with an excess of methyl iodide (>1.2 equiv), the S-alkylated product **5** was accompanied with the N,S-dialkylated product **6**. These two components were formed in 4/1 ratio and were easily separated by chromatography on a silica gel column using a mixture of ethyl acetate/cyclohexane (1/1) as eluent.

Taking into account that the alkylthio group in the imino-thioether function could be extruded easily by nucleophilic displacement,[25] the *S*-methyl derivatives **5** and **6** would constitute valuable platforms to access molecules **1** and **2** (Scheme 2). At the outset, condensation of indolodihydropyridine **5** with anthranilic acid (**7a**) in refluxing dry acetic acid for 24 h allowed an easy access to the expected rutaecarpine alkaloid (**1a**) after recrystallization from anhydrous ethanol (85% yield). Similarly, chlororutaecarpine (**1b**), euxylophoricine A (**1c**), and *N*-methylrutaecarpine (**2a**) were also obtained cleanly and easily in yields ranging from 75% to 81%.[26]



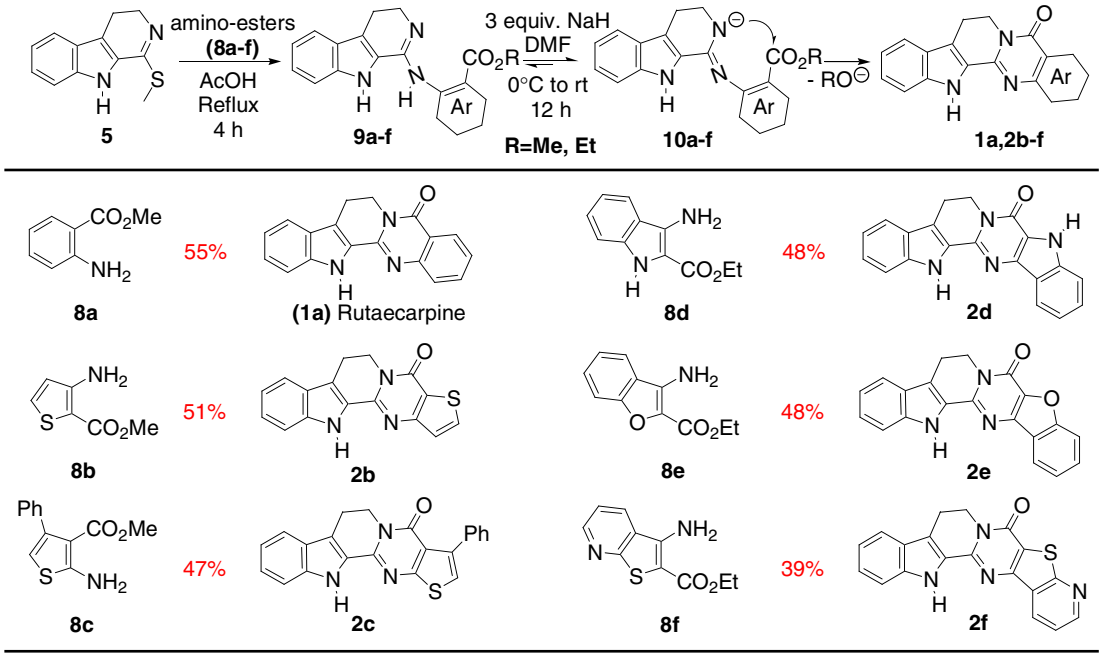
Scheme 1. Scheme leading to triheterocyclic imino-thioethers **5** and **6**.



Scheme 2. Condensation of aromatic amino acids **7a**–**c** with triheterocyclic imino-thioethers **5** and **6**.

Having established the effectiveness of this route for the preparation of the indolopyridoquinazoline derivatives **1a**–**c** and **2a** including the rutaecarpine (**1a**) and the euxylophoricine A (**1c**) alkaloids, we decided to explore aromatic or heteroaromatic amino esters instead of the corresponding amino acids. The amino ester functionality was chosen for the following reasons: 1°—some heterocyclic amino acids are not commercially available; 2°—the amino ester function could be manipulated without specific precautions instead of the corresponding amino acid; and finally 3°—various methods for the synthesis of heterocyclic amino esters are available in the literature, which are short and involve the use of cheap reagents as well as mild conditions.

Thus, methyl anthranilate (**8a**) was treated with 1 equiv of imino-thioether **5** (Scheme 3) in glacial acetic acid at



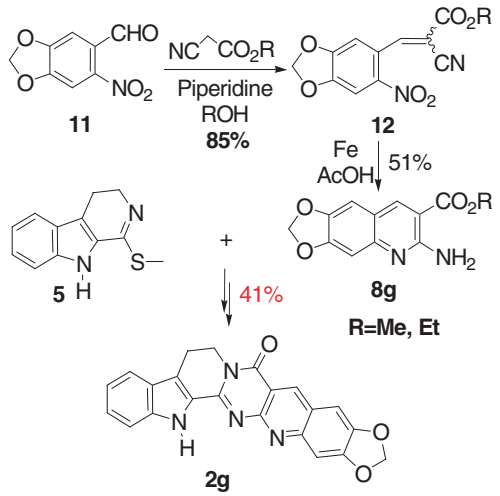
Scheme 3. Fused β-carboline derivatives **1a** and **2b–f** by condensation of aromatic amino esters **8a–f** with triheterocyclic imino-thioether **5** in a two-step procedure under successive acid and base treatment.

reflux for 4 h. After cooling and evaporation of the solvent, analysis of the residue indicated the formation of the amino-imine derivative **9a** as the sole reaction product. This compound was isolated in pure form after recrystallization from dry ethanol in 95% yield.[27] Furthermore, although a variety of reaction times and temperatures were explored the formation of the desired cyclized product **1a** was not observed. This is due probably to the relatively low electrophilicity of the ester function under acidic conditions.

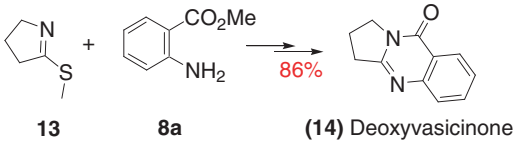
Consistent with the above remark, when amino-imine derivative **9a** was treated with 3 equiv of NaH in dry DMF at 0 °C, then at room temperature for 12 h, the isolated product, after the usual work up and recrystallization of the resulting solid from dry ethanol afforded rutaecarpine (**1a**) in 58% yield. This results from the peptidic coupling process via the intermediate anion **10a**. Interestingly when the reaction was conducted in a one-step procedure starting from the cyclic imino-thioether **5**, evaporation of AcOH and its replacement with dry DMF after 4 h of reaction gave the expected alkaloid **1a** in 55% yield. This is identical to the overall yield reported above for the two separate steps.

Having established the capacity of cyclic imino-thioether **5** to undergo a tandem amino-methylthio displacement/amino ester cyclization to produce rutaecarpine alkaloids, we sought to determine if this mechanism might be extended to heteroaromatic amino esters. Thus, under our optimized conditions (Scheme 3), reaction of the commercial methyl 3-aminothiophene-2-carboxylate (**8b**) with imino-thioether **5** (1 equiv) afforded the fused thieno[3,2-*d*]pyrimidone component **2b** in 51% yield. Its spectroscopic data (NMR, IR, etc.) were in good agreement with those reported earlier by Mohanta and Kim.[22] Similarly, with the known methyl 2-amino-4-phenylthiophene-3-carboxylate (**8c**),[28] the reaction resulted in the formation of the expected and new thienopyrimido-β-carboline **2c** in moderate yield (47%). This is due to the low reactivity of the 2-amino group as compared with the one at the 3-position of the thiophene ring in **8b**. In an effort to further delineate the scope of the cyclization process, the elaboration of other amino ester models, substituted by indolyl, benzofuryl or pyridothienyl groups on the aromatic moiety was explored. Thus, ring closure of the known ethyl 3-amino-1*H*-indole-2-carboxylate (**8d**)[29] to the corresponding indolopyrimido-β-carboline **2d** was performed in 48% yield. The use of the known ethyl 3-aminobenzo[*b*]furane-2-carboxylate (**8e**)[30] and ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate (**8f**),[30b,31] also demonstrate the effectiveness of this protocol since the cyclized benzofuropyrimido-β-carboline **2e** and pyridothienopyrimido-β-carboline **2f** were isolated in 48% and 39% yield, respectively. An additional demonstration of the utility of this methodology was made by the synthesis of a new complex *N*-polyheterocyclic system containing pyridopyrimido-β-carboline. For instance, either methyl or ethyl 6-amino[1,3]dioxolo-[4,5-*g*]quinoline-7-carboxylate (**8g**) (obtained by the modified classical procedure[32] from the commercially available 6-nitrobenzo[1,3]dioxole-5-carbaldehyde (**11**)), were converted successfully into the expected dioxolobenzopyridopyrimido-β-carboline **2g** (Scheme 4). This compound was isolated by chromatography followed by recrystallization from ethanol in 41% yield, which is comparable to that reported for related structures.

We then, finally, tested the behavior of 5-methylsulfanyl-3,4-dihydro-2*H*-pyrrole (**13**) as starting material in our protocol (Scheme 5).



Scheme 4. Scheme leading to complex *N*-polyheterocyclic system **2g**.



Scheme 5. Scheme leading to the deoxyvasicinone alkaloid **14**.

In the event, reaction of **13**, prepared easily from pyrrolidin-2-thione, with 1 equiv of methyl anthranilate (**8a**) furnished cleanly, rapidly and in very good yield (81%), the deoxyvasicinone alkaloid (**14**) which is reported to exhibit anti-inflammatory activity.[33]

3. Conclusion

We have performed successfully in this letter two short and new syntheses of the rutaecarpine and euxylophoricine A alkaloids. Our strategy uses, in a one-pot procedure, the cyclocondensation of aromatic amino acids or the corresponding amino esters with imino-thioethers derived from various thiolactams. This approach was extended to the synthesis of other alkaloid analogues in which the benzene moiety of rutaecarpine and euxylophoricine A is replaced by various substituted benzene rings as well as heterocyclic systems. The extension of the reaction to the synthesis of deoxyvasicinone, starting from pyrrolidin-2-thione was also accomplished efficiently. Furthermore, the friendly reaction conditions, the cheap and readily available reagents used in all the steps make both methods suitable for the large-scale production of these targets. Consequently, they allow an easy and rapid access to original heterocycles of potential pharmaceutical value.

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References and notes

1. For reviews, see: (a) Johne, S.; Groger, D. *Pharmazie* **1970**, *25*, 22–44; (b) Coppola, G. M. *Synthesis* **1980**, 505–536; (c) Johne, S. *Prog. Drug Res.* **1982**, *26*, 259–341; (d) Johne, S. *Prog. Chem. Org. Nat. Prod.* **1984**, *46*, 159–229; (e) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 603–620; (f) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659–677.
2. Chu, J. H. *Sci. Rec. (China)* **1951**, *4*, 279–284; *Chem. Abstr.* **1952**, *46*, 11589b.
3. For isolation of rutaecarpine (**1a**), see: (a) Asahina, Y.; Kashiwaki, K. *Yakugaku Zasshi* **1915**, *405*, 1273–1293; (b) Asahina, Y. *Acta Phytochim.* **1922**, *1*, 67–70; For the first report of rutaecarpine (**1a**), see: (c) Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc.* **1927**, 708–1710.
4. See, for example, Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc.* **1933**, *22*, 716–719.
5. Wu, T.-S.; Yeh, J.-H.; Wu, P.-L.; Chen, K.-T.; Lin, L.-C.; Chen, C.-F. *Heterocycles* **1995**, *41*, 1071–1076.
6. Ikuta, A.; Urabe, H.; Nakamura, T. *J. Nat. Prod.* **1998**, *61*, 1012–1014.
7. Lia, X.-C.; Dunbar, D. C.; El-Sohlya, H. N.; Walker, L. A.; Clark, A. M. *Phytochemistry* **2001**, *58*, 627–629.
8. Christopher, E.; Bedir, E.; Dunbar, C.; Khan, I. A.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M. *Helv. Chem. Acta* **2003**, *86*, 2914–2918.
9. Wattanapiromsakul, C.; Forster, P. I.; Waterman, P. G. *Phytochemistry* **2003**, *64*, 609–615.
10. (a) Matsuda, H.; Yoshikawa, M.; Ko, S.; Iinuma, M.; Kubo, M. *Nat. Med.* **1998**, *52*, 203–206; (b) Moon, T. C.; Murakami, M.; Kudo, I.; Son, K. H.; Kim, H. P.; Kang, S. S.; Chang, H. W. *Inflamm. Res.* **1999**, *4*, 621–625; (c) Woo, H. G.; Lee, C. H.; Noh, M.-S.; Lee, J. J.; Jung, Y.-S.; Baik, E. J.; Moon, C.-H.; Lee, S. H. *Planta Med.* **2001**, *67*, 505–509.
11. (a) Kong, Y. C.; Hu, H. A.; Lu, K. F.; Che, C. T.; Yeng, H. W.; Cheng, S.; Hwang, C. C. *Am. J. Chin. Med.* **1976**, *4*, 105–128; (b) Tang, W.; Eisenbrand, G. E. *Chinese drugs of plant origin.*; Springer: Berlin, 1992, p 508; (c) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66–87.
12. (a) Bergman, J. In *The Alkaloids*; Brossi, A. R., Ed.; The Quinazolinocarboline Alkaloids; Academic Press: New York, 1983; Vol. 21, pp 29–54; (b) King, C. L.; Kong, Y. C.; Wong, N. S.; Yeung, H. W.; Fong, H. H.; Sankawa, U. *J. Nat. Prod.* **1980**, *43*, 577–582.
13. (a) Sheen, W. S.; Tsai, I. L.; Teng, C. L.; Ko, F. N.; Chen, I. S. *Planta Med.* **1996**, *62*, 175–176; (b) Wang, G. J.; Shan, J.; Pang, P. K. T.; Yang, M. C. M.; Chou, C. J.; Chen, C. F. *J. Pharmacol. Exp. Therap.* **1996**, *270*, 1016–1021; (c) Wu, S.-N.; Lo, Y.-K.; Chen, H.; Li, H.-F.; Chiang, H.-T. *Neuropharmacology* **2001**, *41*, 834–843.
14. (a) Chiou, W. F.; Chou, C. J.; Liao, J. F.; Sham, A. Y.; Chen, C. F. *Eur. J. Pharmacol.* **1994**, *257*, 59–66; (b) Wang, W. F.; Wu, C. J.; Chen, C. F.; Lin, L. C.; Huan, Y. T.; Shan, J.; Pang, P. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1237–1244; (c) Hu, C.-P.; Xiao, L.; Deng, H.-W.; Li, Y.-J. *Planta Med.* **2002**, *68*, 705–709; (d) Hu, C.-P.; Xiao, L.; Deng, H.-W.; Li, Y.-J. *Planta Med.* **2003**, *69*, 125–129.
15. Don, M.-J.; Lewis, D. F. V.; Wang, S.-Y.; Tsai, M.-W.; Ueng, Y.-F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2535–2538.
16. (a) Itokawa, H.; Inamatsu, M.; Takeya, K. *Shouyakugaku Zasshi* **1990**, *44*, 135–137; (b) Yang, L.-M.; Chen, C.-F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 465–468; (c)

Yang, L. M.; Lin, S.-J.; Lin, L.-C.; Kuo, Y.-H. *Chin. Pharm. J.* **1999**, *51*, 219–225.
17. (a) Kökösi, J.; Hermecz, I.; Szāsz, G.; Mēszāros, Z. *Tetrahedron Lett.* **1981**, *22*, 4861–4862; (b) Kökösi, J.; Szāsz, G.; Hermecz, I. *Tetrahedron Lett.* **1992**, *33*, 2995–2998; (c) Lee, S. H.; Kim, S. I.; Park, J. G.; Lee, E. S.; Jahng, Y. *Heterocycles* **2001**, *55*, 1555–1560; (d) Chang, H. W.; Kim, S. I.; Jung, H.; Jahng, Y. *Heterocycles* **2003**, *60*, 1359–1366; (e) Chavan, S. P.; Sivappa, R. *Tetrahedron Lett.* **2004**, *45*, 997–999; (f) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2004**, *60*, 3417–3420.
18. (a) Lee, E. S.; Park, J.-G.; Jahng, Y. *Tetrahedron Lett.* **2003**, *44*, 1883–1886; (b) Baruah, B.; Dasu, K.; Vaitilingam, B.; Mamnoor, P.; Venkata, P. P.; Rajagopal, S.; Yeleswarapu, K. R. *Bioorg. Med. Chem.* **2004**, *12*, 1991–1994.
19. Pereira, M.-F.; Picot, L.; Guillon, J.; Léger, J.-M.; Jarry, C. R.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2005**, *46*, 3445–3447.
20. (a) Kametani, T.; Higa, T.; Von Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186–6188; (b) Kametani, T.; Von Loc, C.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306–2309.
21. Bergman, J.; Bergman, S. *J. Org. Chem.* **1985**, *50*, 1246–1255.
22. Mohanta, P. K.; Kim, K. *Tetrahedron Lett.* **2002**, *43*, 3993–3996.
23. Harayama, T.; Hori, A.; Serban, G.; Morikami, Y.; Matsumoto, T.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 10645–10649.
24. For the synthesis of the triheterocyclic thiolactam **4**, see: (a) Benovskyf, P.; Stille, J. R. *Tetrahedron Lett.* **1997**, *38*, 8475–8478; (b) Gittos, M. W.; Robinson, M. R.; Verge, J. P.; Davies, R. V.; Iddon, B.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 33–38.
25. For heteroannulation using this concept and leading to imidazolo-, thiazolo-, and thiazinopyrimidones, see: (a) Sauter, F.; Fröhlich, J.; Blasl, K.; Gewald, K. *Heterocycles* **1995**, *40*, 851–866; (b) Sauter, F.; Fröhlich, J.; Chowdhury, A. Z. M. S.; Hametner, C. *Monatsh .Chem.* **1997**, *128*, 503–508; (c) Sauter, F.; Fröhlich, J.; Chowdhury, A. Z. M. S.; Hametner, C. *Sci. Pharm.* **1997**, *65*, 83–85; (d) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413–1419; (e) Bock, M. G.; DiPardo, R. M.; Pitzenberger, S. M.; Homnick, C. F.; Springer, J. P.; Freidinger, R. M. *J. Org. Chem.* **1987**, *52*, 1646–1647; See also the use of this protocol in dihydroisoquinoline series: (f) Shklyaev, Y. V.; Glushkov, V. A.; Belogub, N. B.; Misyura, N. B. *Chem. Heterocycl. Compd.* **1996**, *32*, 689–695.
26. *General procedure*: The suspension of an equimolecular amount of amino acids **7a–c** (0.15 mol) and iminothioether **5** or **6** (0.15 mol) was refluxed in glacial acetic acid (60 mL) under stirring for 24 h. After cooling, evaporation of the solvent gave a solid which was recrystallized from EtOH to furnish rutaecarpine (**1a**) and its derivatives **1b**,**c** and **2a** in yields ranging from 75% to 85%. Selected data for chlororutaecarpine (**1b**): yellow-orange crystals (EtOH); mp > 300 °C (decomposition); IR (KBr) 3042 (CH), 2975 (CH), 1651 (C=O), 1595 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.12 (t, $J = 6.26$ Hz, 2H, CH_2–CH_2), 4.41 (t, $J = 6.26$ Hz, 2H, CH_2–CH_2), 5.25 (br s, 1H, NH), 7.07 (t, $J = 7.04$ Hz, 1H, H_{ar}), 7.21 (t, $J = 7.04$ Hz, 1H, H_{ar}), 7.41–7.52 (m, 3H, H_{ar}), 7.64 (d, $J = 7.83$ Hz, 1H, H_{ar}), 8.13 (d, $J = 7.83$ Hz, 1H, H_{ar}); ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.8, 41.1, 112.6, 118.6, 119.5, 119.8, 120.1, 124.8, 125.0, 125.3, 126.1, 126.7, 128.7, 138.8, 138.9, 146.6, 148.5, 160.1. Anal. Calcd for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.76; N, 13.06. Found: C, 67.03; H, 3.54; N, 12.96.
27. Selected data for methyl 2-(2,3,4,9-tetrahydro-β-carbolin-1-ylideneamino)benzoate (**9a**): yellow crystals (EtOH); mp 279–281 °C (decomposition); IR (KBr) 3263 (NH broad), 1704 (C=O), 1645 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H, CH_3), 3.20 (t, $J = 6.78$ Hz, 2H, CH_2–CH_2), 4.43 (t, $J = 6.78$ Hz, 2H, CH_2–CH_2), 5.40 (br s, 1H, NH), 7.10 (t, $J = 7.72$ Hz, 1H, H_{ar}), 7.29 (t, $J = 8.62$ Hz, 1H, H_{ar}), 7.45–7.53 (m, 2H, H_{ar}), 7.69 (dd, $J = 7.91$ Hz, 2H, H_{ar}), 7.82 (dt, $J = 0.94$ and 7.62 Hz, 1H, H_{ar}), 8.18 (dd, $J = 0.75$ and 7.81 Hz, 1H, H_{ar}), 11.95 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 40.3, 41.2, 113.0, 118.9, 120.3, 120.5, 120.9, 125.2, 125.4, 126.3, 126.6, 127.1, 135.0, 139.2, 145.8, 147.1, 160.9, 167.5. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.31; H, 5.21; N, 13.09.
28. Perrisin, M.; Luu, D. C.; Narcisse, G.; Bakri-Logeais, F.; Huguet, F. *J. Med. Chem. Chim. Ther.* **1980**, *15*, 563–565.
29. See, for example, the following reference: Unangst, P. C. *J. Heterocycl. Chem.* **1983**, *20*, 495–499.
30. (a) Sangapure, S. S.; Agasimundin, Y. S. *Ind. J. Chem.* **1976**, *14B*, 686–691; (b) Showalter, H. D. H.; Bridges, A. J.; Zhou, H.; Sercel, A. D.; McMichael, A.; Fry, D. W. *J. Med. Chem. Ch.* **1999**, *42*, 5464–5474.
31. Schneller, S. W.; Clough, F. W. *J. Heterocycl. Chem.* **1974**, *11*, 975–977.
32. The reductive cyclization of the nitro derivative **12** to the corresponding bicyclic amino ester **8g** (**8g** with R = Et is already described in the literature, **8g** with R = Me was unknown before this report) was achieved by using $TiCl_4$/Zn, $TiCl_4$/Sm, or SmI_2; in our case we used a combination AcOH/Zn as a cheaper reagent for this purpose.
33. Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, *7*, 3363–3366, and references cited therein.