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First stereoselective total synthesis of stagonolide G

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ABSTRACT

First stereoselective total synthesis of nonenolide stagonolide G involving a convergent strategy is described. The key reactions include Keck allylation and Grubbs ring closing metathesis reaction.

During recent years secondary metabolites are attaining significant interest due to their potent biological properties.[1] Ten-membered ring containing macrolide nonenolides, stagonolides A-I, and modiolides A and B (Fig. 1)[2] are the recent examples which have been isolated very frequently in both liquid and solid cultures of Stagonospora cirsii Davis, a fungal pathogen isolated from Cisium arvense. As these natural products are available in scarce amounts, only a few compounds have been investigated for the biological activities. While stagonolide A was found to be phytotoxic[2a] stagonolide F was found to display both anti-fungal and anti bacterial activities.[2b] Intrigued by the biological properties of these macrolides, we became interested in taking up the total synthesis of these nonenolides. In continuation to our work on the synthesis of lactone containing natural products,[3] recently we have accomplished the total synthesis of stagonolide A[3a] and stagonolide B.[3b] Herein, we report the first stereoselective total synthesis of stagonolide G using a convergent approach.

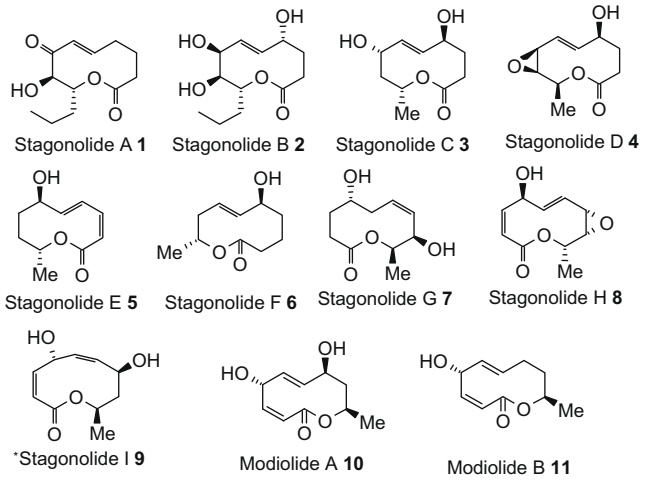
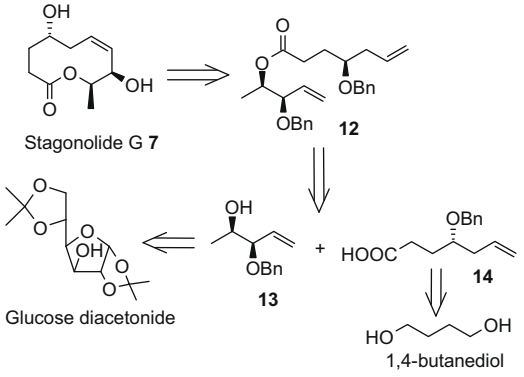


Figure 1.

Retrosynthetically, we envisaged that the target molecule can be obtained from the ester **12** with two terminal olefin moieties by a ring closing metathesis followed by di-debenzylation. The ester **12** in turn is obtained by a coupling/esterification of two key fragments, alcohol **13** and an acid **14** (Scheme 1). While the acid is obtained from commercially available 1,4-butanediol, the alcohol **13** with two stereocenters can be obtained from D-glucose diacetonide involving a chiron pool approach.

Accordingly, we began our synthesis with the protection of the D-glucose diacetonide with benzyl bromide and NaH to provide the corresponding benzyl ether **15**. Compound **15** on selective acetonide deprotection gave the diol **16**. Sequential oxidative cleavage of the diol with $NaIO_4$ followed by reduction with $NaBH_4$ provided alcohol **17**. The primary alcohol was converted to tosylate and reduced with $LiAlH_4$ to give compound **18**. The compound **18** was treated with catalytic amount of con.H_2SO_4 to result in lactol **19**,



Scheme 1. Retrosynthesis.

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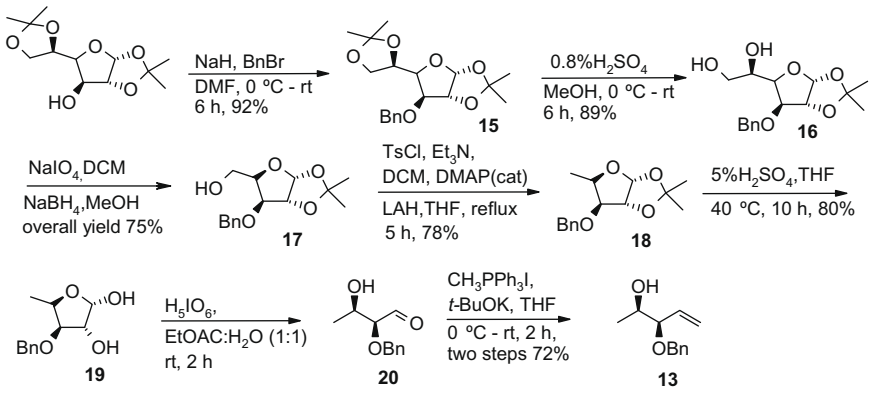


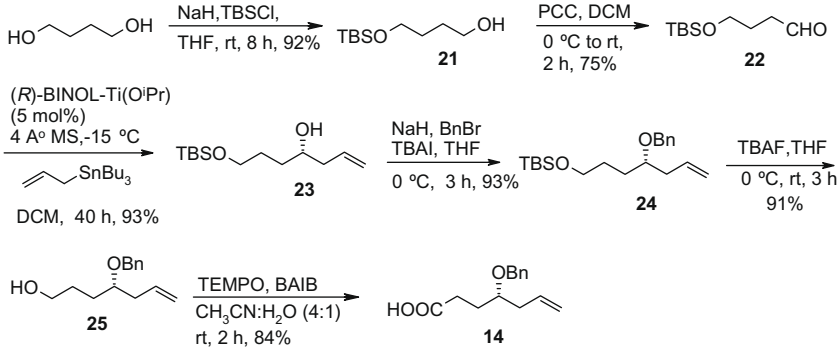
Scheme 2. Synthesis of alcohol.

which was treated with periodic acid to yield the aldehyde **20**. The aldehyde was subjected to one carbon Wittig reaction with methyltriphenylphosphonium iodide in the presence of potassium *tert*-butoxide to yield the key fragment olefinic alcohol **13** (Scheme 2).

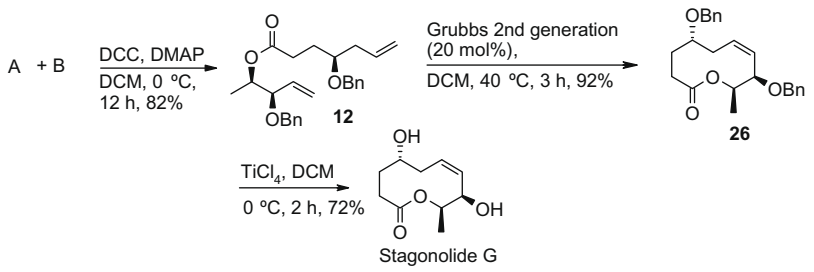
The other key fragment acid **14** was synthesized starting from 1,4-butanediol. Accordingly, 1,4-butanediol was selectively monoprotected as the corresponding TBS ether **21** and the free primary alcohol was converted to aldehyde **22** by PCC oxidation. The aldehyde on Keck allylation[4] provided chiral homoallyl alcohol **23** in 93% yield with 97%ee. The resulting chiral secondary alcohol was protected as the corresponding benzyl ether **24** with NaH and benzyl bromide and then treated with TBAF to yield the free primary alcohol **25** (Scheme 3). Oxidation of the primary alcohol with BAIB and TEMPO yielded the corresponding acid **14**.[5]

With the two intermediates in hand, the stages were set for coupling them together and proceed further for ring closing metathesis reaction. Thus, the acid **14** and the alcohol **13** were coupled together using DCC and DMAP to yield the corresponding ester **12**. When the compound **12** was exposed to Grubbs' 2nd generation catalyst for 3 h at 40 °C in dichloromethane, we were gratified to observe the formation of the desired *Z* isomer exclusively as a single product **26** (Scheme 4).[6] Finally, deprotection of the two benzyl moieties with $TiCl_4$ afforded the target molecule stagonolide G.[7] The spectroscopic data were compared with those of the natural product reported earlier and were found to be similar[2c] in all respects but with a variation in optical rotation.

In conclusion, we have accomplished the total synthesis of stagonolide G following a convergent approach involving chiron pool synthesis. Keck allylation and Grubbs' olefin metathesis reactions are the other key steps utilized for the target synthesis. The synthesis of other stagonolide members and their analogues is currently being investigated for their utility toward biological evaluation.



Scheme 3. Synthesis of acid.



Scheme 4. Synthesis of stagonolide G.

Acknowledgment

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References and notes

1. (a) Arif, T.; Bhosale, J. D.; Kumar, N.; Mandal, T. K.; Bendre, R. S.; Lavekar, G. S.; Dabur, R. *J. Asian Nat. Prod.* **2009**, *11*, 621–638; (b) Piel, J. *Nat. Prod. Rep.* **2009**, *26*, 338–362; (c) Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290–2303; (d) Lu, X.-L.; Xu, Q.-Z.; Liu, X.-Y.; Cao, X.; Ni, K.-Y.; Jiao, B.-H. *Chem. Biodiversity* **2008**, *5*, 1669–1674; (e) Itokawa, H.; Morris-Natschke, S. L.; Akiyama, T.; Lee, K.-H. *J. Nat. Med.* **2008**, *62*, 263–280; (f) Wen, Z.; Guo, Y.-W.; Yucheng, G. *Curr. Med. Chem.* **2006**, *43*, 303–332; (g) Croteau, R.; Kutchan, T. M.; Lewis, N. G. *Natural Products (Secondary Metabolites); Biochemistry and Molecular Biology of Plants*; Rockville: Maryland, 2000. pp 1250–1318; (h) Pietra, F. *Nat. Prod. Rep.* **1997**, 453–464.
2. For isolation of stagonolides: (a) Oleg, Y.; Galin, M.; Alexander, B. *J. Agric. Food Chem.* **2007**, *55*, 7707–7711; (b) Antonio, E.; Alessio, C.; Alexander, B.; Galina, M.; Anna, A.; Andera, M. *J. Nat. Prod.* **2008**, *71*, 31–34; (c) Antonio, E.; Alessio, C.; Alexander, B.; Galina, M.; Anna, A.; Andera, M. *J. Nat. Prod.* **2008**, *71*, 1897–1901; For isolation of modiolides: (d) Tsuda, M.; Mugishima, T.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, J. *J. Nat. Prod.* **2003**, *66*, 412–415.
3. For our recent contributions on lactone containing molecules see: (a) Srihari, P.; Kumaraswamy, B.; Maheswara Rao, G.; Yadav, J. S. *Tetrahedron: Asymmetry* **2010**, *21*, 106–111; (b) Srihari, P.; Kumaraswamy, B.; Somaiah, R.; Yadav, J. S. *Synthesis* **2010**, 1039–1045; (c) Srihari, P.; Vijaya Bhasker, E.; Bal Reddy, A.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 2420–2424; (d) Srihari, P.; Rajendar, G.; Srinivasa Rao, R.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 5590–5592; (e) Yadav, J. S.; Kumar, V. N.; Rao, R. S.; Srihari, P. *Synthesis* **2008**, 1938–1942; (f) Srihari, P.; Kumar, B. P.; Subbarayudu, K.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 6977–6981; (g) Srihari, P.; Bhasker, E. V.; Harshavardhan, S. J.; Yadav, J. S. *Synthesis* **2006**, 4041–4045.
4. Kurosu, M.; Miguel, L. *Synlett* **2005**, 1109–1112.
5. Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295.
6. LCMS analysis of the crude reaction mixture showed the presence of single isomer. ^{1}H NMR analysis revealed the presence of *cis* isomer with the coupling constant value of 11.3 Hz for olefinic protons.
7. *Spectroscopic data for representative examples*: Compound **13**: Yellowish liquid; $[\alpha]_D^{25} = -48.5$ (*c* 1.6, $CHCl_3$); IR (neat): 3448, 2929, 1731, 1453, 1250, 1065, 3029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (d, *J* = 6.8 Hz, 3H), 2.65 (br s, 1H), 3.48 (t, *J* = 7.5 Hz, 1H), 3.65 (m, 1H), 4.47 (ABq, *J* = 12.1 Hz, 2H), 5.28–5.38 (m, 2H), 5.63–5.76 (m, 1H) 7.21–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 69.5, 70.3, 85.9, 120.2, 127.6, 127.8, 128.3, 135.1, 137.9; ESIMS: *m*/*z* 215 (M+Na)$^+$; HRMS for $C_{12}H_{17}O_2$: calcd, 193.1223, found: 193.1214. Compound **14**: Yellowish liquid; $[\alpha]_D^{25} = -28$ (*c* 2.2, $CHCl_3$); IR (neat): 3069, 3031, 2926, 2860, 1705, 1445, 1415, 1208, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.74–1.83 (m, 1H), 1.84–1.95 (m, 1H), 2.24–2.34 (m, 1H), 2.34–2.48 (m, 3H), 3.45–3.54 (m, 1H), 4.51 (ABq, *J* = 11.1 Hz, 2H), 5.04–5.12 (m, 2H), 5.75–5.86 (m, 1H), 7.2–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 30.0, 37.9, 70.9, 77.1, 117.4, 127.5, 127.7, 128.2, 134.1, 138.2, 179.7; ESIMS: *m*/*z* 257 (M+Na)$^+$; HRMS for $C_{14}H_{18}O_3$: calcd 257.1153; found: 257.1156. Stagonolide G **7**: Sticky liquid; $[\alpha]_D^{28} = +7$ (*c* 0.3, $CHCl_3$), Lit.[2c] $[\alpha]_D^{25} = +96$ (*c* 0.1, $CHCl_3$); IR (neat): 3399, 2924, 2855, 1761, 1422, 1180, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.15 (d, *J* = 6.0 Hz, 3H), 1.90–2.10 (m, 1H), 2.29–2.71 (m, 5H), 3.67–3.72 (m, 1H), 4.07–4.15 (m, 1H), 4.50–4.61 (m, 1H), 5.56–5.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6, 27.5, 28.7, 33.7, 70.8, 72.2, 79.6, 127.8, 132.5, 177.0; ESIMS: *m*/*z* 223 (M+Na)$^+$; HRMS for $C_{10}H_{16}NaO_4$: calcd 223.0970; found: 223.0962.