Tetrahedron Letters 55 (2014) 6903–6906

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Studies toward asymmetric synthesis of leiodelide A

Rong-Guo Ren, Ming Li, Chang-Mei Si, Zhuo-Ya Mao, Bang-Guo Wei *

Department of Chemistry and Institutes of Biomedical Sciences, Fudan University, 220 Handan Road, Shanghai 200433, China

ARTICLE INFO

Article history:
Received 9 September 2014
Revised 9 October 2014
Accepted 17 October 2014
Available online 23 October 2014

Keywords:
Natural product
Macrolide
Asymmetric synthesis
Oxazole
Leiodelide

ABSTRACT

An enantioselective route for oxazoline **4**, a key fragment toward the asymmetric synthesis of leiodelide A, is described. We synthesized northern subunit **6** through a Julia–Lythgoe olefination and subsequent Sharpless asymmetric dihydroxylation. Moreover, a highly diastereoselective method using well-established Evans' asymmetric aldol condensation was developed for preparation of southern fragment **5**. The additional feature of this synthetic route is the formation of oxazoline **4** through DAST-promoted cyclization of the amidation product from subunits **5** and **6**.

Introduction

Leiodelides A and B (**1** and **2**) were isolated from the marine sponge Leiodermatium at a depth of 740 feet in Palau by Fenical and co-workers in 2006 (Fig. 1).[1] Based on the spectroscopic analysis, chemical modification, and degradation, the structures of leiodelides A and B were determined to be an oxazole-containing 19-membered macrolides bearing a 10-carbon side chain with a carboxylic acid terminus similar to that of okadaic acid.[2] Most stereo centers of the two metabolites were assigned based on detailed interpretation of spectroscopic data, as well as chemical degradation and application of the modified Mosher ester method. However, the configuration of C13 remains to be unassigned. Both compounds exhibit significant cytotoxic activity against HCT-116 human colon carcinoma, with IC_{50} values of 1.4 μg/mL (2.5 μM) and 3.8 μg/mL (5.6 μM), respectively. Moreover, leiodelide A shows significant cytotoxic activity against HL-60 leukemia (GI_{50} = 0.26 μM), NCI-H522 non-small cell lung cancer (GI_{50} = 0.26 μM), and OVCAR-3 ovarian cancer (GI_{50} = 0.25 μM) cell lines.[1]

Due to the limited supply from nature, as well as their significant biological activities and intriguing structures, leiodelides A and B (**1** and **2**) have attracted great attention of many chemists.[3] The first total synthesis of leiodelide B was accomplished by Fürstner and co-workers,[3a] and two other groups finished the fragments of leiodelide A.[3b,c] Unfortunately, the spectroscopic data of synthetic leiodelide B and its three diastereomers were not identical to the reported data of natural leiodelide B.[3a] As one part of our continuous interests in pursuing some divergent synthesis of alkaloids,[4] and depsipeptides,[5] herein we present an asymmetric synthetic method for the C1–22 fragment of leiodelide A.

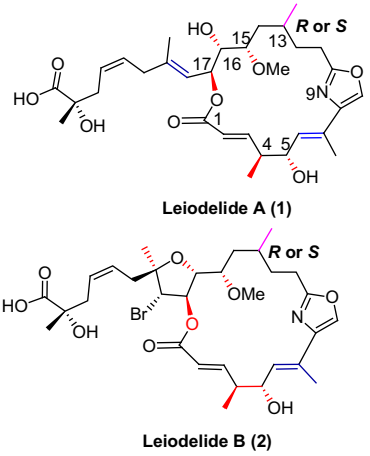
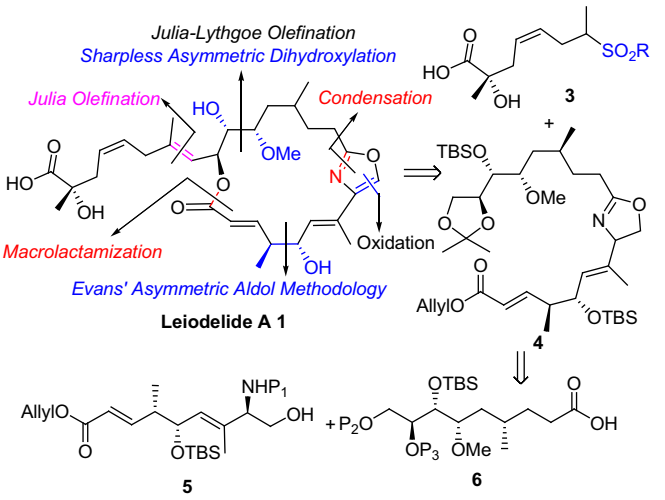


Figure 1. Structures of leiodelides A and B.

Our synthetic strategy for leiodelide A (**1**) is illustrated in Scheme 1, in which the side chain could be introduced by Julia olefination[3b,6] between C23 and C24, and the macrolactonization could be conducted by esterification between C1 and C17. Retrosynthetic analysis led to two key fragments **3** and **4**. We envisioned that the oxazole ring in fragment **4** could be formed by amidation of northern subunit **6** to α,β-unsaturated ester **5** and subsequent

* Corresponding author. Tel./fax: +86 21 54237757.
E-mail address: bgw1974@fudan.edu.cn (B.-G. Wei).

http://dx.doi.org/10.1016/j.tetlet.2014.10.102
0040-4039/



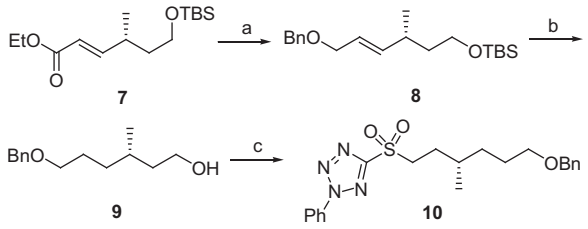
Scheme 1. Retrosynthetic analysis of leiodelides A (**1**).

oxidation–cyclization or dehydrative cyclization–oxidation between C8 and C9.[7] In addition, the stereogenic centers at C15 and C16 of northern subunit **6** could be generated through Sharpless asymmetric dihydroxylation (SAD),[8] and the *R* or *S* stereogenic center of C13 could be achieved by stereo-controlled methylation using Evans' auxiliary.[9]

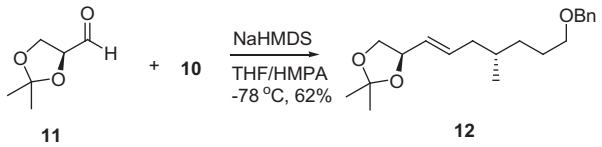
Results and discussion

As shown in Scheme 2, the ester **7**, prepared by known method,[10] was reduced with diisobutyl aluminum hydride (DIBAL-H)[11] and the resulting alcohol was treated with benzyl bromide (BnBr) to give the corresponding ether **8** in 74% overall yield. Removal of the TBS group in **8** with camphor sulfonic acid (CSA) and subsequent reduction with $NaBH_4$ in the presence of $NiCl_6{\cdot}H_2O$[12] afforded the alcohol **9** {$[\alpha]_D^{25}$ −5.1 (*c* 1.41); lit.[13] $[\alpha]_D^{25}$ −5.3 (*c* 1.0)} in 78% overall yield. Further conversion of the alcohol **9** to sulfone **10** was achieved through the Mitsunobu protocol (PT-SH, DIAD, PPh_3)[14] and subsequent oxidation using 3-chloroperbenzoic acid (*m*-CPBA)[15] in 79% overall yield.

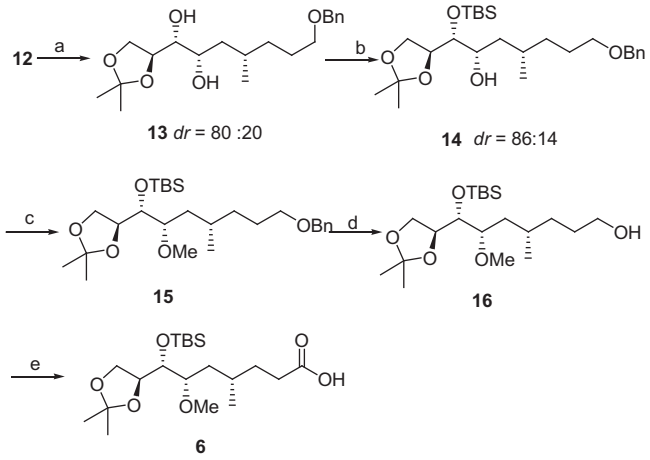
The formation of olefin **12** involved the coupling of sulfone **10** with aldehyde **11** using Julia–Lythgoe protocol.[6,16] Initially, the sulfone **10** was treated with LiHMDS,[17] followed by the addition of aldehyde **11** in THF. To our disappointment, the desired olefination product **12** was not produced at all while the sulfone substrate **10** was decomposed (Scheme 3). Interestingly, when the base was switched to KHMDS,[18] the desired coupling product could be isolated, despite in low yield and poor selectivity. We screened several conditions, and the predominant *E* isomer could be produced in 62% yield when a mixture of sulfone **10** and aldehyde **11** was



Scheme 2. Preparation of sulfone **10**. Reagents and conditions: (a) (i) DIBAL-H, toluene, −78 °C; (ii) NaH, BnBr, THF, 0 °C, 74% (two steps). (b) (i) CSA, MeOH, rt; (ii) $NiCl_2{\cdot}6H_2O$, MeOH, $NaBH_4$, 0 °C, 78% (two steps). (c) (i) DIAD, PPh_3, 1-phenyl-1*H*-tetrazole-5-thiol, 0 °C to rt; (ii) *m*-CPBA, DCM, rt, 79% (two steps).



Scheme 3. Preparation of olefin **12**.

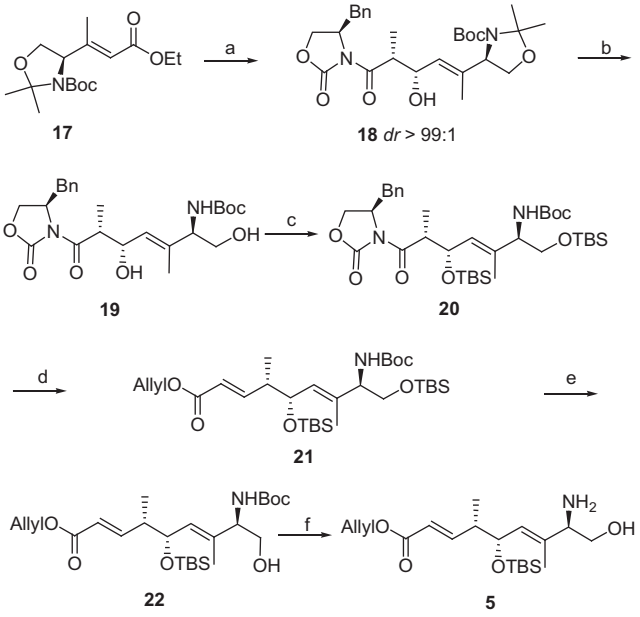


Scheme 4. Preparation of northern subunit **6.** Reagents and conditions: (a) AD-mix-α, K_2CO_3, $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 0 °C to rt, 85%; (b) TBSCl, imidazole, DMAP, DMF, rt, 71%; (c) NaH, CH_3I, DMF, 0 °C, 72%; (d) H_2/Pd/C-Pd(OH)$_2$/C, MeOH, rt, 90%; (e) (i) $(COCl)_2$, DMSO, TEA, DCM, −78 °C; (ii) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH, 2-methylbut-2-ene, 0 °C, 80% (two steps).

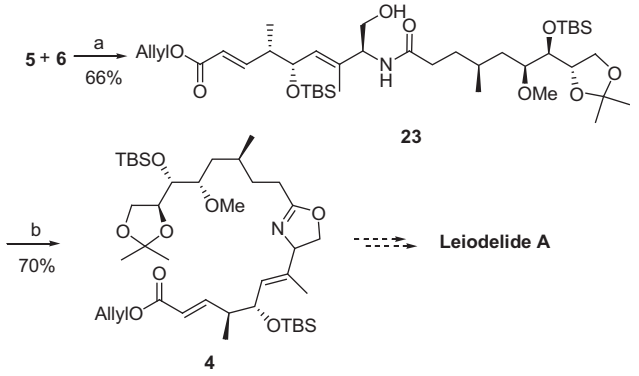
treated with a solution of NaHMDS[19] in dry tetrahydrofuran and hexamethylphosphoramide (THF/HMPA = 4:1) at −78 °C.

With olefin **12** in hand, we turned our attention to synthesize the northern subunit **6** (Scheme 4). First, Sharpless asymmetric dihydroxylation (AD-mix-α, $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$)[8,20] of **12** generated chiral diol **13** with 80:20 diastereoselectivity in 85% combined yield. Separation of the two diastereomers was found to be difficult at diol stage using flash chromatography on silica gel, fortunately, they were readily separated after the selective protection (TBSCl, imidazole). The desired silyl ether **14** was obtained with moderate chemical selectivity (dr = 6:1) in 71% combined yield. Methylation[21] (MeI, NaH) of **14** generated the ether **15** in 72% yield. Debenzylation of **15** using hydrogenation (10% Pd/C) led to the corresponding alcohol **16** in 90% yield. Finally, the desired northern subunit **6** was obtained after Swern oxidation [$(COCl)_2$/DMSO] and subsequent Pinnick oxidation ($NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$)[22] in 80% overall yield.

The synthesis of fragment **5** was shown in Scheme 5. Reduction (DIBAL-H) of the known ester **17**[23] and subsequent oxidation with Swern oxidation generated aldehyde in 78% yield, which was subjected to asymmetric aldol condensation[9b] to afford the desired *syn*-product **18** with high diastereoselectivity (dr >99:1) in 85% yield. Removal of the protective group of **18** in a mixture of acetic acid and water (4:1) led to the diol **19** in 62% yield, and subsequent protection (TBSCl, imidazole) of both hydroxyl groups in **19** afforded **20** in 90% yield. The compound **20** was reduced by lithium borohydride ($LiBH_4$) to obtain the alcohol, which was then converted to aldehyde through Dess–Martin oxidation[24] in 60% overall yield. The aldehyde was subjected to Wittig reaction, generating *trans*-α,β-unsaturated ester **21** in 80% isolated yield. Finally, selective desilylation of **21** with camphor sulfonic acid (CSA) afforded the alcohol **22** in 67% isolated yield, which was treated with TMSOTf[25] and 2,6-lutidine at room temperature to give southern fragment **5**.



Scheme 5. Preparation of southern subunit **5**. Reagents and conditions: (a) (i) DIBAL-H, toluene, −78 °C; (ii) $(COCl)_2$, DMSO, TEA, DCM, −78 °C; (iii) (*R*)-4-benzyl-3-propionyloxazolidin-2-one, Bu_2BOTf, TEA, CH_2Cl_2, −78 °C, 66% (three steps); (b) AcOH, H_2O, 70 °C, 62%; (c) TBSCl, imidazole, DMAP, DMF, 0 °C, 90%; (d) (i) $LiBH_4$, MeOH, Et_2O, 0 °C; (ii) DMP, DCM, rt; (iii) DCM, allyl 2-(triphenylphosphoranylidene)acetate, rt, 48% (three steps); (e) CSA, MeOH, −45 °C, 67%; (f) TMSOTf, 2,6-lutidine, DCM, rt, in quantitative crude yield.



Scheme 6. Preparation of oxazoline **4**. Reagents and conditions: (a) DEPBT, TEA, THF, rt, 66%; (b) DAST, DCM, −78 °C, 70%.

With both southern fragment **5** and northern subunit **6** in hand, we started to investigate the amide coupling and subsequent formation of oxazoline (Scheme 6). We tried several traditional coupling reagents, such as HATU, FDPP,[26] all of them gave the amidation product **23** in quite low yields. Fortunately, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one DEPBT)[27] could realize the amide coupling of **5** and **6** in a much higher yield (66%). The subsequent formation of the oxazoline ring was achieved in 70% yield by treatment of **23** with diethylaminosulfurtrifluoride (DAST).[28] At the stage of compound **4**,[29] we have successfully established all stereo centers and oxazoline ring for the macrolide unit of leiodelide A.

Conclusion

In summary, we completed the enantioselective synthesis of the key intermediate **4** for leiodelide A (**1**) from cheap commercially available material. An asymmetric synthetic method for northern subunit **6** was achieved using Julia olefination and Sharpless asymmetric dihydroxylation as key steps to form C15–C16 double bond and the stereogenic centers at C15 and C16, respectively. Moreover, using well-established Evans' asymmetric aldol methodology, we developed a highly diastereoselective synthesis of southern fragment **5**. Further efforts on the total synthesis of leiodelide A (**1**) is on-going in our laboratory.

Acknowledgments

We thank the National Natural Science Foundation of China (21072034, 21272041, 21472022), and Key Laboratory of Synthetic Chemistry of Natural Substances, SIOC of Chinese Academy of Sciences for financial support. The authors also thank Dr. Han-Qing Dong (Arvinas Inc.) for helpful suggestions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.102.

References and notes

1. Sandler, J. S.; Colin, P. L.; Kelly, M.; Fenical, W. *J. Org. Chem.* **2006**, *71*, 7245.
2. (a) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469; (b) Forsyth, C. J.; Sabes, S. F.; Urbanek, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 8381.
3. Total synthesis of the proposed structure of leiodelide B for see: (a) Larivée, A.; Unger, J. B.; Thomas, M.; Wirtz, C.; Dubost, C.; Handa, S.; Fürstner, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 304; The synthesis of key fragments of leiodelide A for see: (b) Chellat, M. F.; Proust, N.; Lauer, M. G.; Stambuli, J. P. *Org. Lett.* **2011**, *13*, 3246; Asymmetric synthesis of side chain for see: (c) Zhang, X.; Liu, J.; Sun, X.; Du, Y. *Tetrahedron* **2013**, *69*, 1553.
4. (a) Zhou, Q.-R.; Wei, X.-Y.; Li, Y.-Q.; Huang, D.-F.; Wei, B.-G. *Tetrahedron* **2014**, *70*, 4799; (b) Si, C.-M.; Huang, W.; Du, Z.-T.; Wei, B.-G.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 4328.
5. Huang, W.; Ren, R.-G.; Dong, H.-Q.; Wei, B.-G.; Lin, G.-Q. *J. Org. Chem.* **2013**, *78*, 10747.
6. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.
7. The oxidation-cyclization for selective see: (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907; (b) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267; (c) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207; For the selective dehydrative cyclization-oxidation see: (d) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604; (e) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642; (f) Riedrich, M.; Harkal, S.; Arndt, H. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2701.
8. (a) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *13*, 2063; (b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263; For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
9. (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77; (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
10. (a) Bajpai, R.; Yang, F. L.; Curran, D. P. *Tetrahedron Lett.* **2007**, *48*, 7965; (b) Ma, J. G.; Cheon, H. S.; Kishi, Y. *Org. Lett.* **2007**, *9*, 319.
11. (a) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596; (b) Wang, S. Y.; Song, P.; Chan, L. Y.; Loh, T. P. *Org. Lett.* **2010**, *12*, 5166.
12. (a) Hanessian, S.; Grillo, A. T. *J. Org. Chem.* **1998**, *63*, 1049; (b) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.
13. (a) Simmer, R. P.; Moody, D. B.; Feringa, B. L.; Minnaard, A. J. *J. Am. Chem. Soc.* **2001**, *128*, 4546; (b) Jong, A. D.; Arce, E. C.; Cheng, T. Y.; Summeren, R. P.; Feringa, B. L.; Dudkin, V.; Crich, D.; Matsunaga, I.; Minnaard, A. J.; Moody, D. B. *Chem. Biol.* **2007**, *14*, 1232.
14. (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380; (b) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.
15. Ramachandran, P. V.; Srivastava, A.; Hazra, D. D. *Org. Lett.* **2007**, *9*, 157.
16. Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26.
17. (a) Hanessian, S.; Focken, T.; Oza, R. *Org. Lett.* **2010**, *12*, 3172; (b) Tiefenbacher, K.; Arion, V. B.; Mulzer, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2690.
18. (a) Gollner, A.; Mulzer, J. *Org. Lett.* **2008**, *10*, 4701; (b) Fettes, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4098; (c) Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, *11*, 761.
19. (a) 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.* **2002**, *41*, 176; (b) Lzgu, E. V.; Burns, A. C.; Hoye, T. R. *Org. Lett.* **2011**, *13*, 703.
20. Marshall, J. A.; Beaudoin, S. *J. Org. Chem.* **1994**, *59*, 6614.

21. Mulzer, J.; Kaselow, K.; Graske, K. D.; Kühne, H.; Sieg, A.; Martin, H. J. *Tetrahedron* **2004**, *60*, 9569.
22. (a) Bal, B. S.; Childers, Jr., W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091; (b) Armstrong, L. E.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020.
23. (a) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707; (b) Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716; (c) Hoffman, T. J.; Dash, J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 2756.
24. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
25. (a) Sakaiani, M.; Ofune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543; (b) Sakaitani, M.; Ofune, Y. *J. Org. Chem.* **1990**, *55*, 870; (c) Borgulya, J.; Bernauer, K. *Synthesis* **1980**, 545.
26. (a) Sheehan, J.; Cruickshank, P.; Boshart, G. *J. Org. Chem.* **1961**, *26*, 2525; (b) Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711.
27. (a) Li, H.; Jiang, X.; Ye, Y.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91; (b) Kretschmer, M.; Menche, D. *Org. Lett.* **2012**, *14*, 382.
28. (a) Coste, J.; Dufour, M. N.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 669; (b) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1967**, *1991*, 32.
29. $[\alpha]_D^{25} = -12.2$ (*c* 0.21, $CHCl_3$); IR (film): ν_{max} 3416, 2923, 1714, 1649, 1586, 1557, 1462, 1382, 1258, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 16.0, 7.2 Hz, 1H), 6.00–5.93 (m, 1H), 5.84 (dd, *J* = 15.8, 1.3 Hz, 1H), 5.37–5.33 (m, 2H), 5.26 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.66–4.65 (m, 2H), 4.59–4.54 (m, 1H), 4.36 (m, 1H), 4.31–4.26 (m, 2H), 4.04–3.96 (m, 2H), 3.94–3.88 (m, 2H), 3.51–3.50 (m 3H), 3.39–3.37 (m, 1H), 2.50–2.45 (m, 1H), 2.37–2.30 (m, 2H), 1.69–1.63 (m, 8H), 1.59–1.57 (m, 4H), 1.44 (s, 3H), 1.36 (s, 3H), 1.17–1.06 (m, 2H), 1.08–1.06 (m, 3H), 0.97–0.96 (m, 3H), 0.91-0.88 (m, 21H), 0.11–0.02 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 166.3, 151.8, 135.5, 132.4, 128.7, 120.7, 117.9, 107. 9, 82.4, 75.6, 71.9, 70.9, 70.1, 65.7, 64.9, 60.3, 43.4, 40.2, 33.4, 29.4, 26.5, 26.0, 25.8, 25.6, 25.0, 19.7, 18.1, 13.7, 12.7, −4.2, −4.4, −4.9 ppm; HRMS (ESI) calcd for $[C_{40}H_{73}NO_8Si_2+H^+]$: 752.4953, found: 752.4930.