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A unified approach to the important protein kinase inhibitor balanol and a proposed analogue

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Full Research Paper

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Abstract

A common approach to the important protein kinase inhibitor (−)-balanol and an azepine-ring-modified balanol derivative has been developed using an efficient fragment coupling protocol which proceeded in good overall yield.

Introduction

Protein kinase C (PKC) is a family of phospholipid-dependent kinases that phosphorylate serine and threonine residues of a substrate protein by transferring a phosphate group from ATP to the substrate protein [1-3]. This phosphorylation induces conformational changes of the substrate protein leading to initiation of a number of cellular events including signal transduction [4,5]. The human PKC enzyme comprises of a number of isozymes and inappropriate activation of PKC has been linked to a variety of disorders [6,7]. The development of selective PKC inhibitors as novel therapeutics has therefore remained significant [8-14].

Balanol ((−)-**1**, Figure 1), a fungal metabolite [15] is known to inhibit a number of PKC isozymes at nanomolar concentrations [16], a finding that has motivated research related to the total- [17-26] or fragment synthesis [27-47] of this important natural product. Based on the information [48,49] that balanol binds to the ATP-docking site of protein kinase, all the three distinct domains present in the natural product such as the benzophenone core [50-52], the azepine core [53-59] and the

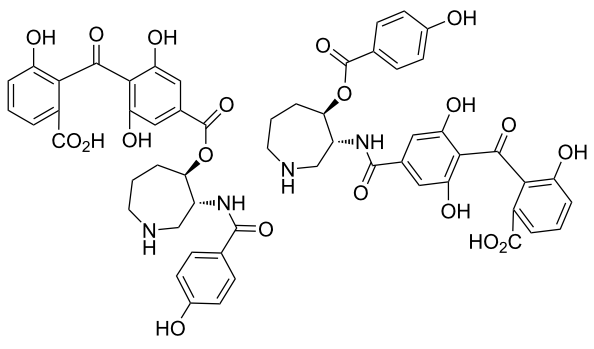


Figure 1: Balanol (**1**) and ophiocordin (**2**).

p-hydroxybenzamide [60,61] unit have been targeted for analogue design in the quest for a more selective drug candidate over the last two decades. Although remarkable achievements have been made, the development of a unified synthetic strategy that would allow access to the natural product itself as well as some of its analogues remains important. A similar target is the closely related natural product ophiocordin (**2**). Herein, we describe a general approach to some of these targets.

Results and Discussion

The key feature of our retrosynthetic analysis (Figure 2) is the identification of the dehydro derivative of balanol **4** as the unified precursor of balanol (**1**) and an azepin ring-modified balanol **3**. Derivative **4** could be obtained through esterification between the carboxylic acid **5** and the allylic alcohol **6**.

We thus focused on the synthesis of the two key fragments **5** and **6**. The synthesis of the benzophenone unit has previously been achieved by several groups [27-30]. We adopted some of these methodologies with a number of modifications to prepare fragment **5** in its protected form **7** (Scheme 1). At first, the reaction of the known [17] bromo compound **8** with the known [27] aldehyde **9** in the presence of butyllithium effected a smooth conversion to the new benzylic alcohol **10**. The latter was oxidized with tetrapropylammonium perruthenate to provide the benzophenone derivative **11** in good yield. Subsequent cleavage of the 1,3-dioxane unit followed by oxidation of the resulting aldehyde **12** furnished carboxylic acid **13** in 73% overall yield over two steps. Concomitant removal of the phenolic MOM ether and the alcoholic TBDPS ether protecting groups in **13** under acidic conditions proceeded without significant loss of product to provide the dihydroxy acid **14** in good yield. Reaction of **14** with an excess of benzyl bromide in the presence of K_2CO_3 afforded simultaneous protection of the phenolic OH and the carboxylic acid functions leaving the primary alcohol function unprotected, as desired. Compound **15** was then converted following a literature procedure into the known [17] benzophenone **7** through two consecutive oxidations involving the aldehyde **16** as the intermediate. Taken as a hole the described synthesis of **7** from **8** and **9** proceeded in eight linear steps in an overall yield of 22%.

The synthesis of the azepine unit [31-47] was achieved following our preliminary report [62]. Thus, reductive amination of Garner's aldehyde **17** (Scheme 2) with allylamine produced amine **18** which was N-protected with CbzCl to obtain **19** in an overall yield of 89% over three steps. The oxazolidine ring in compound **19** was then cleaved under acidic conditions and the resulting primary alcohol **20** was oxidized carefully under modified Swern conditions [63] to provide the α-chiral aldehyde **21** which was used directly in the next step. Addition of vinylmagnesium bromide to aldehyde **21** under optimized conditions gave a separable mixture of the allylic alcohols **22** and **23** in a combined yield of 64% over two steps. The undesired *anti*-isomer **23** could be effectively converted to the desired *syn*-isomer **22** by a Mitsunobu-type inversion [64].

The major *syn*-isomer **22** was then acetylated and the resulting diene **24** was subjected to ring-closing metathesis [65] in the presence of Grubbs' second generation catalyst, benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(tricyclohexylphosphine)ruthenium (**25**). Pleasingly, the desired cycloalkene **26** was obtained in a gratifying yield of 89%. The sequential removal of the *O*-acetyl group leading to **27** followed by removal of the *N*-Boc group in the latter was executed under standard conditions to provide amine **28**. This was then coupled with 4-benzyloxybenzoic acid using EDC as activating agent to obtain the corresponding amide

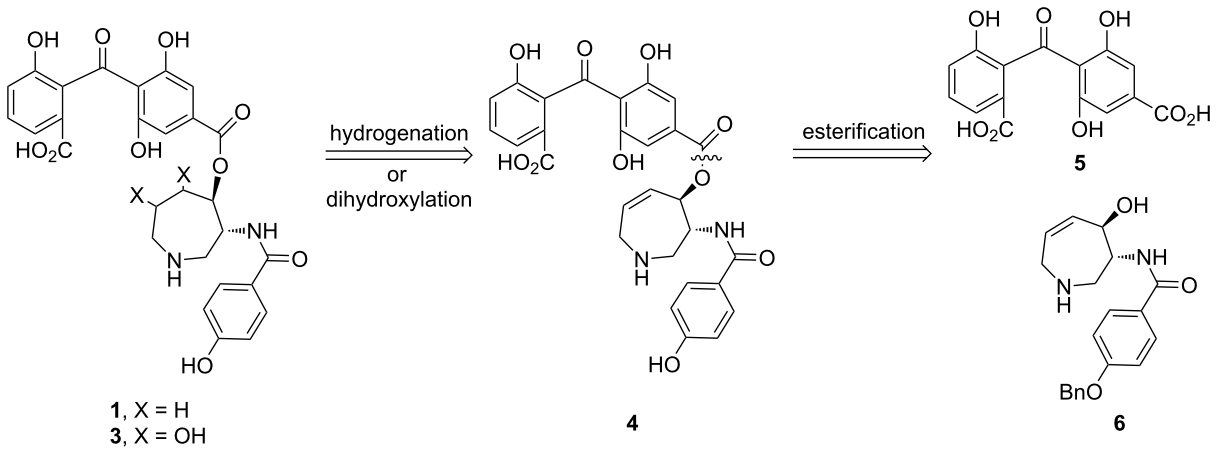
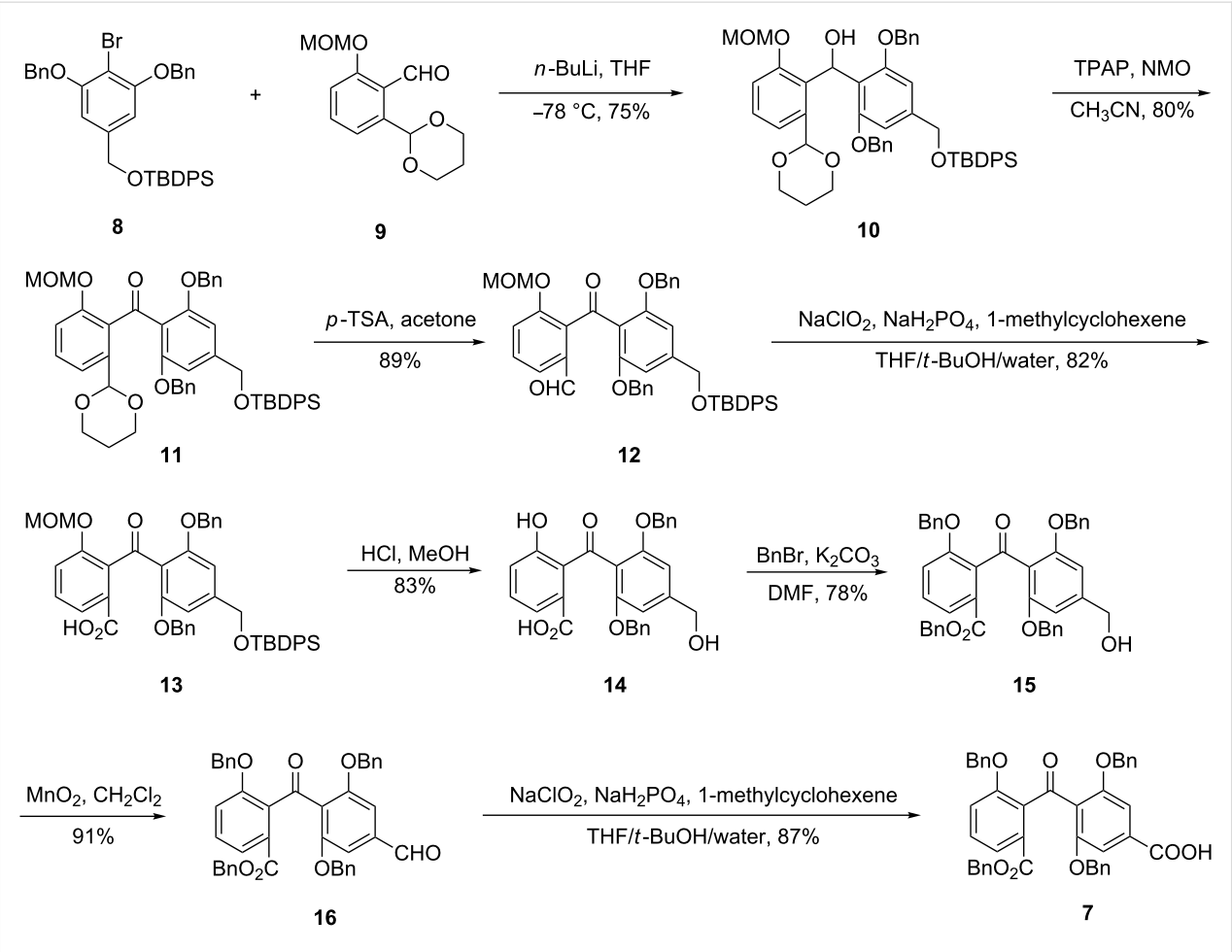


Figure 2: Strategic bond disconnections of balanol.



Scheme 1: Synthesis of the benzophenone fragment of balanol.

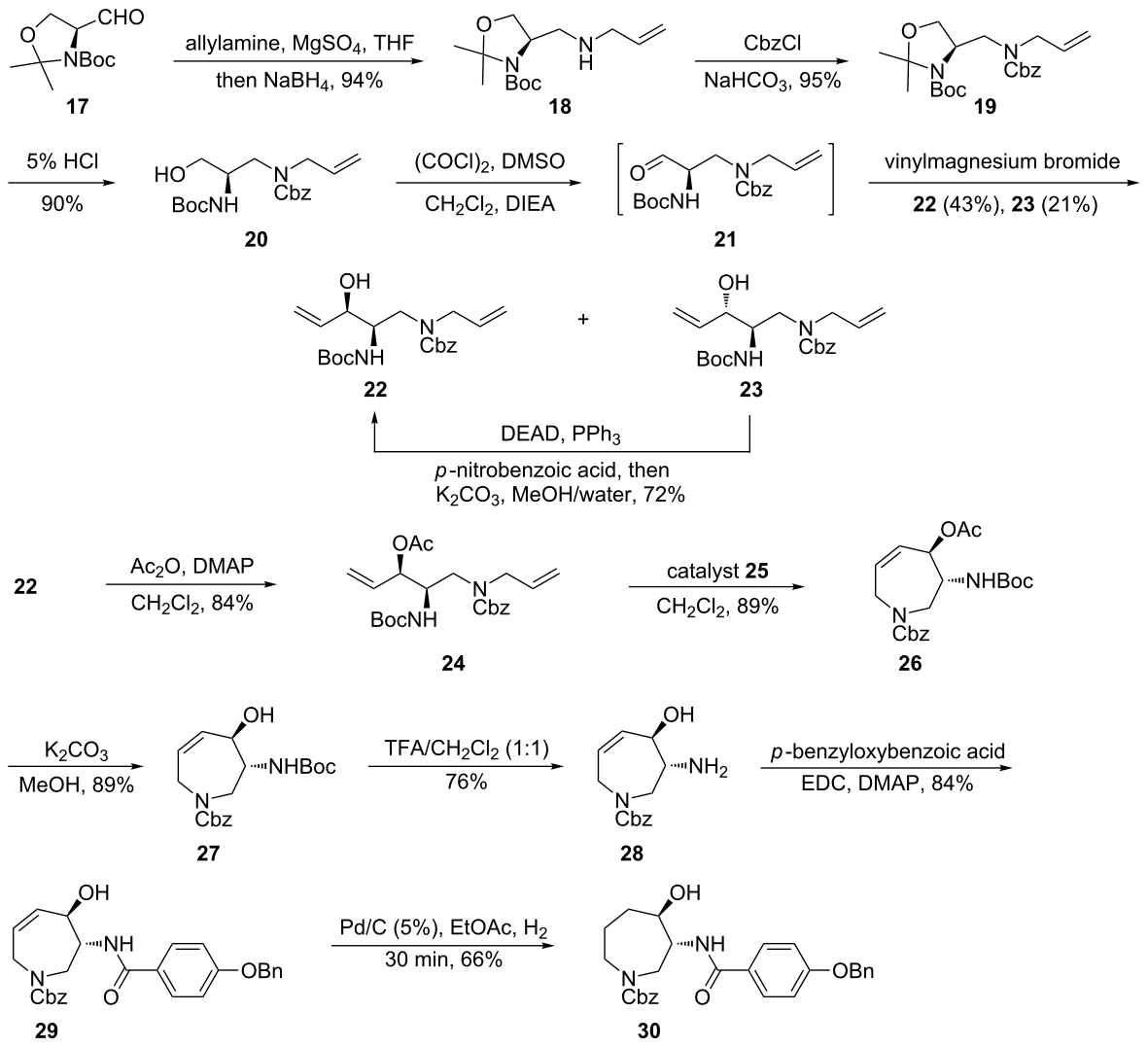
derivative **29** in an overall yield of 20% over eleven steps from **17**. The stereochemical identity of this tetrahydroazepine derivative was confirmed by its selective conversion to the corresponding known azepane derivative **30** which displayed optical and ^{13}C NMR data nearly overlapping with those reported by Nicolaou et al [17].

With the two key fragments **29** and **7** in hand, we next focused on their convergent combination. The esterification of the allylic alcohol **29** with the acid **7** (Scheme 3) proceeded best in the presence of Mukaiyama's reagent [66], 2-chloro-1-methylpyridinium iodide, to provide the ester **31** in 73% yield. Simultaneous hydrogenolytic removal of the *O*-benzyl groups and the *N*-Cbz group under reported conditions finally provided the natural (−)-balanol in a yield of 41%. The product thus obtained displayed spectroscopic and optical data in close agreement to those reported for natural balanol [17].

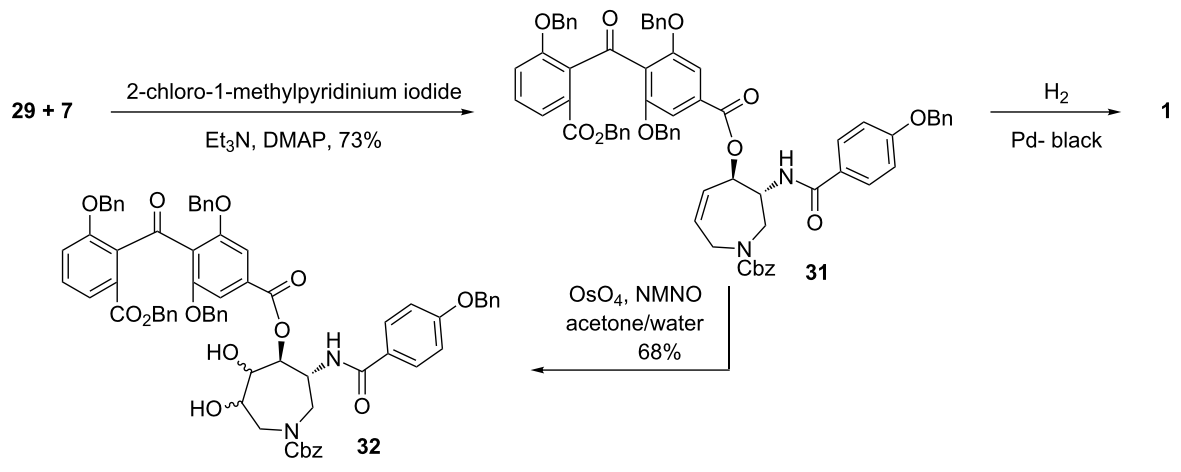
We next focused our attention to demonstrate the utility of the intermediate coupled product **31** in a possible synthesis of an azepane ring-modified balanol derivative along the projected pathway. To this end, dihydroxylation of the adduct **31** was next attempted. Pleasingly, the dihydroxylation of **31** proceeded smoothly; however, unfortunately to provide an inseparable mixture of the two possible dihydroxylated isomers **32** in a combined yield of 68%. The isomeric composition of **32** was determined to be 81:19 by HPLC.

Conclusion

In conclusion, we have developed a concise synthetic approach to the naturally occurring (−)-balanol (**1**) from easily available starting materials and reagents. Most of the synthetic steps proceeded in good to very good overall yield and stereocontrol. The developed synthesis may therefore be a complement to the existing literature. An attempted synthesis of an azepane ring-modified balanol derivative from a common precursor unfortunately was unsuccessful due to difficulty in separating stereoisomeric products. However, the intermediate **31** may prove to be useful in the synthesis of other analogues.



Scheme 2: Synthesis of the hexahydroazepine core of balanol.



Scheme 3: Synthesis of balanol and an analogue.

Supporting Information

Supporting Information File 1

Experimental details and characterization data for the prepared compounds, copies of ^{1}H and ^{13}C NMR spectra of all new compounds, and data for the comparison of **30** and **1** with reported data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-327-S1.pdf]

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References

1. Nishizuka, Y. *Nature* **1984,** *308,* 693–698. doi:10.1038/308693a0
2. Nishizuka, Y. *Science* **1986,** *233,* 305–312. doi:10.1126/science.3014651
3. Newton, A. C. *J. Biol. Chem.* **1995,** *270,* 28495–28498. doi:10.1074/jbc.270.48.28495
4. Nishizuka, Y. *FASEB J.* **1995,** *9,* 484–496.
5. Roffey, J.; Rosse, C.; Linch, M.; Hibbert, A.; McDonald, N. Q.; Parker, P. J. *Curr. Opin. Cell Biol.* **2009,** *21,* 268–279. doi:10.1016/j.ceb.2009.01.019
6. Wong, C. F.; Bairy, S. *Curr. Pharm. Des.* **2013,** *19,* 4739–4754. doi:10.2174/1381612811319260006
7. Mochly-Rosen, D.; Das, K.; Grimes, K. V. *Nat. Rev. Drug Discovery* **2012,** *11,* 937–957. doi:10.1038/nrd3871
8. Nishizuka, Y. *Nature* **2002,** *334,* 661–665. doi:10.1038/334661a0
9. Mellor, H.; Parker, P. J. *Biochem. J.* **1998,** *332,* 281–292.
10. Gomez, D. E.; Skilton, G.; Alonso, D. F.; Kazanietz, M. G. *Oncol. Rep.* **1999,** *6,* 1363–1370.
11. Lee, M. R.; Duan, W.; Tan, S.-L. *Expert Opin. Ther. Targets* **2008,** *12,* 535–552. doi:10.1517/14728222.12.5.535
12. Teicher, B. A. *Clin. Cancer Res.* **2006,** *12,* 5336–5345. doi:10.1158/1078-0432.CCR-06-0945
13. Hofmann, J. *Curr. Cancer Drug Targets* **2004,** *4,* 125–146. doi:10.2174/1568009043481579
14. Cohen, P. *Nat. Rev. Drug Discovery* **2002,** *1,* 309–315. doi:10.1038/nrd773
15. Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B. *J. Am. Chem. Soc.* **1993,** *115,* 6452–6453. doi:10.1021/ja00067a087
16. Ohshima, S.; Yanagisawa, M.; Katoh, A.; Fujii, T.; Sano, T.; Matsukuma, S.; Furumai, T.; Fujiu, M.; Watanabe, K.; Yokose, K.; Arisawa, M.; Okuda, T. *J. Antibiot.* **1994,** *47,* 639–647. doi:10.7164/antibiotics.47.639
17. Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994,** *116,* 8402–8403. doi:10.1021/ja00097a072
18. Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994,** *59,* 5147–5148. doi:10.1021/jo00097a014
19. Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996,** *61,* 4572–4581. doi:10.1021/jo952280k
20. Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc., Perkin Trans. 1* **1995,** 2355–2362. doi:10.1039/P19950002355
21. Tanner, D.; Almario, A.; Högberg, T. *Tetrahedron* **1995,** *51,* 6061–6070. doi:10.1016/0040-4020(95)00264-9
22. Tanner, D.; Tedenborg, L.; Almario, A.; Pettersson, I.; Csöregh, I.; Kelly, N. M.; Andersson, P. G.; Högberg, T. *Tetrahedron* **1997,** *53,* 4857–4868. doi:10.1016/S0040-4020(97)00167-1
23. Barbier, P.; Stadlwieser, J. *Chimia* **1996,** *50,* 530–532.
24. Miyabe, H.; Torieda, M.; Kiguchi, T.; Naito, T. *Synlett* **1997,** 580–582. doi:10.1055/s-1997-3236
25. Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998,** *63,* 4397–4407. doi:10.1021/jo980208r
26. Srivastava, A. K.; Panda, G. *Chem.–Eur. J.* **2008,** *14,* 4675–4688. doi:10.1002/chem.200701991
27. Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994,** *59,* 6703–6709. doi:10.1021/jo00101a032
28. Storm, J. P.; Andersson, C.-M. *Org. Lett.* **1999,** *1,* 1451–1453. doi:10.1021/ol9910060
29. Laursen, B.; Denieul, M.-P.; Skrydstrup, T. *Tetrahedron* **2002,** *58,* 2231–2238. doi:10.1016/S0040-4020(02)00096-0
30. Patil, M. L.; Deshpande, V. H.; Ramlingam, S.; Borate, H. B. *Tetrahedron* **2004,** *60,* 1869–1873. doi:10.1016/j.tet.2003.12.029
31. Oh, H.-S.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2012,** *33,* 3895–3898. doi:10.5012/bkcs.2012.33.11.3895
32. Louvel, J.; Chemla, F.; Demont, E.; Ferreira, F.; Pérez-Luna, A.; Voituriez, A. *Adv. Synth. Catal.* **2011,** *353,* 2137–2151. doi:10.1002/adsc.201100333
33. Hudlický, T. *Pure Appl. Chem.* **2010,** *82,* 1785–1796. doi:10.1351/PAC-CON-09-10-07
34. Gilmet, J.; Sullivan, B.; Hudlicky, T. *Tetrahedron* **2009,** *65,* 212–220. doi:10.1016/j.tet.2008.10.070
35. Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, T. *Angew. Chem., Int. Ed.* **2007,** *46,* 6123–6125. doi:10.1002/anie.200700835
36. Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006,** *45,* 7066–7069. doi:10.1002/anie.200602782
37. Raghavan, S.; Kumar, C. N. *Tetrahedron Lett.* **2006,** *47,* 1585–1588. doi:10.1016/j.tetlet.2005.12.123
38. Yadav, J. S.; Srinivas, C. *Tetrahedron* **2003,** *59,* 10325–10329. doi:10.1016/j.tet.2003.09.089
39. Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000,** *65,* 1738–1742. doi:10.1021/jo991611g
40. Masse, C. E.; Morgan, A. J.; Panek, J. S. *Org. Lett.* **2000,** *2,* 2571–2573. doi:10.1021/ol0061034
41. Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000,** *65,* 5382–5390. doi:10.1021/jo000538n
42. Phansavath, P.; de Paule, S. D.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem.* **2000,** 3903–3907. doi:10.1002/1099-0690(200012)2000:23<3903::AID-EJOC3903>3.0.CO;2-Q
43. Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999,** *1,* 615–618. doi:10.1021/ol990705+
44. Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997,** *38,* 1693–1696. doi:10.1016/S0040-4039(97)00192-5
45. Albertini, E.; Barco, A.; Benetti, S.; Risi, C. D.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1997,** *53,* 17177–17194. doi:10.1016/S0040-4020(97)10139-9

46. Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996,** *44,* 624–626. doi:10.1248/cpb.44.624
47. Hu, H.; Jagdmann, G. E., Jr.; Hughes, P. F.; Nichols, J. B. *Tetrahedron Lett.* **1995,** *36,* 3659–3662. doi:10.1016/0040-4039(95)00623-K
48. Narayana, N.; Diller, T. C.; Koide, K.; Bunnage, M. E.; Nicolaou, K. C.; Brunton, L. L.; Xuong, N.-H.; Ten Eyck, L. F.; Taylor, S. S. *Biochemistry* **1999,** *38,* 2367–2376. doi:10.1021/bi9820659
49. Koide, K.; Bunnage, M. E.; Gomez Paloma, L.; Kanter, J. P.; Taylor, S. S.; Brunton, L. L.; Nicolaou, K. C. *Chem. Biol.* **1995,** *2,* 601–608. doi:10.1016/1074-5521(95)90124-8
50. Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem.–Eur. J.* **1995,** *1,* 454–466. doi:10.1002/chem.19950010711
51. Lampe, J. W.; Biggers, C. K.; Defauw, J. M.; Foglesong, R. J.; Hall, S. E.; Heerding, J. M.; Hollinshead, S. P.; Hu, H.; Hughes, P. F.; Jagdmann, G. E., Jr.; Johnson, M. G.; Lai, Y.-S.; Lowden, C. T.; Lynch, M. P.; Mendoza, J. S.; Murphy, M. M.; Wilson, J. W.; Ballas, L. M.; Carter, K.; Darges, J. W.; Davis, J. E.; Hubbard, F. R.; Stamper, M. L. *J. Med. Chem.* **2002,** *45,* 2624–2643. doi:10.1021/jm020018f
52. Breitenlechner, C. B.; Wegge, T.; Berillon, L.; Graul, K.; Marzenell, K.; Friebe, W.-G.; Thomas, U.; Schumacher, R.; Huber, R.; Engh, R. A.; Masjost, B. *J. Med. Chem.* **2004,** *47,* 1375–1390. doi:10.1021/jm0310479
53. Lai, Y.-S.; Stamper, M. *Bioorg. Med. Chem. Lett.* **1995,** *5,* 2147–2150. doi:10.1016/0960-894X(95)00364-Y
54. Lai, Y.-S.; Menaldino, D. S.; Nichols, J. B.; Jagdmann, G. E., Jr..; Mylott, F.; Gillespie, J.; Hall, S. E. *Bioorg. Med. Chem. Lett.* **1995,** *5,* 2151–2154. doi:10.1016/0960-894X(95)00365-Z
55. Mendoza, J. S.; Jagdmann, G. E., Jr.; Gosnell, P. A. *Bioorg. Med. Chem. Lett.* **1995,** *5,* 2211–2216. doi:10.1016/0960-894X(95)00382-4
56. Crane, H. M.; Menaldino, D. S.; Jagdmann, G. E., Jr.; Darges, J. W.; Buben, J. A. *Bioorg. Med. Chem. Lett.* **1995,** *5,* 2133–2138. doi:10.1016/0960-894X(95)00361-V
57. Defauw, J. M.; Murphy, M. M.; Jagdmann, G. E., Jr.; Hu, H.; Lampe, J. W.; Hollinshead, S. P.; Mitchell, T. J.; Crane, H. M.; Heerding, J. M.; Mendoza, J. S.; Davis, J. E.; Darges, J. W.; Hubbard, F. R.; Hall, S. E. *J. Med. Chem.* **1996,** *39,* 5215–5227. doi:10.1021/jm960581w
58. Hu, H.; Hollinshead, S. P.; Hall, S. E.; Kalter, K.; Ballas, L. M. *Bioorg. Med. Chem. Lett.* **1996,** *6,* 973–978. doi:10.1016/0960-894X(96)00151-5
59. Lai, Y.-S.; Mendoza, J. S.; Jagdmann, G. E., Jr.; Menaldino, D. S.; Biggers, C. K.; Heerding, J. M.; Wilson, J. W.; Hall, S. E.; Jiang, J. B.; Janzen, W. P.; Ballas, L. M. *J. Med. Chem.* **1997,** *40,* 226–235. doi:10.1021/jm960497g
60. Jagdmann, G. E., Jr.; Dafauw, J. M.; Lampe, J. W.; Darges, J. W.; Kalter, K. *Bioorg. Med. Chem. Lett.* **1996,** *6,* 1759–1764. doi:10.1016/0960-894X(96)00311-3
61. Hu, H.; Mendoza, J. S.; Lowden, C. T.; Ballas, L. M.; Janzen, W. P. *Bioorg. Med. Chem.* **1997,** *5,* 1873–1882. doi:10.1016/S0968-0896(97)00125-9
62. Roy, S. P.; Chattopadhyay, S. K. *Tetrahedron Lett.* **2008,** *49,* 5498–5501. doi:10.1016/j.tetlet.2008.07.031
63. Mancuso, A. J.; Swern, D. *Synthesis* **1981,** 165–185. doi:10.1055/s-1981-29377
64. Grubbs, R. H.; Schrock, R. R.; Fürstner, A., Eds. Olefin Metathesis. *Adv. Synth. Catal.* **2007,** *349,* 1–265. doi:10.1002/adsc.200790000
65. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979,** *18,* 707–721. doi:10.1002/anie.197907073
66. Mitsunobu, O. *Synthesis* **1981,** 1–28. doi:10.1055/s-1981-29317

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