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SYNTHESIS OF OPEN-CHAIN C21-C40 FRAGMENT OF AZASPIRACID-1

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Abstract – Here, we report a synthesis of a differentially protected, open-chain C21–C40 fragment of azaspiracid-1, corresponding to the lower half EFGHI-ring domain. The synthesis features modular coupling of three advanced intermediates, aiming for diverted analogue synthesis. A new method for construction of E-ring moiety amenable to the diverted synthesis is also reported.

Azaspiracid-1 (AZA-1, **1**) is a marine toxin responsible for azaspiracid poisoning prevailed at a coastal region in Europe since 1995 (Figure 1). The toxin was first isolated from contaminated mussels (*Mytilus edulis*) from Killary Harbor, Ireland, and characterized by a group led by Yasumoto and Satake in 1998,[1] and the structure was synthetically settled by a Nicolaou group in 2004.[2] Ten AZA congeners have been determined thereafter,[3] and the other congeners have been proposed.[4] The structure of **1** is quite unique; 1) a C6–C17 bisspiroketal fused to a C17–C20 tetrahydrofuran, and 2) an unusual C33–C40 azaspiro ring fused with C28–C40 2,9-dioxabicyclo[3.3.1]nonane. The lethality of **1** against mice was found to be highly potent (LD_{50} = 0.2 mg/kg),[5] although the mechanism for the biological action of **1**, however, still remains unsolved. Recently, AZAs have received increasing attention because of the wider geographical occurrence; AZAs are now detected also in brown crabs from coast of Norway and Sweden,[6] and in several kinds of shellfishes from Portuguese coast.[7]

In order to study the biological function of AZAs precisely, highly pure analogues and/or partial structure are required.[2,8] We have been studying a synthesis of **1**, and the synthesis of the lower half domain has been recently accomplished.[9,10] In this letter, we report a second-generation synthesis of a differentially protected, open-chain fragment corresponding to the lower half of **1**, amenable to diverted synthesis of various AZA analogues.[11] In addition, a new synthetic approach toward E-ring moiety has been newly developed here.

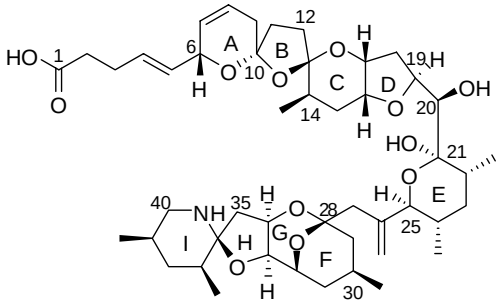
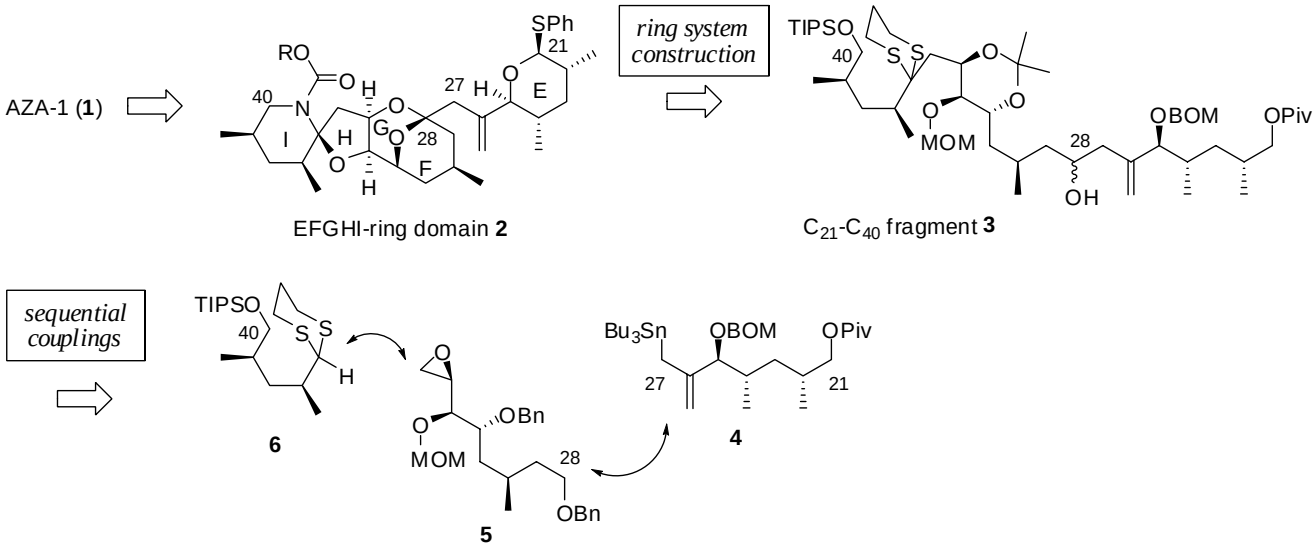


Figure 1. Structure of azaspiracid-1 (AZA-1, **1**)

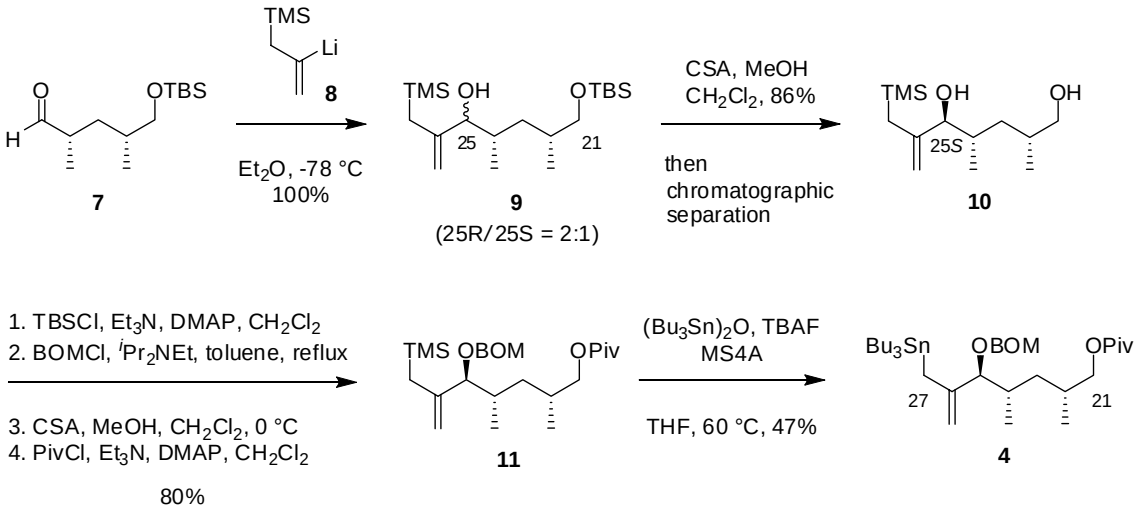
Our strategy, aiming for diverted synthesis of the lower half EFGHI-ring domain **2**, is shown in Scheme 1. In this plan, differentially protected open-chain fragment **3** is a direct precursor for **2** and analogues. The fragment **3** would be synthesized from three advanced intermediates **4**, **5**, and **6**, which may have structural variants as branching points.[11] For a short-step and high-yield synthesis of natural product, construction of ring systems is generally performed prior to fragment assembly in a convergent way. In contrast, longer steps are generally required in a diverted synthesis, where fragment assembly is performed at an earlier stage in synthesis. The current diverted strategy, however, is expected to require 39 steps for the longest linear route which is only 2 steps longer than our previous convergent synthesis (37 steps),[9] as shown below.



Scheme 1. Second-generation strategy amenable to analogue synthesis. Fragments **4**–**6** may have structural variants, and **3** is a direct precursor for **2** and analogues.

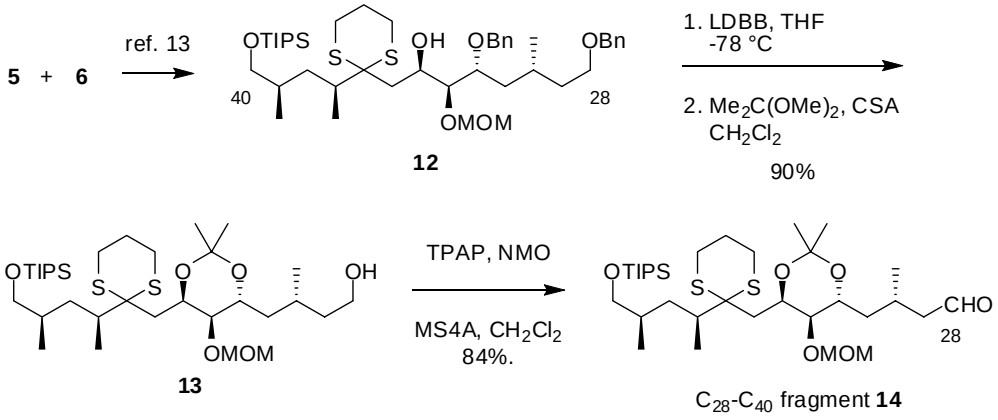
Preparation of C21–C27 allylic stannane **4**,[12] corresponding to the E-ring moiety, is shown in Scheme 2. The experiment started with optically active aldehyde **7**,[13] which was reacted with vinylic lithium species **8** prepared from 2-bromo-3-(trimethylsilyl)prop-1-ene[14] and *tert*-BuLi. The reaction proceeded quantitatively to give alcohol **9** as a diastereomeric mixture (25*R*/25*S* = 2:1).[15] After acidic removal of the TBS group, desired (25*S*)-**9** was separated to give diol **10**. The reaction was proceeded in 86% yield, and

desired diol **10** was isolated in 50% yield after a single chromatographic separation. Undesired (25*R*)-*epi*-**10** can be also converted into **10** in 72% yield over 4-step reactions including oxidation–reduction sequence using DIBALH with 1:5 (25*R*/25*S*) diastereoselectivity (other data not shown). Primary hydroxy group of diol **10** was selectively protected as TBS ether and the remaining C25 hydroxy group was protected by BOM group. The TBS ether was removed by CSA in MeOH, and generated C21 hydroxy group was again protected by Piv group to furnish **11** in 80% overall yield for 4 steps. The allylic TMS group was then replaced with tri-*n*-butylstannyl group by $(Bu_3Sn)_2O$ and TBAF,[16] giving rise to C21–C27 allylic stannane **4** in 47% yield.[17] Here, main side reaction is protonolysis of the TMS group in 29% yield, which could not be suppressed under these reaction conditions.



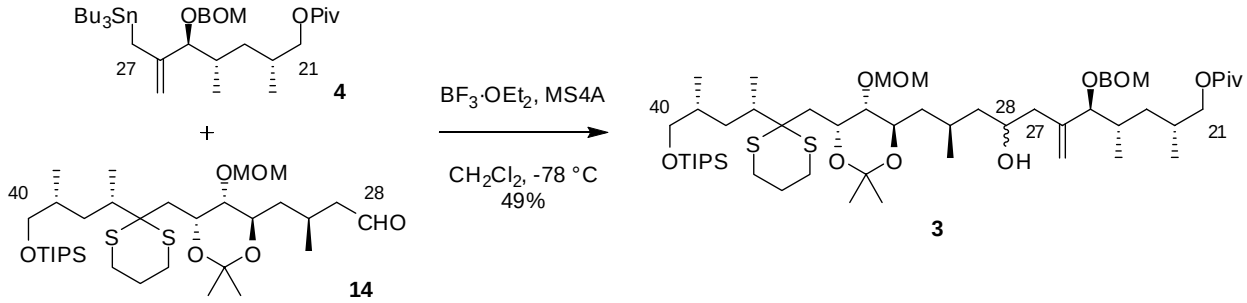
Scheme 2. Synthesis of the C21–C27 fragment **4**

C28–C40 fragment aldehyde **14**, corresponding to the FGHI-ring domain, was prepared from a known compound **12** generated by coupling of advanced intermediates **5** and **6** (Scheme 3).[13] Thus, two Bn groups were quantitatively removed by LDBB[18] at –78 °C, and isopropylidene formation for 1,3-diol protection provided alcohol **13** in 90% yield. Finally, oxidation of the hydroxy group with TPAP[19] gave C28–C40 aldehyde **14**, ready for coupling with allylic stannane **4**.



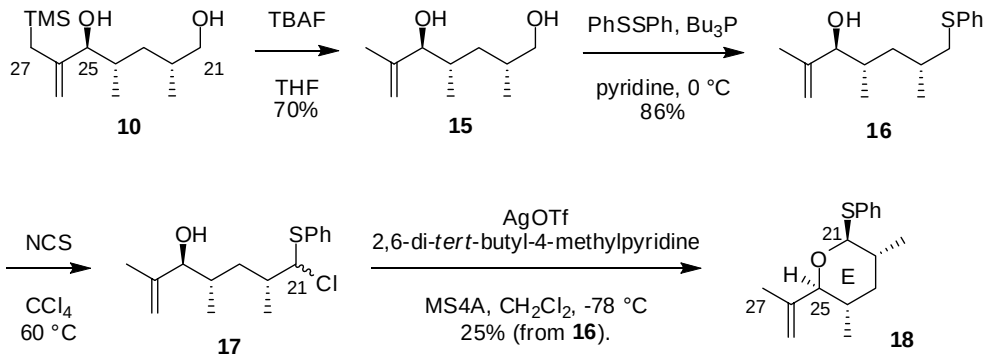
Scheme 3. Synthesis of the C28–C40 fragment **14**

Elaboration of the two fragments **4** and **14** to the C21–C40 open-chain fragment **3**, corresponding to the lower half of AZA-1 (**1**), is shown in Scheme 4. First, the coupling was attempted with $MgBr_2 \cdot OEt_2$ which had been employed in our synthetic study of a model compound.[13] However, no reaction was observed and both coupling components were recovered intact. We therefore employed rather reactive $BF_3 \cdot OEt_2$ for this coupling reaction. Gratifyingly, we found that the reaction proceeded smoothly in CH_2Cl_2 at –78 °C in the presence of MS4A, giving rise to desired open-chain C21–C40 fragment **3** in 49% yield as a diastereomeric mixture (6:5). The structure was fully confirmed by spectroscopic analysis including NMR.[20]



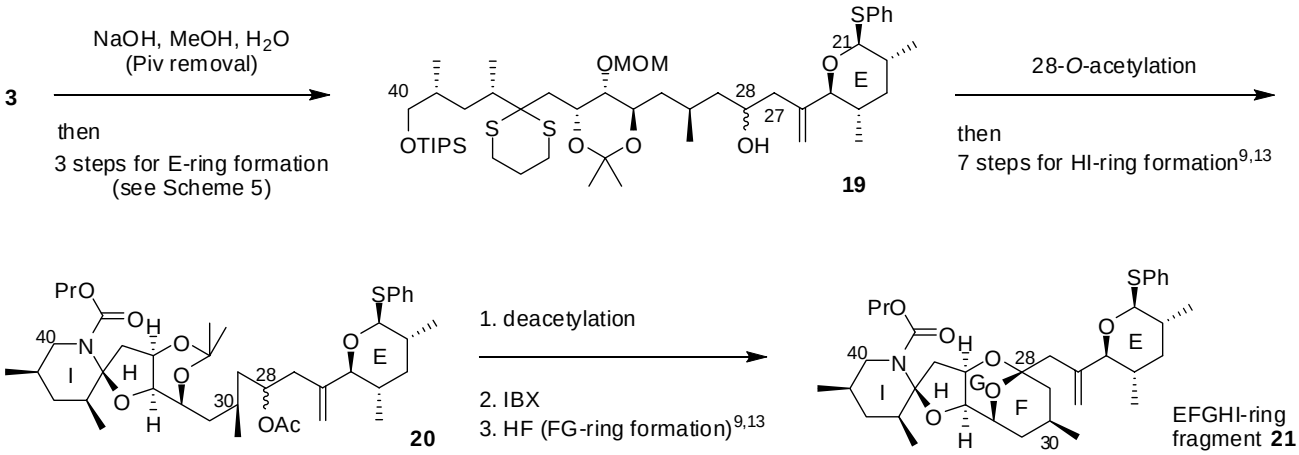
Scheme 4. Synthesis of differentially protected C21–C40 open-chain fragment **3**

A method for construction of the E-ring moiety, amenable to the present synthetic plan, was finally explored. Here, we decided to employ intramolecular etherification between C25 hydroxy group and C21 α-chlorosulfide, inspired by a methodology reported by Hirama.[21] The TMS group of **10** was removed by TBAF, as it is not required in this preliminary experiment. From diol **15**, the construction of the E-ring was successfully performed without protecting C25 hydroxy group as follows. First, phenylthio group was regioselectively introduced to the C21 position to give **16** in 86% yield,[22] which, in turn, was treated with NCS[23] at 60 °C to provide α-chlorosulfide **17** as a diastereomeric mixture at the C21 position (ratio not determined). It should be noted that chlorination of the sulfide followed by migration of the chloride anion does not take place below 60 °C. Without purification, **17** was subjected to treatment with AgOTf[21] at –78 °C to furnish E-ring pyranoside **18** in 25% yield over 2 steps from **16**. Diastereomer at C21 position was not detected at all, indicating that this reaction is thermodynamically controlled process. ^{1}H NMR analysis revealed that all substituents on the 6-membered ring are oriented equatorially in **18**.[24] The low yield in the last reaction is due to an instability of intermediary α-chlorosulfide **17**, and improvement of this process is currently under study.



Scheme 5. Model study for construction of the E-ring

In conclusion, we have successfully synthesized differentially protected open-chain fragment for the lower half of azaspiracid-1 (**1**). A new method for construction of the E-ring moiety has been also developed. In combination with the FGHI-ring formation method,[9,13] the complete ring system is expected to be constructed from **3** in 15 steps which is only 2 steps longer (in total) than our previous route as shown in Scheme 6.[9] Studies are currently underway to synthesize the EFGHI-ring domain **2** and the structural analogues from **3**, and the result will be reported as a full account in due course.



Scheme 6. An expected 15-step transformation of **3** to the EFGHI-ring fragment **21** (in progress)

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke, and T. Yasumoto, *J. Am. Chem. Soc.*, 1998, **120**, 9967.
2. For Nicolaou's total synthesis of AZA-1 (**1**), see; K. C. Nicolaou, S. Vyskocil, T. V. Koftis, Y. M. A. Yamada, T. T. Ling, D. Y. K. Chen, W. J. Tang, G. Petrovic, M. O. Frederick, Y. W. Li, and M. Satake,

Angew. Chem. Int. Ed., 2004, **43**, 4312; K. C. Nicolaou, T. V. Koftis, S. Vyskocil, G. Petrovic, T. T. Ling, Y. M. A. Yamada, W. J. Tang, and M. O. Frederick, *Angew. Chem. Int. Ed.*, 2004, **43**, 4318.

3. K. Ofuji, M. Satake, T. McMahon, J. Silke, K. J. James, H. Naoki, Y. Oshima, and T. Yasumoto, *Nat. Toxins*, 1999, **7**, 99; K. Ofuji, M. Satake, T. McMahon, K. J. James, H. Naoki, Y. Oshima, and T. Yasumoto, *Biosci. Biotechnol. Biochem.*, 2001, **65**, 740; K. J. James, M. D. Sierra, M. Lehane, A. B. Magdalena, and A. Furey, *Toxicon*, 2003, **41**, 277; C. Alfonso, A. Alfonso, P. Otero, P. Rodriguez, M. R. Vieytes, C. Elliotc, C. Higgins, and L. M. Botana, *J. Chromatogr. B*, 2008, **865**, 133.
4. N. Rehmann, P. Hess, and M. A. Quilliam, *Rapid Commun. Mass Spectrom.*, 2008, **22**, 549.
5. K. Ofuji, M. Satake, Y. Oshima, H. Naoki, and T. Yasumoto, In '43rd Symposium on the Chemistry of Natural Products', 2001, pp 353-358, Osaka.
6. T. Torgensen, N. B. Bremnes, T. Rundberget, and T. Aune, *Toxicon*, 2008, **51**, 93.
7. P. Vale, R. Bire, and P. Hess, *Toxicon*, 2008, **51**, 1449.
8. For Evans' total synthesis of AZA-1 (**1**), see; D. A. Evans, L. Kvaerno, J. A. Mulder, B. Raymer, T. B. Dunn, A. Beauchemin, E. J. Hava, M. Juhl, and K. Kagechika, *Angew. Chem. Int. Ed.*, 2007, **46**, 4693; D. A. Evans, T. B. Dunn, L. Kvaerno, A. Beauchemin, B. Raymer, E. J. Olhava, J. A. Mulder, M. Juhl, K. Kagechika, and D. A. Favor, *Angew. Chem. Int. Ed.*, 2007, **46**, 4698.
9. M. Oikawa, T. Uehara, T. Iwayama, and M. Sasaki, *Org. Lett.*, 2006, **8**, 3943.
10. For another synthetic study of the lower half domain of AZA-1 (**1**), see; C. J. Forsyth, J. Y. Xu, S. T. Nguyen, I. A. Samdal, L. R. Briggs, T. Rundberget, M. Sandvik, and C. O. Miles, *J. Am. Chem. Soc.*, 2006, **128**, 15114.
11. For diverted total synthesis of natural products, see; R. M. Wilson and S. J. Danishefsky, *J. Org. Chem.*, 2006, **71**, 8329.
12. Azaspiracid numbering is used throughout this paper.
13. M. Sasaki, Y. Iwamuro, J. Nemoto, and M. Oikawa, *Tetrahedron Lett.*, 2003, **44**, 6199.
14. B. M. Trost, T. A. Grese, and D. M. T. Chan, *J. Am. Chem. Soc.*, 1991, **113**, 7350.
15. The stereochemistry was determined by modified Mosher's method after converting into MTPA esters. For modified Mosher's method, see; I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
16. B. P. Warner and S. L. Buchwald, *J. Org. Chem.*, 1994, **59**, 5822.
17. Stannane **4** has been also used in our previous model study for C27-C28 bond formation, but the synthetic procedure has not been reported yet, see reference 9.
18. P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924; R. E. Ireland and M. G. Smith, *J. Am. Chem. Soc.*, 1988, **110**, 854.
19. W. P. Griffith, S. V. Ley, G. P. Whitcombe, and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987,

1625.

20. Spectroscopic data for **3**: $[\alpha]_D^{25}$ -39.0 (*c* 0.80, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 5.09 (s, 2H), 4.67 (s, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.55 (d, *J* = 6.5 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.29 (s, 1H), 4.00 (d, *J* = 10.5 Hz, 1H), 3.85-3.62 (m, 5H), 3.40-3.32 (m, 2H), 3.37 (s, 3H), 2.80-2.62 (m, 4H), 2.31-2.15 (m, 3H), 2.11-1.98 (m, 2H), 1.97-1.87 (m, 5H), 1.81 (s, 1H), 1.78 (s, 1H), 1.68 (br s, 1H), 1.64-1.45 (m, 4H), 1.37 (s, 3H), 1.35 (s, 3H), 1.23 (s, 1H), 1.18 (s, 9H), 1.17 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 21H), 0.96-0.95 (m, 10H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.7, 145.1, 130.3, 128.5, 128.3 (× 2), 127.9 (× 2), 116.5, 101.3, 98.0, 92.4, 85.8, 85.6, 71.9, 70.0, 69.0, 68.7, 68.3, 67.9, 60.0, 55.7, 44.8, 42.2, 42.0, 40.9, 38.9, 37.5, 37.1, 36.6, 35.6, 34.5, 33.3, 30.8 (× 2), 27.4 (× 3), 26.0 (× 2), 25.8, 24.4, 21.0, 19.2, 19.0, 18.4 (× 6), 17.0, 16.2, 12.4 (× 3); HRMS (FAB) calcd for $C_{56}H_{100}O_{10}S_2SiNa$ $[(M+Na)^+]$ 1047.6425, found 1047.6432.
21. M. Inoue, G. Xing, X. Wang, J. Wang, and M. Hirama, *Org. Lett.*, 2002, **4**, 3439.
22. I. Nakagawa and T. Hata, *Tetrahedron Lett.*, 1975, 1409.
23. T. Mukaiyama, T. Sugaya, S. Marui, and T. Nakatsuka, *Chem. Lett.*, 1982, 1555; B. M. Dilworth and M. A. McKervey, *Tetrahedron*, 1986, **42**, 3731.
24. Spectroscopic data for **18**: $[\alpha]_D^{25}$ +67.8 (c 0.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.17 (m, 5H), 4.93-4.88 (m, 2H), 4.35 (d, *J* = 10.2 Hz, 1H), 3.42 (d, *J* = 9.9 Hz, 1H), 1.87 (m, 1H), 1.74 (s, 3H), 1.71-1.59 (m, 2H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.98 (m, 1H), 0.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 144.2, 132.2, 128.8, 128.3 (× 2), 127.9 (× 2), 113.9, 91.4, 89.4, 42.0, 35.6, 32.4, 19.1, 17.5, 17.3; HRMS (EI) calcd for $C_{16}H_{22}OS$ (M^+) 262.1391, found 262.1391.