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Tetrahedron Letters 47 (2006) 1319–1323
Tetrahedron Letters

Synthetic investigations of (1,3′)-bistetrahydroisoquinolines: towards pentacyclic analogues of piperazine core alkaloids

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Received 21 November 2005; revised 8 December 2005; accepted 12 December 2005
Available online 28 December 2005

Abstract—Synthetic investigations of (1,3′)-bistetrahydroisoquinolines are reported as the key intermediates for the synthesis of ecteinascidin and phthalascidin pentacyclic structure analogues through successive Pictet–Spengler cyclization and intramolecular peptide coupling. The direct Pictet–Spengler reaction between a derivative of L-DOPA and N-protected-α-aminoaldehyde was first extended to the synthesis of *cis*-(1,3′)-bistetrahydroisoquinoline. After introduction of the required amino acid moiety, an efficient six-membered ring intramolecular peptide coupling gave rise to piperazine derivative structures. Complete structural assignments were corroborated by NMR and X-ray spectroscopic methods. Nevertheless, the optical integrity of the N-protected-α-aminoaldehyde seems to be sensitive to the reaction conditions. Pentacylic structures, having an *anti* C3–C11 backbone stereochemistry, were obtained from cyclization *para*- and *ortho*- to the 3-OH group of the L-DOPA derivative.

The synthesis of tetrahydroisoquinoline alkaloids has received particular attention in the field of medicinal chemistry due to their biological activity.[1] The most bioactive member of this family, ecteinascidin 743 (**1**, Et 743), was isolated from Caribbean tunicate *Ecteinascidia turbinate*[2] (Fig. 1) and revealed potent antitumour activity under phase II/III clinical trials for various human cancer cell lines.[3]

So far, two successful total syntheses, performed by Corey[4] and Fukuyama,[5] respectively, and a semi-synthesis achieved by Cuevas[6] have been reported. However, a synthetic analogue, phthalascidin 650 (**2**, Pt 650),[7] which exhibits a similar biological activity to the natural product, has also been prepared (Fig. 1). Their antiproliferative activity on tumour cells was essentially due to DNA minor groove alkylation[8] as previously demonstrated for saframycin S (**3**), the most active compound of this alkaloid series.[9] More recently, the construction of these alkaloid architectures[10–16] was improved by several groups, and the closing of the 10-membered sulfur-containing lactone in Et 743 construction was investigated.[11c,17]

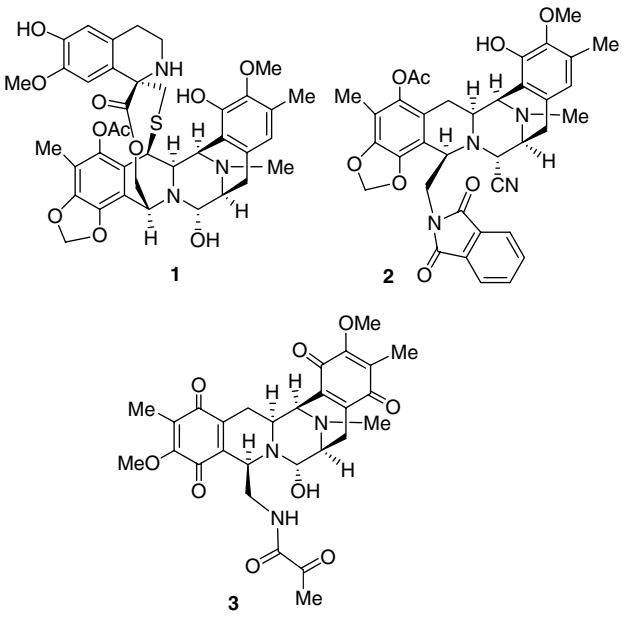

Figure 1. Tetrahydroisoquinoline alkaloids.

Several groups have reported an intermolecular peptide-coupling connecting both subunits by amide bond formation to a secondary amine.[4,11b,13] Nevertheless,

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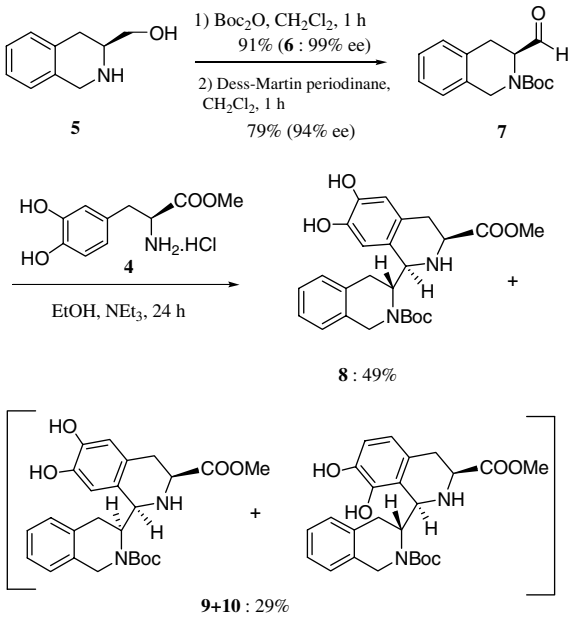
doi:10.1016/j.tetlet.2005.12.056

the direct synthesis of tetrahydroisoquinolines incorporating heterocyclic structures received little attention.[18,19] As far as we know, the direct synthesis of (1,3′)-bistetrahydroisoquinolines was not done using the Pictet–Spengler condensation. According to the study here, we propose a new and short methodology dedicated to the synthesis of piperazine pentacyclic structure analogues. Based on the use of the direct Pictet–Spengler phenolic cyclization,[20] condensation between *N*-Boc-1,2,3,4-tetrahydroisoquinoline-3-carboxaldehyde **7** and L-3,4-dihydroxyphenylalanine methyl ester hydrochloride **4** afforded (1,3′)-bistetrahydroisoquinolines as synthetic intermediates of the desired pentacyclic structures **17** and **19** (vide infra).

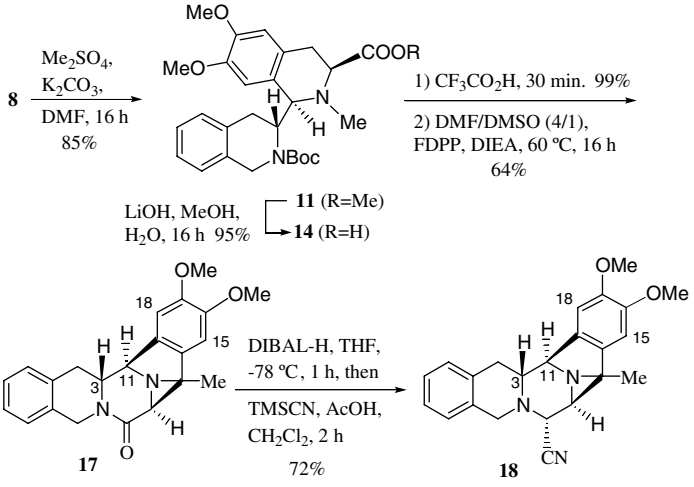
Starting from the commercially available (*S*)-(−)-1,2,3,4-tetrahydroisoquinolinemethanol **5**, protection of the amino group with Boc_2O provided **6** in 91% yield and 99% ee.[21] Oxidation of **6** with Dess–Martin periodinane reagent[22] in CH_2Cl_2 afforded the *N*-Boc-α-aminoaldehyde **7**[23] in 79% yield and up to 94% ee after silica gel column chromatography (Scheme 1). The optical purity[24] of **6** and **7** was assessed by HPLC analyses (Chiralcel OD) of the racemic mixture. As established by Kametani and co-workers,[25] condensation of **7** with L-3,4-dihydroxyphenylalanine methyl ester hydrochloride **4** under the non-acidic conditions of the Pictet–Spengler reaction (EtOH, NEt_3, rt) led to the formation of three (1,3′)-bistetrahydroisoquinolines, **8**, **9** and **10**, obtained as a mixture of three isomers with a complete *cis*-stereoselectivity. Isomers **8** and **9** arised from cyclization *para*- to the 3-phenolic group of **4**, and **10** from cyclization *ortho*- to the same 3-phenolic group.

Purification by chromatography afforded pure **8** in 49% yield and an inseparable mixture of **9** and **10** in a 50/50 ratio (29% yield). Two rotamers were characterized for each compound **8**, **9** and **10**. Configurational elucidation of **8** was determined by 2D NMR experiments (including HSQC, COSY and NOESY techniques). ^1H NMR experiment in DMSO-d_6 at 80 °C, confirmed the composition of the mixture of **9** and **10**. The structure of **10** was established by two doublets at 6.45 ppm ($J = 8$ Hz) and



Scheme 1. Synthesis of (1,3′)-bistetrahydroisoquinolines **8**, **9** and **10**.

6.65 ppm ($J = 8$ Hz) corresponding to the adjacent aromatic protons. Nevertheless, epimerization of the aldehyde stereocenter occurred during the cyclization step affording **8** and **10**, and was confirmed at a later stage of this synthetic sequence by single-crystal X-ray analysis of **12** and **19**.[26] This event occurred at the aldehyde stereocenter, which can be configurationally unstable in solution.[24] Successively, three synthetic steps of functionalization were conducted to introduce the required amino acid moiety of the (1,3′)-bistetrahydroisoquinolines. Thus, the trimethylation of **8** with an excess of Me_2SO_4 and K_2CO_3 in DMF at room temperature afforded the amino ester **11** in 85% yield (Scheme 2). Hydrolysis of the ester **11** with LiOH in a mixture of MeOH/H_2O (3/1) was performed to give **14** in 95% yield. The direct deprotection/cyclization of **11** as described by Liu[13] with CF_3CO_2H in CH_2Cl_2 did not produce the corresponding pentacyclic structure, with any reaction conditions tried (TMSOTf,[27] K_2CO_3/MeOH).



Scheme 2. Synthetic procedure for the pentacyclic system **18**.

This could be explained by the relatively low nucleophilicity of the secondary amine intermediate. The *N*-Boc linkage was then cleaved by CF_3CO_2H and the corresponding amino acid intermediate was engaged in the next step without further purification. Usual activation agents of the carboxyl groups with DCC and DMAP,[28a] EDC and HOBt[28b–d] or PyBoP®[28e] were inefficient (Table 1, entries 1–4), affording **17** in poor yields. Finally, after investigation of reaction conditions (Table 1), the six-membered intramolecular peptide coupling[29] efficiently takes place with pentafluorophenyl diphenylphosphinate (FDPP)[30] as coupling agent allowing the increase of the peptide coupling yield from 24% to 32% in CH_2Cl_2 (entry 5) or DMF (entries 6–8). The best conditions of those investigated of the six-membered intramolecular peptide coupling were obtained in a mixture of DMF/DMSO (entries 9–12) and provided the pentacyclic compound **17** exclusively in 64% yield (entry 12). At starting material concentrations higher than 0.15 mol/L, oligomerization increased dramatically.

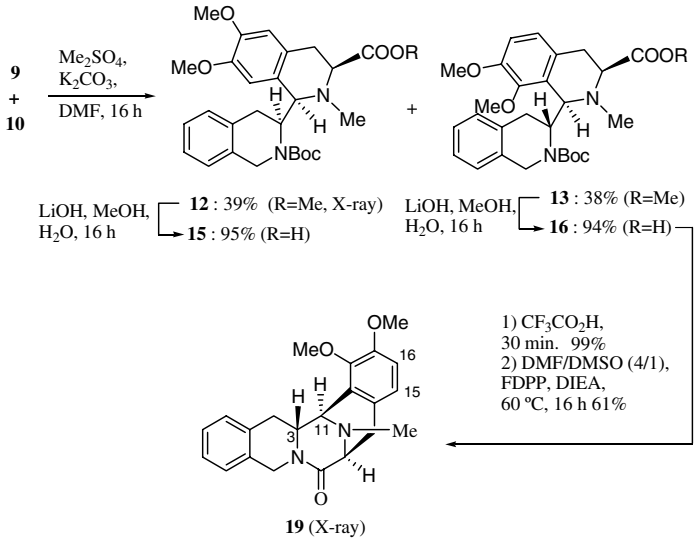
Taking into account the reasons for the antiproliferative activities of this alkaloid family, the reduction of the lactam ring of **17** was explored with DIBAL-H in THF at −78 °C, achieving the corresponding carbinolamine which was converted, under acidic conditions with trimethylsilyl cyanide, to amino nitrile **18** in 72% yield. The structure of **18** was determined on the basis of the 500 MHz NOESY spectrum by measurement of the interproton distances from the ratio analysis of the cross and diagonal peak intensities.[31] According to this study, this compound exhibited the opposite C3–C11 backbone stereochemistry recurrent in this alkaloid family.

To complete the synthetic sequence from **9** and **10**, an N- and O-methylation step was also done affording the trimethylated compounds **12** and **13** (Scheme 3). Structural elucidation of **12** was established by single-crystal X-ray analysis.[26] Surprisingly, after hydrolysis of ester **12** and deprotection of the *N*-Boc linkage of the corresponding acid, the final cyclization step failed. Due to the steric hindrance imposed by the activated acid intermediate, the intramolecular peptide coupling was inefficient. However, hydrolysis of ester **13** and cleavage of the *N*-Boc linkage provided the corresponding amino acid derivative, which was immediately cyclized under the best conditions of peptide coupling (entry 12: FDPP, DIEA, DMF/DMSO: 4/1, 0.15 mol/L) affording the pentacyclic compound **19** in 61% yield.

Complete structural characterization of **19** was achieved by NMR and X-ray spectroscopic methods.

Table 1. Intramolecular peptide coupling optimization

Entry	Coupling agent	Solvent	Base (equiv)	Concentration (mol/L)	Temperature (°C)	Time (h)	Yield **17** (%)
1	DCC/DMAP	CH_2Cl_2	Net_3 (3)	0.05	rt	24	15
2	EDC/HOBt	DMF	Net_3 (3)	0.05	rt	24	20
4	PyBop®	DMF	Net_3 (3)	0.05	rt	24	18
5	FDPP	CH_2Cl_2	DIEA (5)	0.05	rt	24	24
6	FDPP	DMF	DIEA (5)	0.06	rt	24	28
7	FDPP	DMF	DIEA (5)	0.01	60	24	19
8	FDPP	DMF	DIEA (5)	0.06	60	24	32
9	FDPP	DMF/DMSO (4/1)	DIEA (5)	0.06	rt	16	32
10	FDPP	DMF/DMSO (4/1)	DIEA (5)	0.06	60	16	36
11	FDPP	DMF/DMSO (4/1)	DIEA (5)	0.10	60	16	41
12	**FDPP**	**DMF/DMSO (4/1)**	**DIEA (5)**	**0.15**	**60**	**16**	**64**



Scheme 3. Separation of **12** and **13** and synthesis of pentacycle **19**.

Interpretation of the room temperature ^{1}H NMR spectrum revealed that the typical doublets corresponding to the AB system of the catechol protons of intermediates **13** and **16** collapsed to a singlet at 6.86 ppm for compound **19**. This phenomenon results from a degenerated spin coupling effect of H-15 and H-16 resonance signals which possess the same chemical shift. Moreover, HSQC experiment confirmed this hypothesis, exhibiting two cross-peaks between the proton resonance signal at 6.86 ppm and the carbon peaks at 112.4 and 124.4 ppm. Nevertheless, the X-ray diffraction analysis of **19**[26] revealed an *anti* C3–C11 backbone stereochemical relationship according to the epimerization of the N-protected-α-aminoaldehyde **7** during the Pictet–Spengler cyclization step. As previously observed by several groups, the epimerization at C3 occurred through the phenolic cyclization step.[11d,12d]

Acknowledgements

The authors wish to thank the 'Ministère de l'Enseignement Supérieur et de la Recherche', for the Grant to S.A.'s Ph.D. and wish to thank Dr. Christine Clozel-Fox and Dr. Igor Kazmierski, for correcting the manuscript.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.12.056.

References and notes

1. For a review, see: Scott, J.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
2. (a) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Perun, T. J., Jr.; Seigler, D. S.; Wilson, G. R.; Shield, L. S. *Pure Appl. Chem.* **1990**, *62*, 1277–1280; (b) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Sun, F.; Li, H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512–4515; (c) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnel, O. J. *J. Org. Chem.* **1990**, *55*, 4508–4512; (d) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. H.-J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456–11460; (e) Sakai, R.; Jares-Erijaman, E.; Manzanares, I.; Elipe, M. V.; Rinehart, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 9017–9023; (f) Suwanboriux, K.; Chapurant, K.; Amnuoypol, S.; Pummangura, S.; Kubo, A.; Saito, N. *J. Nat. Prod.* **2002**, *65*, 935–937.
3. (a) Zelek, L.; Yovine, A.; Etienne, B.; Jimeno, J.; Taama, A.; Martin, C.; Spielmann, M.; Cvitkovic, E.; Misset, J. L. Ecteinacsidin-743 in taxane/antracycline pretreated advanced/metastatic breast cancer patients: preliminary results with the 24 h continuous infusion Q3 week schedule. Presented at the American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, 20–23 May, 2000; Abstract number 592; (b) Delaloge, S.; Yovine, A.; Taama, A.; Cottu, P.; Riofrio; M.; Raymond, E.; Brain, E.; Marty, M.; Jimeno, J.; Cvitkovic, E.; Misset, J. L. Preliminary evidence of activity of Ecteinascidin-743 (ET-743) in heavily pretreated patients with bone and soft tissue sarcomas. Presented at the American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, 20–23 May, 2000; Abstract number 2181; (c) Le Cesne, A.; Judson, I.; Blay, J. Y.; Radford, J.; van Oosterom, A.; Lorigan, P.; Rodenhuis, E.; Donato Di Paoula, E.; Van Glabbeke, M.; Jimeno, J.; Verweij, J. Phase II of ET-743 in advance soft tissue sarcoma in adult: a STBSG-EORTC trial. Presented at the American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, 20–23 May, 2000; Abstract number 2182; (d) Ryan, D. P.; Supko, J. G.; Eder, J. P.; Seiden, M. V.; Demetri, G.; Lynch, T. J.; Fischman, A. J.; Davis, J.; Jimeno, J.; Clark, J. W. *Clin. Cancer Res.* **2001**, *7*, 231–242; (e) Takashi, N.; Li, W.; Banerjee, D.; Guan, Y.; Wada-Takahashi, Y.; Brennan, M. F.; Chou, T. C.; Scotto, K. W.; Bertino, J. R. *Cancer Res.* **2002**, *62*, 6909–6915; (f) Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545–555; (g) Blay, J.-Y.; Le Cesne, A.; Verweij, J.; Scurr, M.; Seynaeve, C.; Bonvalot, S.; Hogendoorn, P.; Jimeno, J.; Evrard, V.; Van Glabbeke, M.; Judson, I. *Eur. J. Cancer* **2004**, *40*, 1327–1331.
4. (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203; (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993–996.
5. Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554.
6. (a) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2*, 2545–2548; (b) Menchaca, R.; Martínez, V.; Rodríguez, A.; Rodríguez, N.; Flores, M.; Gallego, P.; Manzanares, I.; Cuevas, C. *J. Org. Chem.* **2003**, *68*, 8859–8866.
7. Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496–3501.
8. (a) Pommier, Y.; Kolhagen, G.; Bailly, C.; Waring, M.; Mazumder, A.; Kohn, K. W. *Biochemistry* **1996**, *35*, 13303–13309; (b) Moore, B. M., II; Seaman, F. C.; Wheelhouse, R. T.; Hurley, L. H. *J. Am. Chem. Soc.* **1998**, *120*, 2490–2491.
9. Mikami, Y.; Yokoyama, K.; Tabeta, H.; Nakagaki, K.; Arai, T. *J. Pharm. Dyn.* **1981**, *4*, 282–286.
10. (a) Saito, N.; Tashiro, K.; Maru, Y.; Yamaguchi, K.; Kubo, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 53–69; (b) Saito, N.; Kamayachi, H.; Tachi, M.; Kubo, A. *Heterocycles* **1999**, *51*, 9–12; (c) Saito, N.; Tachi, M.; Seki, R.; Kamayachi, H.; Kubo, A. *Chem. Pharm. Bull.* **2000**, *48*, 1549–1557; (d) Saito, N.; Seki, R.; Kameyama, N.; Sugimoto, R.; Kubo, A. *Chem. Pharm. Bull.* **2003**, *51*, 821–831.
11. (a) Zhou, B.; Edmonson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2039–2042; (b) Zhou, B.; Guo, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043–2046; (c) Zhou, B.; Guo, J.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 43–46; (d) Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596–4598.
12. (a) Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 543–546; (b) Jin, W.; Williams, R. M. *Tetrahedron Lett.* **2003**, *44*, 4635–4639; (c) Jin, W.; Metebo, S.; Williams, R. M. *Org. Lett.* **2003**, *5*, 2095–2098; (d) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690.
13. Tang, Y.-F.; Liu, Z.-Z.; Chen, S.-Z. *Tetrahedron Lett.* **2003**, *44*, 7091–7094.
14. (a) De Paolis, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2003**, 2896–2897; (b) De Paolis, M.; Chen, X.; Zhu, J. *Synlett* **2004**, 729–731; (c) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408.

15. (a) Magnus, P.; Mathews, K. S.; Lynch, V. *Org. Lett.* **2003**, *5*, 2181–2184; (b) Magnus, P.; Mathews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476–12477.
16. (a) González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron Lett.* **2003**, *44*, 4395–4398; (b) González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2004**, *60*, 6319–6326; (c) González, J. F.; Salazar, L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2005**, *61*, 7447–7455.
17. De Paolis, M.; Blankenstein, J.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2002**, *4*, 1235–1238.
18. (a) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402; (b) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829.
19. Aubry, S.; Pellet-Rostaing, S.; Faure, R.; Lemaire, M. *J. Heterocycl. Chem.* **2006**, *43*.
20. For a review, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.
21. Pagé, D.; Nguyen, N.; Bernard, S.; Coupal, M.; Gosselin, M.; Lepage, J.; Adam, L.; Brown, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1585–1589.
22. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
23. Schiller, P. W.; Weltrowska, G.; Nguyen, T. M.-D.; Wilkes, B. C.; Chung, N. N.; Lemieux, C. *J. Med. Chem.* **1993**, *36*, 3182–3187.
24. For a review, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164.
25. (a) Kametani, T.; Fukumoto, K.; Agui, H.; Yagi, H.; Kigasawa, K.; Sugushura, H.; Hiiragi, M.; Hayasaka, T.; Ishimaru, M. *J. Chem. Soc. (C)* **1968**, 112–118; (b) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H. *J. Heterocycl. Chem.* **1970**, *7*, 51–54.
26. Crystallographic data (excluding structure factors) for **12** and **19** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 287225 and 286961. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
27. Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227–3230.
28. (a) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *19*, 4475–4478; (b) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788–798; (c) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 2024–2033; (d) König, W.; Geiger, R. *Chem. Ber.* **1973**, *106*, 3626–3635; (e) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205–208.
29. For a review, see: Humphrey, J. M.; Chamberlain, A. R. *Chem. Rev.* **1996**, *97*, 2243–2266.
30. Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711–6714.
31. (a) Bodenhausen, G.; Ernst, R. R. *J. Am. Chem. Soc.* **1982**, *104*, 1304–1309; (b) Reggelin, M.; Hoffmann, H.; Köck, M.; Mierke, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 3272–3277.