Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
ELSEVIER
Bioorganic & Medicinal Chemistry Letters 14 (2004) 1905–1908

Synthesis and evaluation of lasonolide A analogues

Jung Min Joo, Hyo Shin Kwak, Jin Hyun Park, Ho Young Song and Eun Lee*

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-747, South Korea

Received 16 December 2003; revised 27 January 2004; accepted 28 January 2004

Abstract—Homolasonolide A and 10-desmethyllasonolide A are biologically less active than lasonolide A. The ethyl ester analogue of lasonolide A exhibited higher activity than the parent compound in some biological test.

The structure of lasonolide A originally put forward[1] was in error, and the correct structure turned out to be the (17*E*,25*Z*)-isomer.[2] In addition, the (−)-enantiomer (**1**) was found to be much more active than the (+)-enantiomer providing compelling evidence that (−)-lasonolide A is the natural product.[3,4] In view of the high cytotoxicity against some tumor cell lines,[1] we were interested to prepare analogues of **1** for screening tests. Homolasonolide A (**2**) was our first candidate, because synthesis of this homologue requires omission of several steps from the original scheme for **1**. 10-Desmethyllasonolide A (**3**) was also an interesting candidate, because it incorporated minimum perturbation of the original structure. We were also interested to test ester analogues **4** and **5** as they would yield information on the side chain requirements (Fig. 1).

Acetonide protection of the known diol **6**[4] and subsequent debenzylation and oxidation provided the aldehyde **7**. Kocienski–Julia reaction[5] of the sulfone **8** and the aldehyde **7** proceeded smoothly, and the product (*E*)-olefin was converted into a second sulfone **10** via TBDPS-deprotection, Mitsunobu-type substitution of the hydroxy group with the sulfide **9**, and selective oxidation (Scheme 1). Reaction of the known aldehyde **11**[4] with **10** accomplished the crucial connection of the two components by forming another *trans* double bond, and the product was converted into the macrolide **13** via acetonide-deprotection, selective TBS-protection of the primary hydroxy group, esterification with the acid **12**,

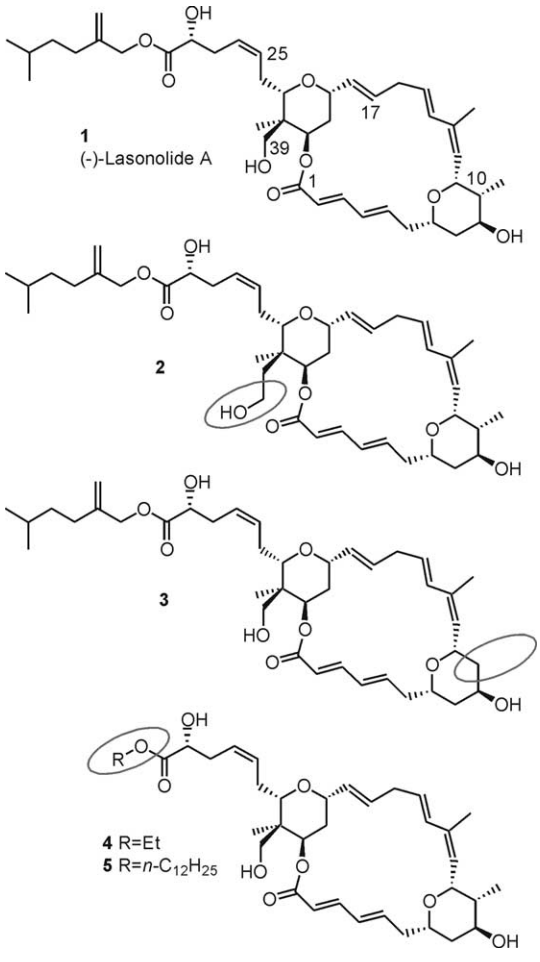
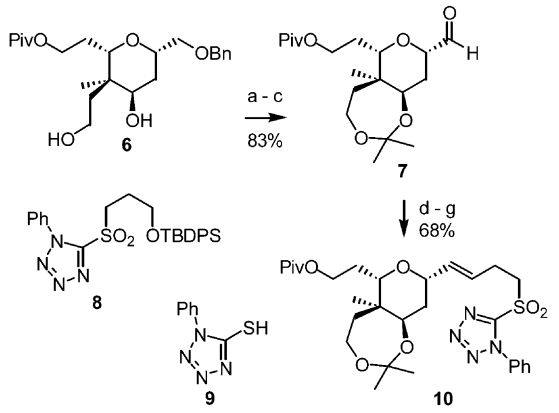


Figure 1. Lasonolide A and analogues.

* Corresponding author. Tel.: +82-2-880-6646; fax: +82-2-889-1568; e-mail: eunlee@snu.ac.kr

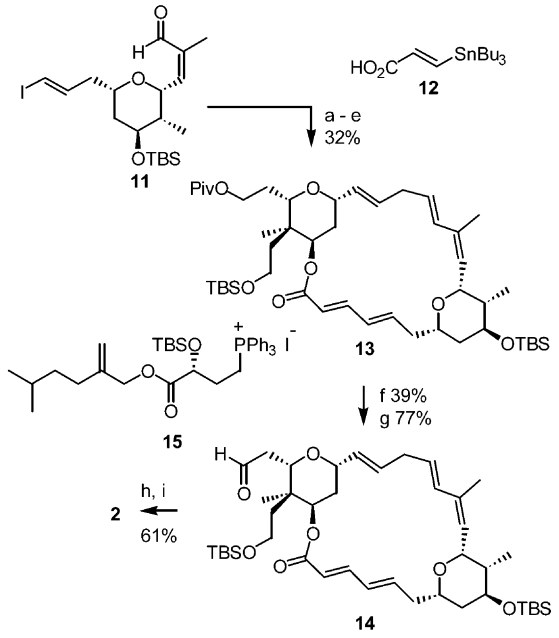
0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.01.088



Scheme 1. (a) $Me_2C(OMe)_2$, CSA, acetone; (b) H_2, $Pd(OH)_2/C$, MeOH; (c) SO_3·pyridine, TEA, DMSO–DCM (1:1), 0 °C; (d) **8**, LiHMDS, DMF–HMPA (4:1), −35 °C; **7**, −35 °C–rt; (e) TBAF, THF; (f) **9**, DIAD, Ph_3P, THF, 0 °C; (g) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0 °C–rt.

and intramolecular Stille coupling reaction. Selective reduction of the pivaloate group and oxidation provided the macrolide aldehyde **14**, which was converted into **2** via reaction with the ylide from the phosphonium salt **15**[4] and global TBS-deprotection (Scheme 2).

Synthesis of 10-desmethyllasonolide A (**3**) was initiated by conversion of the known ester **16**[4] into the enone **17** via vinyl Grignard reaction of the corresponding Weinreb amide. *Syn* reduction[6] of the enone **17**, benzylidene acetal formation, regioselective DIBAL reduction, cleavage of the double bond, sodium borohydride reduction, and TBS-protection of the primary hydroxy group led to the intermediate **18**. The β-alkoxyacrylate **19** was

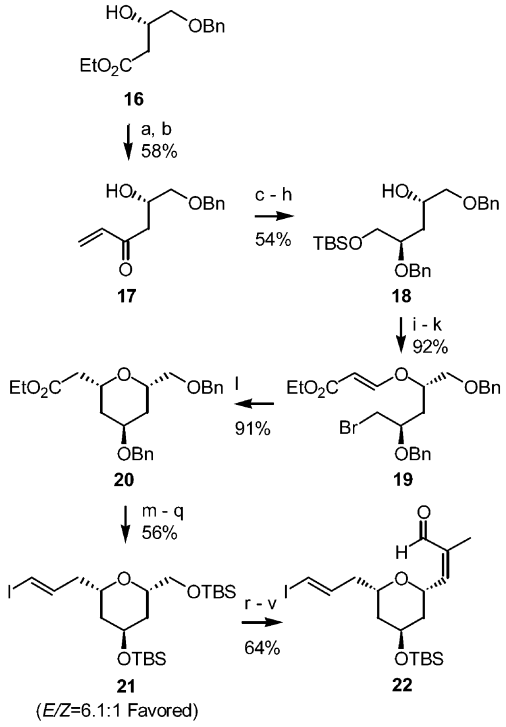


Scheme 2. (a) **10**, LiHMDS, THF, −78 °C; **11**, −78 °C–rt; (b) CSA, $(HOCH_2)_2$, MeOH; (c) TBSCl, imidazole, DCM; (d) **12**, DIC, DMAP, DCM; (e) Pd_2dba_3, DIPEA, $Ph_2PO_2NBu_4$, DMF; (f) $LiEt_3BH$, THF, −78 °C, (s.m. 35%); (g) SO_3·pyridine, TEA, DMSO–DCM (1:1), 0 °C; (h) **15**, KHMDS, THF, −78 °C; **14**, −78 °C–rt; (i) HF·pyridine, pyridine, THF.

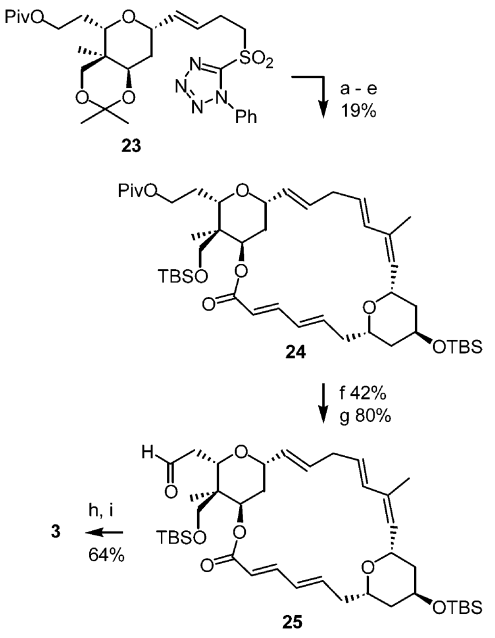
prepared from **18** via reaction with ethyl propiolate, TBS-deprotection, and bromide substitution. Radical cyclization of **19** in the presence of tris(trimethylsilyl)-silane and AIBN in hot benzene proceeded smoothly to yield the tetrahydropyran **20**.[7] Debenzylation via hydrogenolysis, TBS-protection of the hydroxy groups, lithium borohydride reduction of the ester functionality, and oxidation provided the corresponding aldehyde, which was converted into the vinyl iodide **21** via Takai protocol.[8] Selective TBS-deprotection, oxidation, and olefination under Still–Gennari conditions[9] provided the corresponding (*Z*)-enoate, which was converted into the enal **22** via reduction and oxidation (Scheme 3).

Kocienski–Julia reaction of the aldehyde **22** with the known sulfone **23**[4] provided a new triene, which was converted into the macrolide **24** via a 4-step sequence as employed in the preparation of **13**. The macrolide aldehyde **25** was prepared following the known reaction protocol, and **3** was finally obtained from **25** via Wittig reaction and TBS-deprotection (Scheme 4).

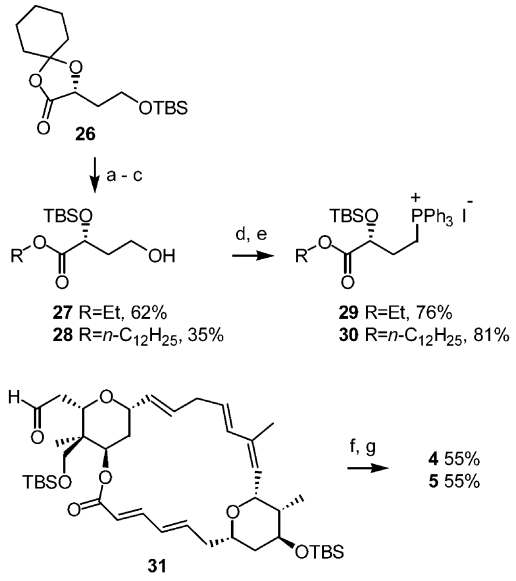
Synthesis of the ester analogues **4**/**5** utilized the known acetal lactone **26**,[4] which was reacted with ethanol and *n*-dodecanol to yield the primary alcohols **27**/**28** after TBS-protection and -deprotection. The phosphonium salts **29**/**30** obtained from **27**/**28** were employed in the



Scheme 3. (a) MeNH(OMe)·HCl, Me_3Al, THF; (b) $H_2CCHMgBr$, THF; (c) Et_3B, $NaBH_4$, THF–MeOH (4:1), −78 °C; (d) $PhCH(OMe)_2$, CSA, DCM; (e) DIBAL, DCM; (f) OsO_4, NMO, acetone–H_2O (3:1); $NaIO_4$; (g) $NaBH_4$, EtOH, 0 °C; (h) TBSCl, imidazole, DCM, 0 °C; (i) $HCCCO_2Et$, NMM, MeCN; (j) HCl, MeOH, 0 °C; (k) CBr_4, Ph_3P, pyridine, DCM; (l) $(TMS)_3SiH$, AIBN, benzene, reflux; (m) H_2, Pd/C, MeOH; (n) TBSOTf, 2,6-lutidine, DCM; (o) $LiBH_4$, ether; (p) SO_3·pyridine, TEA, DMSO–DCM (1:1), 0 °C; (q) $CrCl_2$, CHI_3, dioxane–THF (6:1); (r) CSA, MeOH; (s) SO_3·pyridine, TEA, DMSO–DCM (1:1), 0 °C; (t) $MeO_2C(Me)CHPO(OCH_2CF_3)_2$, KHMDS, 18-c-6, THF, −78 °C; (u) DIBAL, DCM, −78 °C; (v) MnO_2, DCM.



Scheme 4. (a) LiHMDS, THF, −78 °C; **22**, −78 °C–rt; (b) CSA, $(HOCH_2)_2$, MeOH, (s.m. 25%); (c) TBSCl, imidazole, DCM; (d) **12**, DIC, DMAP, DCM; (e) Pd_2dba_3, DIPEA, $Ph_2PO_2NBu_4$, DMF; (f) $LiEt_3BH$, THF, −78 °C, (s.m. 9%); (g) SO_3·pyridine, TEA, DMSO–DCM (1:1), 0 °C; (h) **15**, KHMDS, THF, −78 °C; **25**, −78 °C–rt; (i) HF·pyridine, pyridine, THF.



Scheme 5. (a) NaHMDS, EtOH, 0 °C or n-$C_{12}H_{25}OH$, NaHMDS, THF; (b) TBSCl, imidazole, DMAP, DCM; (c) HF·pyridine, pyridine, THF, 0 °C; (d) Ph_3P, I_2, imidazole, THF; (e) Ph_3P, MeCN, reflux; (f) **29** or **30**, KHMDS, THF, −78 °C; **31**, −78 °C–rt; (g) HF·pyridine, pyridine, THF.

reaction with the known macrolide aldehyde **31** to yield the ester analogues **4**/**5** (Scheme 5).

The samples prepared were subjected to cytotoxicity test.[10] Homolasonolide A (**2**) displayed much lower activity than that of lasonolide A (**1**). It appears that the position of the hydroxy functionality at C39 is quite important for the bioactivity. Surprisingly, 10-desmethyllasonolide A (**3**) also exhibited relatively low cytotoxicity against the three cell lines than expected. The bioactivity of the *n*-dodecanyl ester **5** was low, but the cytotoxicity of the ethyl ester **4** against the A549 cell line was actually higher than that of **1** (Table 1).

Table 1. GI_{50} (μM) values for lasonolide A and analogues against selected cell lines

Compd	A549	HCT-116	NCI-H460
1	0.015	0.003	<0.003
2	0.800	1.800	1.000
3	0.100	0.045	0.065
4	0.007	0.100	0.015
5	0.390	0.190	0.170

Acknowledgements

The authors thank the Ministry of Science and Technology, Republic of Korea, and KISTEP for a National Research Laboratory grant (1999). Brain Korea 21 graduate fellowship grants to H. S. Kwak and J. H. Park are gratefully acknowledged. The authors also thank Dr. ShinWu Jeong, and Mr. Ji Hyun Park of LG Life Science/R&D for the biological assay.

References and notes

1. Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015.
2. Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384.
3. Lee, E.; Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Hong, C. Y.; Jeong, S.; Jeon, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3519.
4. Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080.
5. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
6. Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923.
7. (a) For selected examples of β-alkoxyacrylate radical cyclizations, see: Lee, E.; Choi, S. J.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 176. (b) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655. (c) For further references, see: Lee, E. In *Radicals in Organic Synthesis, Vol. 2: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; p 303.
8. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
9. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
10. Experimental details are given in the ref 3.
^{13}C NMR (75.5 MHz, $CDCl_3$) and optical rotation data for the analogues:
2: δ 174.0, 167.4, 146.3, 143.8, 143.7, 138.7, 134.6, 131.4, 129.5, 129.4, 129.3, 128.8, 125.9, 124.6, 120.0, 112.4, 80.7, 77.2, 74.7, 72.7, 70.8, 70.3, 68.9, 67.6, 58.5, 39.4, 39.0, 38.4, 37.9, 37.8, 36.7, 34.3, 33.6, 32.6, 31.1, 27.8, 27.6, 22.5, 21.0, 17.0, 11.4; $[\alpha]_D^{24}$ −8.6 (*c* 0.38, $CDCl_3$).

3: δ 174.0, 168.5, 148.4, 145.1, 143.7, 138.5, 134.4, 130.9, 129.7, 129.1, 128.9, 128.8, 127.9, 125.2, 118.2, 112.4, 77.8, 77.2, 74.4, 71.3, 70.3, 67.6, 66.8, 65.6, 64.5, 41.3, 38.9, 38.3, 38.2, 36.6, 34.8, 33.4, 32.5, 31.0, 28.0, 27.7, 22.5, 20.8, 15.2; $[\alpha]_D^{18}$ −25.2 (*c* 0.41, $CDCl_3$).

4: δ 174.3, 168.6, 148.4, 145.1, 139.0, 134.3, 130.8, 129.7, 129.1, 129.0, 128.9, 125.1, 124.5, 118.2, 77.9, 77.2, 74.6, 72.4, 70.7, 70.2, 68.9, 65.6, 61.5, 41.2, 38.5, 38.3, 35.0, 33.7, 33.7, 32.5, 28.0, 21.1, 15.2, 14.2, 11.4; $[\alpha]_D^{13}$ −72.0 (*c* 0.30, $CDCl_3$).

5: δ 174.4, 168.6, 148.4, 145.1, 138.9, 134.2, 130.8, 129.7, 129.1, 129.0, 128.9, 125.1, 124.5, 118.3, 78.0, 77.2, 74.7, 72.4, 70.7, 70.2, 68.9, 65.6, 41.2, 38.5, 38.3, 35.0, 33.8, 33.7, 32.5, 31.9, 29.6, 29.6, 29.5, 29.3, 29.2, 28.6, 28.0, 25.8, 22.7, 21.1, 15.2, 14.1, 11.4; $[\alpha]_D^{20}$ −33.2 (*c* 0.39, $CDCl_3$).