Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3185–3188
Tetrahedron Letters

Studies towards the total synthesis of narbonolide: stereoselective preparation of the C1–C10 fragment ☆

C. Prasad Narasimhulu [a,b], Javed Iqbal [a], Khagga Mukkanti [b], Parthasarathi Das [a,*]

[a] Discovery Research, Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500 049, AP, India
[b] Chemistry Division, Institute of Science and Technology, JNT University, Kukatpally, Hyderabad 500 085, AP, India

Received 10 December 2007; revised 15 February 2008; accepted 16 February 2008
Available online 21 February 2008

Abstract

An efficient stereoselective synthesis of the C1–C10 fragment of narbonolide is reported. The stereocentres at C2, 3, 4, 5, 8 and 9 in fragment **5** can be generated via an iterative asymmetric acyl-thiazolidinethione aldol reaction, whereas the stereocentre at C6 is installed by means of Myers alkylation.

Ketolides[1] are a new class of macrolide antibiotics that have been shown to be active against a variety of bacteria including macrolide-resistant bacteria and mycobacteria. Ketolides differ from erythromycin A by harbouring a 3-keto group instead of a L-cladinose group. The 3-ketone modification has imparted this class of compounds with excellent activities against drug resistant bacterial infections especially the clinically important respiratory tract pathogen *Streptococcus pneumoniae*.[2]

The therapeutic promise shown by ketolides has led to a resurgence in macrolide antibiotic research in the pharmaceutical industry,[3] with successful clinical candidates such as telithromycin[4a] (**1**) from Aventis Pharma, and cethromycin (**2**) from Abbott Laboratories[4b,c] (Fig. 1).

Narbonolide **3** is a 14-membered polyketide macrolactone biosynthesized by the pikromycin polyketide synthase (PKS) system of *Streptomyces venezuelae* ATCC 15439.[5] Macrolide **3** consists of seven stereocentres including the sensitive chiral centre at C2. Its significant therapeutic potential, and structural similarity to the macrocytes in

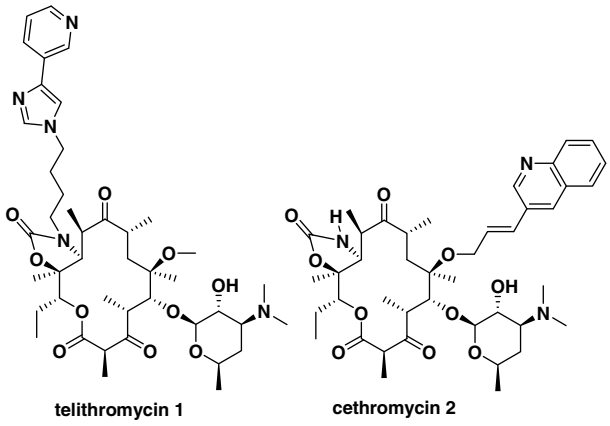


Fig. 1.

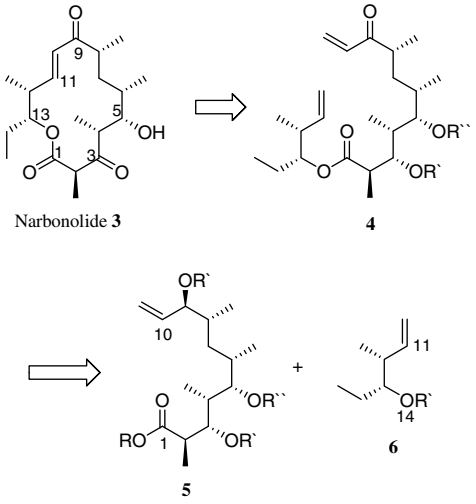
telithromycin and cethromycin have resulted in total syntheses from the groups of Masamune[6a] and Fecik.[6b,c] However, these syntheses have one or more complicating factors such as a low yield of the key macrocyclization reaction, inability to differentiate the C3 and C5 positions for chemoselective reactions and highly optimized protecting group strategies that decrease the synthetic efficiency.

In considering an alternate strategy for the synthesis of narbonolide and its structural analogues, we envisaged that

☆ DRL Publication No. 670.

* Corresponding author. Tel.: +91 40 2304 5439; fax: +91 40 2304 5438.
E-mail addresses: parthasarathi@drreddys.com, parthads@yahoo.com (P. Das).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.099



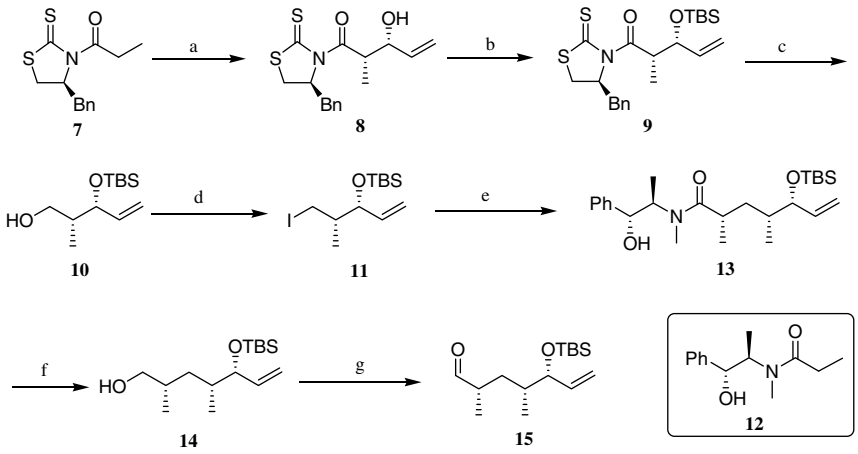
Scheme 1.

the core structure of narbonolide **3** could be constructed via ring closing metathesis of the bis olefin **4**, which in turn could be made via esterification of the C1–C10 fragment **5** and C11–O14 fragment **6**. The stereocentres at C2, 3, 4, 5, 8 and 9 in fragment **5** can be generated via iterative asymmetric acyl-thiazolidinethione aldol reactions, whereas the stereocentre at C6 can be installed by means of Myers alkylation (Scheme 1). Herein, we report the stereoselective synthesis of the C1–C10 fragment of narbonolide.

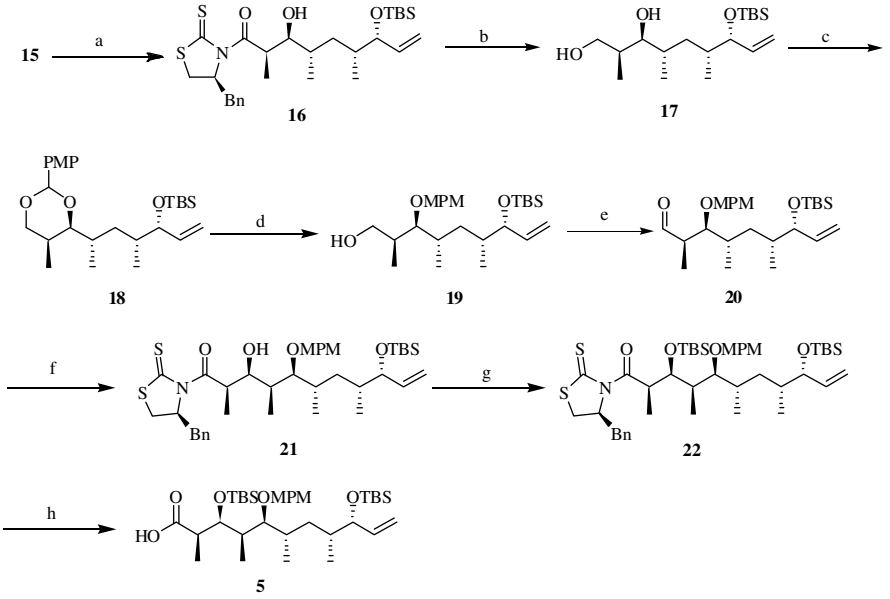
Accordingly, our synthesis began with the aldolization of *N*-propionyl thiazolidinethione[7] **7** with acrolein utilizing the Crimmins protocol[8,9] (titanium mediated enolization using (−)-sparteine (1 equiv) and *N*-methyl-2-pyrrolidinone (1 equiv)) to yield the desired Evans *syn* aldol product **8**[10] in 80% with excellent diastereoselectivity (20:1). Silylation of the aldol product **8** with TBSOTf afforded **9** in good yield. Reductive removal of the chiral auxiliary from thione **9** with $LiBH_4$ and subsequent iodination of the resulting alcohol **10** yielded iodide **11**. Iodide **11** was then subjected to Myers alkylation[11]conditions. Treatment of iodide **11** with (*R*,*R*)-pseudoephedrine propionate **12** at 40 °C proceeded cleanly to furnish amide **13** in 77% yield. Removal of the chiral auxiliary was accomplished with lithium amidotrihydroborate[12] to produce alcohol **14**,[13] which was further oxidized to aldehyde **15**, in the presence of TEMPO and iodosobenzene diacetate (Scheme 2).

Aldolization of aldehyde **15** with *N*-propionyl thiazolidinethione **7** gave the non-Evans *syn* aldol product **16** via the Crimmins protocol (titanium mediated enolization using 1 equiv of diisopropylethylamine as base).[8a] The reaction was readily scalable, providing reproducible results in terms of both yield and diastereoselectivity (20:1). Reductive removal of the thiazolidinethione of **16** with $NaBH_4$ produced diol **17**. The 1,3-diol in **17** was then protected with 4-methoxybenzaldehyde dimethylacetal affording the corresponding acetal **18** which after reductive hydrolysis with DIBAL-H afforded primary alcohol **19** in good yield.[14] The resulting alcohol was oxidized to the corresponding aldehyde **20** and subjected to aldol reaction with thiazolidinethione **7** to give non-Evans *syn* aldol adduct **21** in 83% yield and excellent diastereoselectivity ($\geqslant$96%).[8] The aldol product was silylated to give **22**, which on subsequent oxidative hydrolysis afforded C1–C10 fragment **5**[15] with all the required stereocentres (Scheme 3).

In summary, an efficient route for the synthesis of the C1–C10 fragment of narbonolide has been developed, which features aldol reactions to afford both Evans and non-Evans *syn* aldol products from thiazolidinethione **7**, and Myers alkylation as key steps. Studies towards the total synthesis of narbonolide and its structural analogues for biological studies are currently underway in our laboratory.



Scheme 2. Reagents and conditions: (a) $TiCl_4$, (−)-sparteine, NMP, acrolein, CH_2Cl_2, −78 °C to 0 °C, 80% (20:1); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 85%; (c) $LiBH_4$, Et_2O, H_2O, rt, 76%; (d) PPh_3, I_2, imidazole, Et_2O: CH_3CN (4:1), rt, 79%; (e) **12**, $^iPr_2NH$, *n*-BuLi, THF, 77%; (f) $^iPr_2NH$, *n*-BuLi, BH_3NH_3, THF, 90%; (g) TEMPO, iodosobenzene diacetate, CH_2Cl_2, rt, 95%.



Scheme 3. Reagents and conditions: (a) **7**, $TiCl_4$, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 74% (20:1); (b) $NaBH_4$, EtOH, rt, 81%; (c) $(OMe)_2CHC_6H_4OMe$, CSA, CH_2Cl_2, rt, 92%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 79%; (e) TEMPO, iodosobenzene diacetate, CH_2Cl_2, rt, 95%; (f) **7**, $TiCl_4$, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 83% (24:1); (g) TBSOTf, $^iPr_2NEt$, CH_2Cl_2, 0 °C to rt, 81%; (h) LiOH, 30% H_2O_2, THF:H_2O, 0 °C, 65%.

Acknowledgements

We thank Dr. Reddy's Laboratories Ltd for financial support and encouragement. Help from the analytical department in recording spectral data is appreciated.

References and notes

1. (a) Agouridas, C.; Denis, A.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080; (b) Zhanel, G. G.; Walters, M.; Noreddin, A.; Vercaigne, L. M.; Wierzbowski, A.; Embil, J. M.; Gin, A. S.; Douthwaite, S.; Hoban, D. J. *Drugs* **2002**, *62*, 12.
2. Ma, Z.; Clark, R. F.; Brazzale, A.; Wang, S.; Rupp, M. J.; Li, L.; Griesgraber, G.; Zhang, S.; Yong, H.; Phan, L. T.; Nemoto, P. A.; Chu, D. T. W.; Plattner, J. J.; Zhang, X.; Zhong, P.; Cao, Z.; Nilius, A. M.; Shortridge, V. D.; Flamm, R.; Mitten, M.; Meulbroek, J.; Ewing, P.; Alder, J.; Or, Y. S. *J. Med. Chem.* **2001**, *44*, 4137.
3. Henninger, T. C. *Expert Opin. Ther. Pat.* **2003**, *13*, 787.
4. (a) Denis, A.; Agouridas, C.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N.; Pejac, J.-M.; Perron, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3075; (b) Plata, D. J.; Leanna, M. R.; Rasmussen, M.; McLaughlin, M. A.; Condon, S. L.; Kerdesky, F. A. J.; King, S. A.; Peterson, M. J.; Stoner, E. J.; Wittenberger, S. J. *Cheminform* **2005**, *36*, 10; (c) Henninger, T. C.; Xu, X.; Abbanat, D.; Baum, E. Z.; Foleno, B. D.; Hilliard, J. J.; Bush, K.; Hlasta, D. J.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4495.
5. (a) Hori, T.; Maezawa, I.; Nagahama, N.; Suzuki, M. *J. Chem. Soc., Chem. Commun.* **1971**, 304; (b) Maezawa, I.; Hori, T.; Kinumaki, A.; Suzuki, M. *J. Antibiot.* **1973**, *26*, 771; (c) Xue, Y.; Zhao, L.; Liu, H.-W.; Sherman, D. H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12111; (d) Xue, Y.; Sherman, D. H. *Metall. Eng.* **2001**, *3*, 15.
6. (a) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612; (b) Venkatraman, L.; Aldrich, C. C.; Sherman, D. H.; Fecik, R. A. *J. Org. Chem.* **2005**, *70*, 7267; (c) Venkatraman, L.; Salomon, C. E.; Sherman, D. H.; Fecik, R. A. *J. Org. Chem.* **2006**, *71*, 9853.
7. (a) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418; (b) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391; (c) Romero-Ortega, M.; Colby, D. A.; Olivo, H. F. *Tetrahedron Lett.* **2002**, *43*, 6439.
8. (a) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775; (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894; (c) Crimmins, M. T.; Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128.
9. (a) Sai Baba, V.; Das, P.; Mukkanti, K.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 7927; (b) Nyayavadi, V.; Nanduri, S.; Vasu Dev, R.; Naidu, A.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 6667.
10. (a) Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810; (b) Crimmins, M. T.; Vanier, G. S. *Org. Lett.* **2006**, *8*, 2887.
11. (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361; (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
12. Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.
13. *Spectral data of compound* **14**: $[\alpha]_D^{25}$ +16.4 (*c* 0.50, $CHCl_3$); IR (neat): 3334, 2956, 2927, 1251, 1028, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 5.78$ (ddd, $J = 17.0$, 10.5, 6.5 Hz, 1H), 5.12 (dd, $J = 17.0$, 1.5 Hz, 1H), 5.08 (dd, $J = 10.5$, 1.5 Hz, 1H), 3.96–3.93 (m, 1H), 3.53 (dd, $J = 10.5$, 4.5 Hz, 1H), 3.39 (dd, $J = 10.5$, 6.5 Hz, 1H), 1.75–1.73 (m, 1H), 1.72–1.60 (m, 2H), 1.53–1.48 (m, 2H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.89 (s, 9H), 0.87 (d, $J = 7.0$ Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 139.7$, 114.8, 77.5, 67.8, 37.0, 35.9, 33.1, 25.9, 18.2, 17.9, 15.7, −4.3, −4.9; ESI-MS: *m/z* (%) = 273 (100) $[M+H]^+$; HRMS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{32}O_2SiNa$: 295.2071; found 295.2069.
14. Anderson, J. C.; McDermott, B. P.; Griffin, E. J. *Tetrahedron* **2000**, *56*, 8747.
15. *Spectral data of compound* **5**: $[\alpha]_D^{25}$ +1.6 (*c* 1.00, $CHCl_3$); IR (neat): 2954, 2929, 1707, 1514, 1249, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.26$ (d, $J = 8.5$ Hz, 2H), 6.79 (d, $J = 8.5$ Hz, 2H), 5.74 (ddd, $J = 17.0$, 10.5, 6.5 Hz, 1H), 5.05 (dd, $J = 17.0$, 2.0 Hz, 1H), 5.00

(dd, $J = 10.5$, 1.2 Hz, 1H), 4.47 (d, $J = 11.0$ Hz, 1H), 4.36 (d, $J = 11.0$ Hz, 1H), 4.02–3.99 (m, 1H), 3.90–3.88 (m, 1H), 3.73 (s, 3H), 3.14 (dd, $J = 5.5$, 3.5 Hz, 1H), 2.67 (dd, $J = 7.0$, 3.5 Hz, 1H), 2.02–1.98 (m, 1H), 1.83–1.80 (m, 1H), 1.68–1.61 (m, 4H), 1.13 (d, $J = 7.0$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H), 0.94 (d, $J = 6.5$ Hz, 3H), 0.90 (s, 3H), 0.905 (s, 9H), 0.88 (s, 9H), 0.02 (s, 6H), 0.001 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 179.2$, 159.0, 140.1, 131.1, 129.0, 114.7, 113.6, 83.6, 76.4, 74.9, 73.1, 55.2, 43.0, 39.5, 37.5, 36.2, 33.6, 26.1, 25.9, 23.8, 20.8, 18.3, 16.9, 16.8, 11.2, 10.9, −4.0, −4.1, −4.2, −4.8; ESI-MS: m/z (%) = 659 (100) $[M+Na]^+$, 637 (95) $[M+H]^+$; HRMS (ESI): $[M+H]^+$ calcd for $C_{35}H_{65}O_6Si_2$: 637. 0687; found 637. 0661.