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The furan approach to azacyclic compounds

Isela García, Manuel Pérez, Zoila Gándara, Generosa Gómez *, Yagamare Fall *

Departamento de Química Orgánica, Facultad de Química, Universidad de Vigo, 36200 Vigo, Spain

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Abstract

We describe an efficient new approach to the synthesis of azacyclic compounds that extends our recently developed methodology based on the oxidation of a furan ring with singlet oxygen followed by an intramolecular hetero Michael addition. The new approach gives access to the readily opened bicyclic lactones and novel tricyclic heterocycles containing the piperidine ring.

Keywords: Azacyclic compounds; Piperidine; Singlet oxygen; Alkaloids; Triazolines

The ring system of piperidine is a structural sub-unit found in many natural compounds with interesting physical and biological properties,[1] including such pharmacologically relevant alkaloids as compounds **1**–**5** (Fig. 1). Pharmacological interest in febrifugine (**4**) and isofebrifugine (**5**), which were first isolated from *Dichroa febrifuga*[2] and *Hydrangea umbellata*,[3] and whose absolute structures were determined in 1999,[4] derives from their potentially powerful antimalarial activity.[5] The in vivo activity of febrifugine is similar to that of the widely used drug chloroquine,[5a,b] but side effects such as diarrhoea, liver toxicity[6] and vomiting[7] prevent its medical use. Given the urgent need for new antimalarial drugs,[8] derivatives and analogues that are just as effective as **4** but lack its adverse effects are accordingly being sought.

Numerous syntheses of piperidines have been devised.[9] In the work described here, with a view to the eventual synthesis of febrifugine analogues, we approached these compounds by adapting the methods we have developed for the synthesis of oxacyclic compounds from methoxyallene

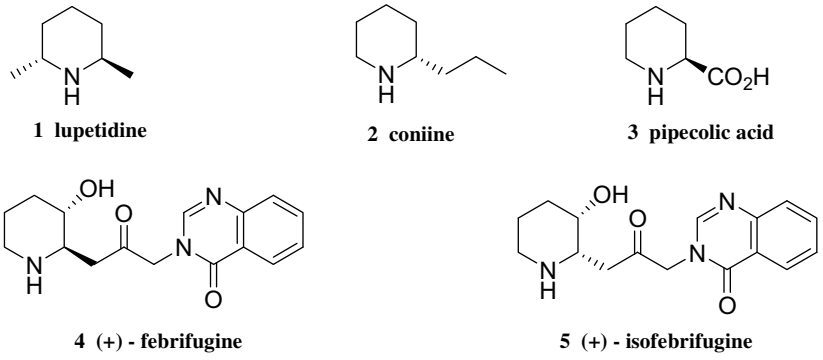

Fig. 1. Structures of natural products containing a piperidine ring.

* Corresponding authors. Tel.: +34 986 812320; fax: +34 986 81 22 62 (Y.F.).
E-mail addresses: ggomez@uvigo.es (G. Gómez), yagamare@uvigo.es (Y. Fall).

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or furan.[10] This methodology has given access to chiral butenolides,[11a] natural oxacyclic products,[11b] polyoxepanes[11c] and polytetrahydropyrans,[11d] and has also been extended to the synthesis of carbocyclic systems.[12] We have now embraced the synthesis of azacyclic compounds.

The bicyclic lactone **11** is a possible precursor of the piperidine moiety of **4** and **5**, previous work having shown that this kind of lactone is easily opened using lithium aluminium hydride.[10d] We envisaged that compound **11** could be prepared from the commercially available furan derivative **6** via compound **9** as shown in Scheme 1. As expected, compound **6** (from Avocado Research Chemicals Ltd) reacted with LAH in ether to give alcohol **7** (89% yield), and alcohol **7** was then easily converted into tosylate **8**[13] (97% yield), which upon reaction with sodium azide in DMF (90%) gave azide **9**.[13]

As anticipated, the oxidation of furan **9** with singlet oxygen, followed by treatment with acetic anhydride in pyridine, gave butenolide **10** (99% from **9**, crude yield). Unfortunately, azide **10** proved to be rather unstable,[14] and upon standing underwent quantitative [3+2] cycloaddition to the tricyclic triazoline **12**,[15] thus hampering its conversion to bicyclic lactone **11** under Staudinger conditions.[16] The relative stereochemistry of **12** was confirmed by NOE experiments (Fig. 2). Although we could not observe NOE between the methoxy group and the cis hydrogens of the fused five-membered rings, we know from the previous work[11e] that the fusion between the five- and six-membered rings is cis.

In view of the above result, we decided to convert azide **9** into a protected amine before proceeding further. Accordingly, **9** was transformed under Staudinger conditions[16] into the corresponding free amine, which without isolation was reacted with Boc_2O, giving the Boc-protected amine **13**[13] in excellent yield (96% from azide **9**). The oxidation of furan **13** with singlet oxygen, followed by treatment with acetic anhydride in pyridine, then afforded butenolide **14**[13] (99%, two steps, crude yield); and the treatment of **14** with sodium hydride in DMF gave the targeted bicyclic lactone **15**[17] through an intramolecular Michael reaction (Scheme 2). The yield of **15** is currently being optimized.

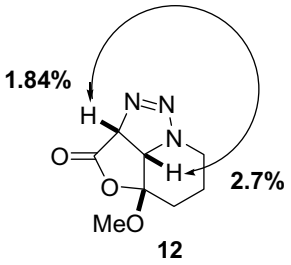
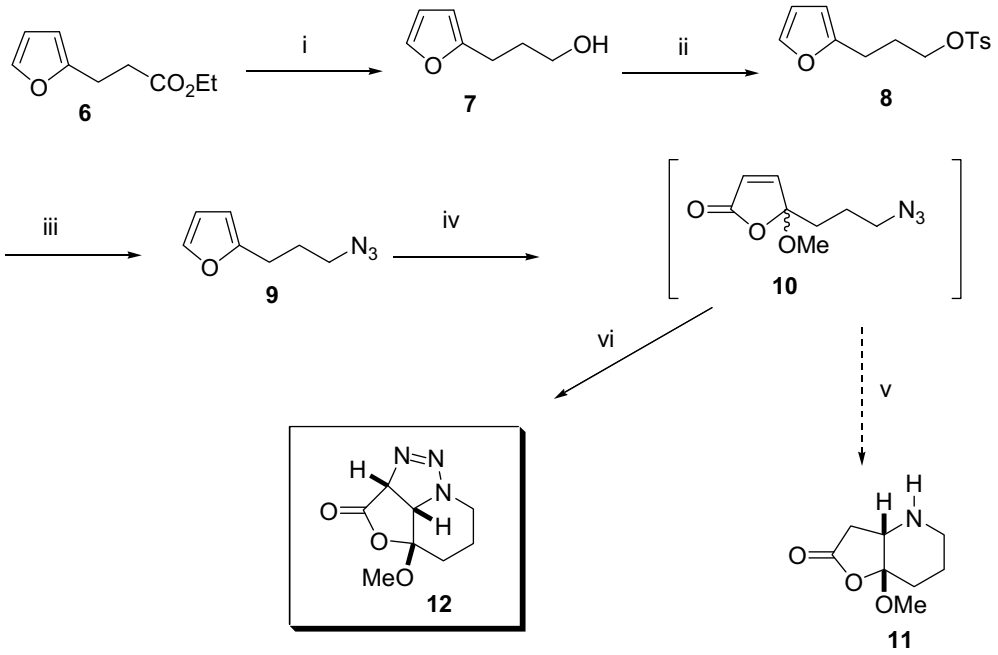


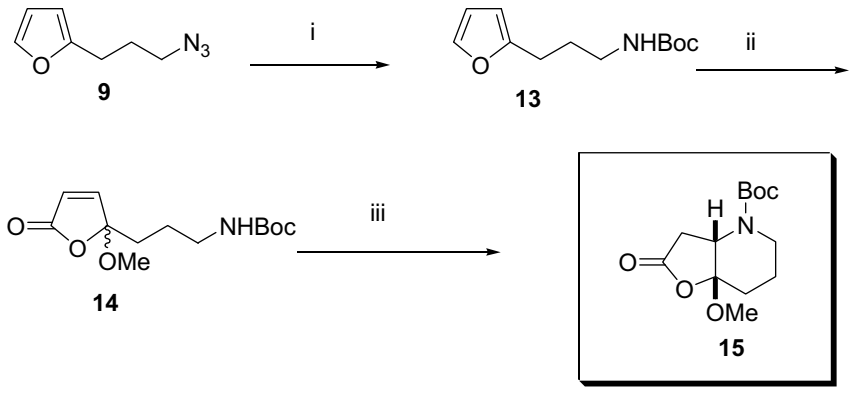
Fig. 2. NOE correlations of **12**.

Finally, noting that triazoline **12** might itself be a useful synthon for the preparation of compounds with piperidine rings, and as chiral furan **16** was available in our laboratory,[11b] we decided to attempt the preparation of chiral triazolines **20a** and **21a** as shown in Scheme 3.

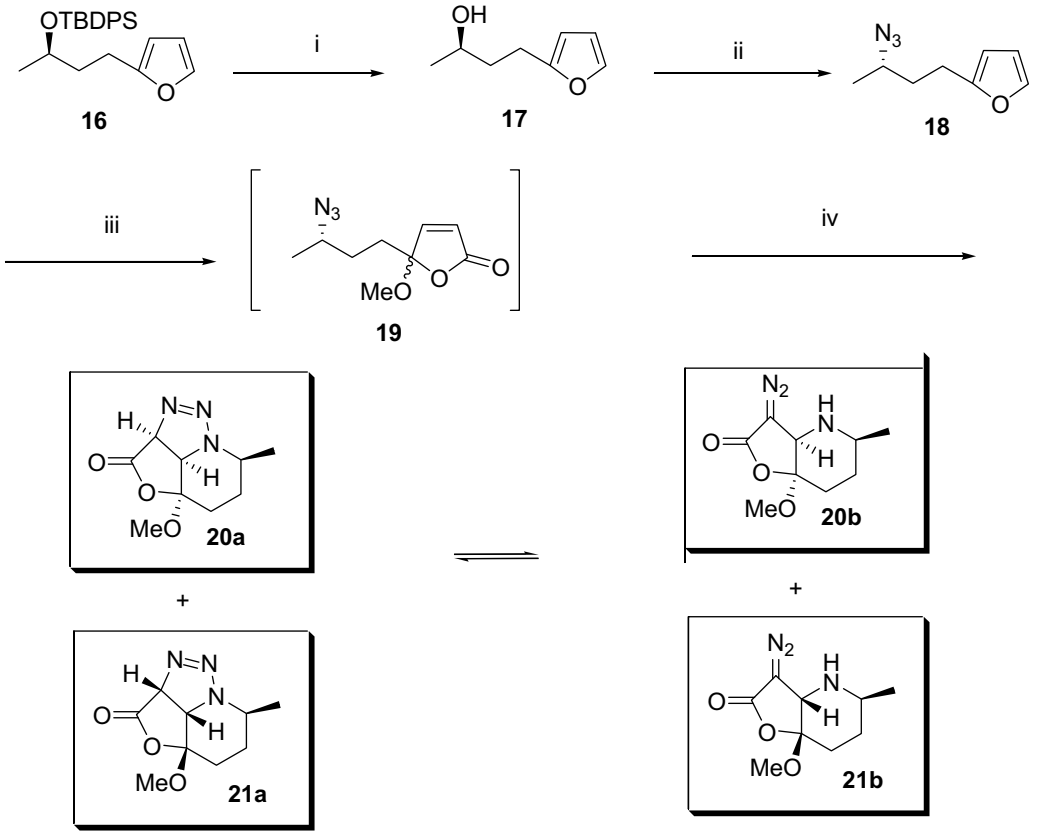
The deprotection of **16** with TBAF afforded a 68% yield of alcohol **17**,[13] which was transformed into azide **18**[13] by mesylation followed by azidation (74% from **17**). The oxidation of **18** with singlet oxygen, followed by treatment with acetic anhydride in pyridine, led to butenolide **19**, which upon standing afforded a mixture of two inseparable



Scheme 1. Reagents and conditions: (i) $LiAlH_4$, Et_2O (89%); (ii) pTsCl, pyr (97 %); (iii) NaN_3, DMF (90%); (iv) (a) $^1O_2$, MeOH, rose bengal, *hv*; (b) Ac_2O, py, DMAP (99%, two steps); (v) PPh_3, THF, H_2O; (vi) **10** is converted on standing into **12** (quantitative).



Scheme 2. Reagents and conditions: (i) (a) PPh_3, THF, H_2O; (b) Boc_2O, $NaHCO_3$ (96%, two steps); (ii) (a) $^1O_2$, MeOH, rose bengal, *hv*; (b) Ac_2O, py, DMAP (99%, two steps); (iii) NaH, DMF (30%).



Scheme 3. Reagents and conditions: (i) TBAF, THF (68%); (ii) (a) MsCl, Pyr, 0 °C; (b) NaN_3, DMF (74%, two steps); (iii) (a) $^1O_2$, MeOH, rose bengal, *hv*; (b) Ac_2O, pyr, DMAP (77%, two steps, crude yield); (iv) **19** is converted on standing into **20a** and **21a**.

chiral triazolines, **20a**[13] and **21a**.[13] Herdeis and Schiffer[14a] reported that triazolines underwent quantitative isomerization to the corresponding diazoamines, but in our case no trace of the formation of diazoamines **20b** and **21b** was observed (Scheme 3).

In conclusion, we have shown that the furan approach to oxacycles we developed some years ago can be extended to the synthesis of azacyclic systems. Work is now in progress on the use of building blocks **12**, **15**, **20a** and **21a** in the synthesis of natural products containing the piperidine moiety.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.010.

References and notes

1. (a) Sugasawa, T.; Adachi, M.; Sasakura, K.; Matsushita, A.; Eigyo, M.; Shiomi, T.; Shintaku, H.; Takahara, Y.; Murata, S. *J. Med. Chem.* **1985**, *28*, 699–707; (b) Groopman, J. E. *Rev. Infect. Dis.* **1990**, *12*, 931–937; (c) Karlsson, G. B.; Butters, T. D.; Dwek, R. A.; Platt, F. M. *J. Biol. Chem.* **1993**, *268*, 570–576; (d) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935–944; (e) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605–611; (f) Treadway, J. L.; Mendys, P.; Hoover, D. J. *Exp. Opin. Invest. Drugs* **2001**, *10*, 439–454; (g) Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Sudhakar Babu, Y.; Bantia, S.; Elliot, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379–4392.
2. (a) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1837; (b) Koepfli, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 1048–1054.
3. (a) Ablondi, F.; Gordon, S.; Morton, J., II; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 14–18; (b) Kato, M.; Inaba, M.; Itahana, H.; Ohara, E.; Nakamura, K.; Uesato, S.; Inouye, H.; Fujita, T. *Shoyakugaku Zasshi* **1990**, *44*, 288–292.
4. (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175–2178; (b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833–6841.
5. (a) Murata, K.; Takano, F.; Fushiya, S.; Oshima, Y. *J. Nat. Prod.* **1998**, *61*, 729–733; (b) Takaya, Y.; Tasaka, H.; Chiba, T.; Uwai, K.; Tanitsu, M.; Kim, H.-S.; Wataya, Y.; Miura, M.; Takeshita, M.; Oshima, Y. *J. Med. Chem.* **1999**, *42*, 3163–3166; (c) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193–3195; (d) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953–955; (e) Zhu, S.; Meng, L.; Zhang, Q.; Wei, L. *Bioorg. Med. Chem.* **2006**, *16*, 1854–1858; (f) Kikuchi, H.; Yamamoto, K.; Horoiwa, S.; Hirai, S.; Kasahara, R.; Hariguchi, N.; Matsumoto, M.; Oshima, Y. *J. Med. Chem.* **2006**, *49*, 4698–4706.
6. De Smet, P. A. G. M. *Drugs* **1997**, *54*, 801–840.
7. (a) Fishman, M.; Cruickshank, P. A. *J. Med. Chem.* **1970**, *13*, 155–156; (b) Chien, P.-L.; Cheng, C. C. *J. Med. Chem.* **1970**, *13*, 867–870.
8. Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274–5293.
9. (a) Tamaru, Y.; Kawamura, S.-i.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z.-i. *J. Org. Chem.* **1988**, *53*, 5491–5501; (b) Freville, S.; Bonin, M.; Celerier, J.-P.; Husson, H.-P.; Lhommet, G.; Quirion, J.-C.; Thuy, V. M. *Tetrahedron* **1997**, *53*, 8447–8456; (c) Lorthiois, E.; Marek, I.; Normant, J. F. *J. Org. Chem.* **1998**, *63*, 566–574; (d) Poerwono, H.; Higashiyama, K.; Takahashi, H. *J. Org. Chem.* **1998**, *63*, 2711–2714; (e) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633–640; (f) Katritzky, A. R.; Luo, Z.; Cui, X.-L. *J. Org. Chem.* **1999**, *64*, 3328–3331; (g) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261–263; (h) Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4231–4237; (i) Haddad, M.; Larchevêque, M. *Tetrahedron Lett.* **2001**, *42*, 5223–5225; (j) Reddy, M. S.; Narender, M.; Rao, K. R. *Tetrahedron* **2007**, *63*, 331–336.
10. (a) Fall, Y.; Gómez, G.; Fernández, C. *Tetrahedron Lett.* **1999**, *40*, 8307–8308; (b) Fall, Y.; Vidal, B.; Alonso, D.; Gómez, G. *Tetrahedron Lett.* **2003**, *44*, 4467–4469; (c) Pérez, M.; Canoa, P.; Gómez, G.; Teijeira, M.; Fall, Y. *Synthesis* **2005**, 411–414; (d) Alonso, D.; Pérez, M.; Gómez, G.; Covelo, B.; Fall, Y. *Tetrahedron* **2005**, *61*, 2021–2026.
11. (a) Teijeira, M.; Suárez, P. L.; Gómez, G.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2005**, *46*, 5889–5892; (b) García, I.; Gómez, G.; Teijeira, M.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2006**, *47*, 1333–1335; (c) Canoa, P.; Pérez, M.; Covelo, B.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2007**, *48*, 3441–3443; (d) Canoa, P.; Vega, N.; Pérez, M.; Generosa, G.; Fall, Y. *Tetrahedron Lett.* **2008**, *49*, 1149–1151; (e) García, I.; Pérez, M.; Besada, P.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2008**, *49*, 1344–1347.
12. Gómez, G.; Rivera, H.; García, I.; Estévez, L.; Fall, Y. *Tetrahedron Lett.* **2005**, *46*, 5819–5822.
13. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR, analytical, and/or high resolution mass spectral data.
14. The formation of triazolines from azides is not unprecedented. See: (a) Herdeis, C.; Schiffer, T. *Tetrahedron* **1996**, *52*, 14745–14756; (b) Haddad, M.; Larchevêque, M.; Tong, H. M. *Tetrahedron Lett.* **2005**, *46*, 6015–6017; (c) Rejzek, M.; Stockman, R. A.; van Maarseveen, J. H.; Hughes, D. L. *J. Chem. Soc., Chem. Commun.* **2005**, 4661–4662.
15. Selected data for compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 5.49 (1H, d, $J = 9.90$ Hz, CH-3), 4.41 (1H, m, CH_2-7), 3.96 (1H, d, $J = 9.90$ Hz, CH-2), 3.39 (3H, s, OMe), 3.29 (1H, m, CH_2-7), 2.53 (1H, m, CH_2-5), 1.79 (2H, m, CH_2-5, CH_2-6), 1.74 (1H, m, CH_2-6); ^{13}C NMR ($CDCl_3$), δ: 168.99 (CO), 106.16 (C-4), 82.19 (CH-3), 57.96 (CH-2), 50.18 (OMe), 45.12 (CH_2-7), 28.55 (CH_2-5), 21.08 (CH_2-6).
16. (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646; (b) Knousi, N.; Vaultier, M.; Carrié, R. *Bull. Soc. Chim. Fr.* **1985**, *5*, 815–819; (c) Aragones, S.; Bravo, F.; Diaz, Y.; Matheu, M. I.; Castillon, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1847–1856.
17. Selected data for compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.57 (1H, t, $J = 7.92$ Hz, CH-6), 3.70 (1H, m, CH-4), 3.35 (3H, s, OCH_3), 2.99 (1H, m, CH-4), 2.87 (1H, dd, $J = 8.36$ and 17.92 Hz, CH-7), 2.58 (1H, dd, $J = 7.62$ and 17.94 Hz, CH-7), 1.99 (2H, m, CH-2), 1.68 (1H, m, CH-3), 1.60 (1H, m, CH-3), 1.4 (9H, s, ^{t}Bu); ^{13}C NMR ($CDCl_3$), δ: 172.64 (CO, C-8), 154.97 (CO, Boc), 107,41 (C), 80.77 (C), 54.54 (CH), 50.46 (OCH_3), 48.20 (CH_2), 33.96 (CH_2), 29.56, 28.44, 28.29, 28.21, 28.00 (CH_3, tBu), 27.91 (CH_2), 19.48 (CH_2).