HETEROCYCLES, Vol. 70, 2006, pp. 161 - 167. © The Japan Institute of Heterocyclic Chemistry
Received, 25th September, 2006, Accepted, 17th November, 2006, Published online, 21st November, 2006. COM-06-S(W)50

SYNTHESIS OF ARTIFICIAL LADDER-SHAPED POLYETHERS CONTAINING A 6/7 *CIS*-FUSED RING SYSTEM

Kohei Torikai, Hiroshi Yari, Michio Murata, and Tohru Oishi*

Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan
E-mail: oishi@ch.wani.osaka-u.ac.jp

Abstract – Ladder-shaped tetracyclic and heptacyclic ethers containing a 6/7 *cis*-fused ring system have been synthesized. The synthesis features convergent coupling of monocyclic building blocks through esterification, ring-closing reaction using a low-valent titanium complex, and hydroxy dithioacetal cyclization. The double reaction strategy enabled expeditious synthesis of the heptacyclic ether in only thirteen steps from the building blocks.

Naturally occurring ladder-shaped polyethers (LSPs)[1] including brevetoxins[2] and ciguatoxins[3] have been identified as unique products of dinoflagellates. Including their congeners, more than fifty of these compounds have been identified. These LSPs possess the general structural motif of continuous *trans/syn/trans*-fused ether rings. Various combination of the number of rings, ring sizes (5~9-membered rings), and the order of the ring connection result in considerable skeletal diversity, which can be classified into around ten categories.[1] Although the LSPs are thought to interact with different transmembrane (TM) proteins to elicit their potent biological activities, e.g. brevetoxins and ciguatoxins bind to the voltage-sensitive sodium channels,[4] their precise mode of action at the molecular level remains unknown mainly due to the short supply of LSPs from natural resources. Remarkable progress

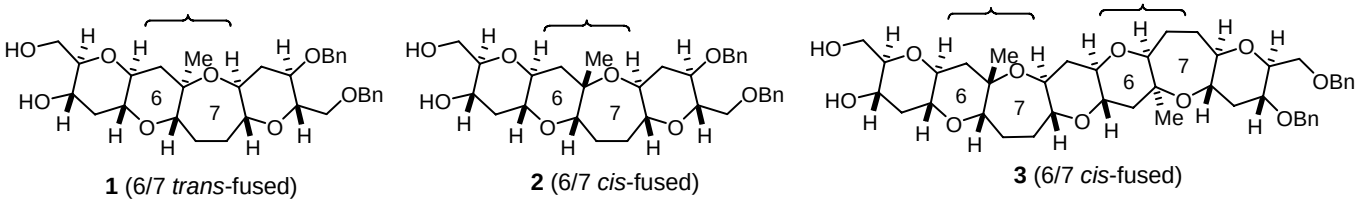
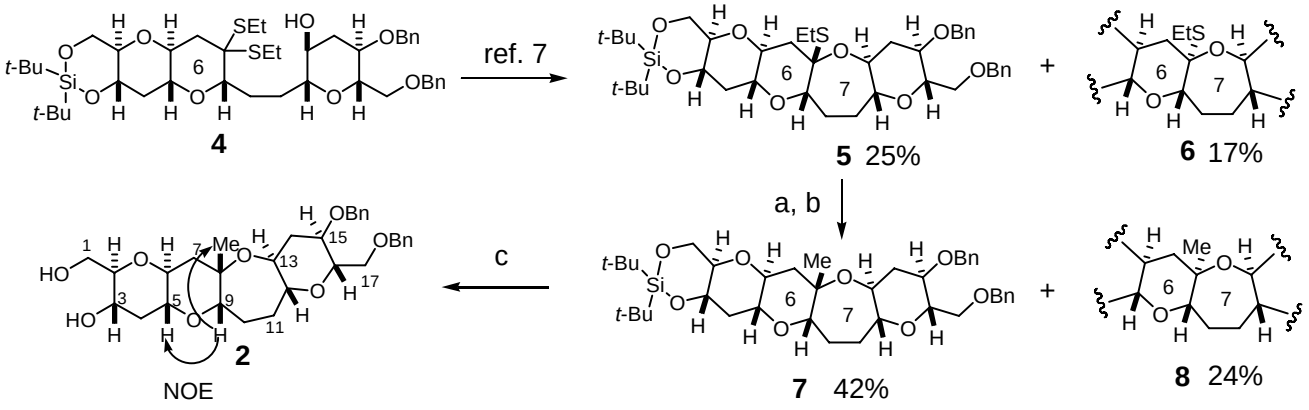


Figure 1. Structures of artificial ladder-shaped polyethers (ALPs).

§ Dedicated to Professor Steven M. Weinreb in celebration of his 65th birthday.

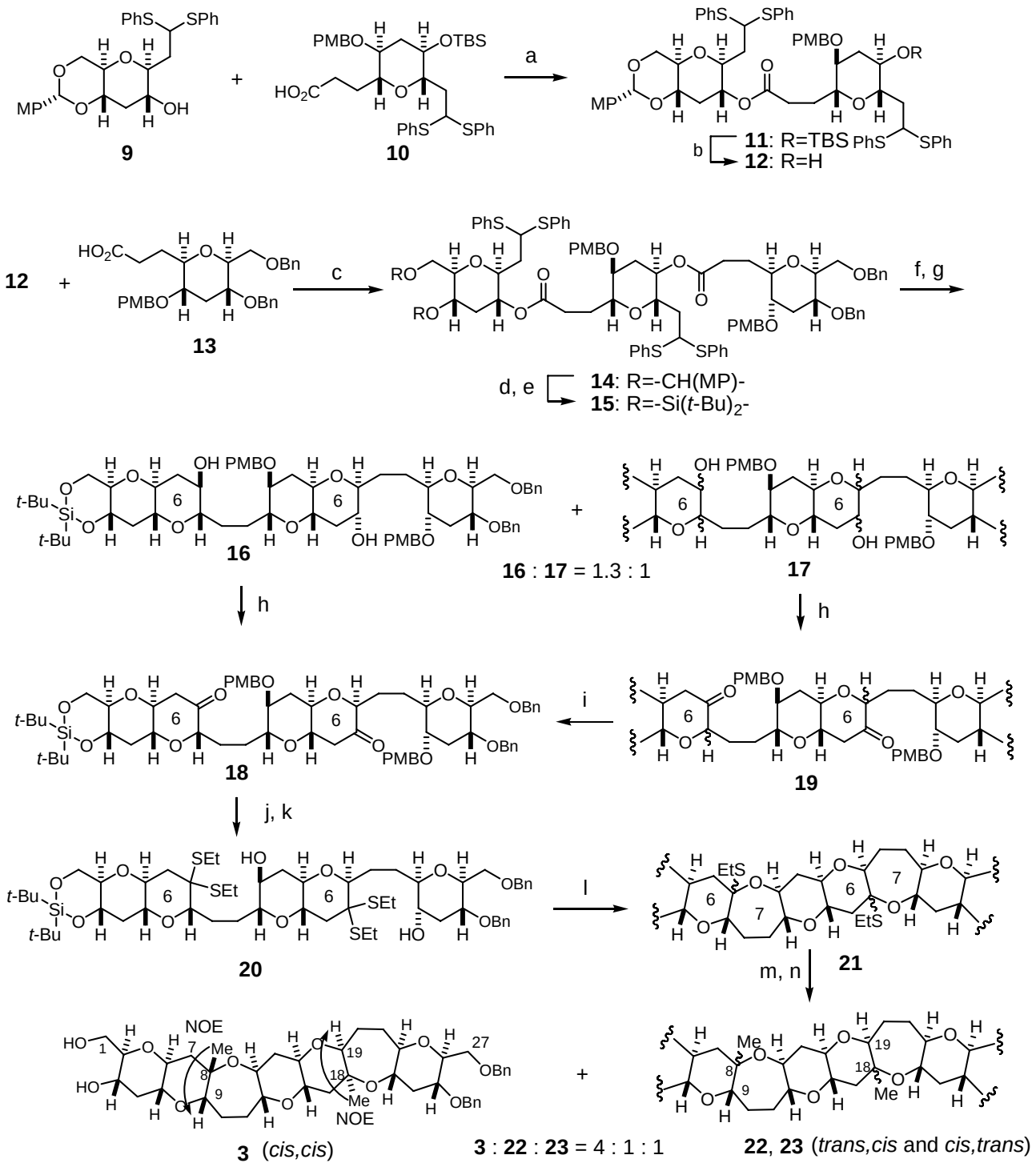
has recently been made in the total synthesis of LSPs,[5] however, full assembly of the complex molecule can only be achieved using a large number of steps. In the course of our program to elucidate the interactions between LSPs and TM proteins, we have designed and synthesized an artificial ladder-shaped polyether (ALP) **1** (Figure 1), and found that the tetracyclic ether could interact with a TM protein, glycophorin A, as well as natural LSPs.[6,7] In order to study the structure-activity relationship in more detail by expanding the skeletal diversity, we planned to synthesize ALPs containing a *cis*-fused ring system as molecular probes that are not available from natural resources. Herein, we describe convergent syntheses of tetracyclic (**2**) and heptacyclic (**3**) ALPs containing a 6/7 *cis*-fused system (Figure 1).[8]

Although a number of methodologies and strategies for synthesizing LSPs have been developed,[5] to our knowledge, there are no reports on the convergent synthesis of 6/7 *cis*-fused ring systems possessing an angular methyl group.[9] During the course of synthetic studies of ALPs,[7] we found that the 6/7 *cis*-fused system in ALP (**2**) could be obtained from a 6/7 *cis*-fused mixed thioacetal (**5**) prepared from the hydroxy dithioacetal (**4**), which is a common synthetic intermediate of ALPs (**1**) (Scheme 1). Oxidation of the mixed thioacetal (**5**) with *m*CPBA to give the sulfone, followed by treatment with Me_3Al, afforded the desired 6/7 *cis*-fused product (**7**) (42%) concomitant with *trans*-fused epimer (**8**) (24%), whereas the *trans*-fused mixed thioacetal (**6**) provided **8** (52%) as a single isomer as already reported.[7] Removal of the silyl group of **7** using TBAF furnished **2**,[10] whose structure was determined by NOE experiments. Even though a reasonable explanation for the *cis*-selective methylation could not be offered, the alkylation presumably occurred from the convex face of the oxocarbenium ion intermediate in a *cis*-decalin like conformation by an S_N1 mechanism,[9] but the possible contribution of an alternative S_Ni pathway could not be ruled out.



Scheme 1. *Reagents and conditions*: (a) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 20 min; (b) Me_3Al, CH_2Cl_2, -50 to -20 °C, 1.5 h, **7** : 42%, **8** : 24% (two steps); (c) TBAF, THF, rt, 2 h, 33%.

Then, we moved on to the synthesis of the heptacyclic ALP (**3**) as shown in Scheme 2. We envisaged that the convergent method for synthesizing tetracyclic ALP (**2**) could be doubly applied to the construction of the two 6/7 *cis*-fused ring system of **3**. The double reaction strategy, in which two discrete reaction sites are manipulated in a single synthetic operation, should significantly reduce the total number of steps, while alternative one-pot strategies have already been reported, e.g. two-directional syntheses[11] and epoxide-opening cascades.[12] Sequential coupling of three building blocks (**9**), (**10**),[13] and (**13**) via iterative esterification[14] afforded diester (**14**) in good yields, and subsequent protective group manipulation of the *p*-methoxybenzylidene acetal (**14**) yielded silylene (**15**). The first key step of the double reaction strategy, double cyclization of the diester (**15**) equipped with two dithioacetal moieties by means of Takeda reaction,[15] was carried out.[7,16,17] Treatment of **15** with the low valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ yielded bis(cyclic enol ether), which was immediately subjected to a hydroboration-oxidation sequence to afford the desired diol (**16**) concomitant with **17** as an inseparable mixture of the other three possible diastereomers (**16** : **17** = 1.3 : 1).[18] The total yield of **16** and **17** (23% to 34% for two steps) is somewhat low, but the average yield per reaction site was calculated to be 69% to 76%. After separation of the diol (**16**) from **17** by flash column chromatography, Dess-Martin oxidation of **16** gave diketone (**18**) in 90% yield. Meanwhile, the undesired isomers (**17**) were also successfully converted to **18** through the oxidation (81%), followed by epimerization of the resulting diketone (**19**) by treatment with DBU (77%). Then, the PMB groups of **18** were removed using DDQ (73%), and the resulting bis(hydroxy ketone) was converted to the corresponding bis(hydroxy dithioacetal) (**20**) by treatment with TMSSEt in the presence of TMSOTf (72%). These conventional transformations from **16** and **17** to **20** were estimated to proceed with an average yield per reaction site of 86%. The second key reaction of the present strategy, formation of the bis(mixed thioacetal) (**21**) was carried out according to Nicolaou's report.[19] As expected, double cyclization of **20** proceeded by treatment with $AgClO_4$ in the presence of $NaHCO_3$, silica gel and MS4A in nitromethane to afford **21**, but in moderate yield (13% to 30% yield, average yield per reaction site: 36% to 55%).[20] Although **21** was obtained as an inseparable mixture of diastereomers and the structures and ratio of isomers could not be determined at this stage, the 8,9-*cis*-18,19-*cis* isomer was deduced to be a major product based on the results of the corresponding tetracyclic system (Scheme 1).[7] The final double methylation was achieved through successive one-pot oxidation of **21** with *m*CPBA followed by treatment of the resulting sulfone with Me_3Al.[19,21] Finally, deprotection with TBAF afforded the desired 8,9-*cis*-18,19-*cis* heptacyclic ALP (**3**) and the other two diastereomers (**22**) and (**23**) in 43 % yield for three steps (87% average yield per reaction site), which were separated by HPLC (**3** : **22** : **23** = 4 : 1 :1). The structure of *cis,cis*-**3**[22] was determined by NOE experiments as shown in Scheme 2, while those of **22** and **23** were tentatively assigned as *trans,cis* isomers based on the ^{1}H NMR chemical shifts of the angular methyl groups.[23] Although the yields of the key cyclization steps should be improved, the double reaction



Scheme 2. *Reagents and conditions*: (a) EDC·HCl, DMAP, CSA, CH_2Cl_2, reflux, 19.5 h, 99%; (b) TBAF, THF, rt, 11 h, 89%; (c) EDC·HCl, DMAP, CSA, CH_2Cl_2, reflux, 17.5 h, 94%; (d) *p*-TsOH·H_2O, THF, MeOH, H_2O, rt, 7 h, 87%; (e) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, DMF, rt, 1 h, 93%; (f) Cp_2Ti $[P(OEt)_3]_2$, MS4A, THF, rt, 45 min, reflux, 3 h; (g) BH_3·THF, THF, -50 to -20 ^oC, 2.5 h, then H_2O_2, $NaHCO_3$, aq.THF, -35 ^oC to rt, 4 h, 23 to 34% (two steps), **16** : **17** = 1.3 : 1; (h) Dess-Martin periodinane, CH_2Cl_2, rt, 3.5 h, 90% (from **16** to **18**), 81% (from **17** to **19**); (i) DBU, benzene, rt, 39.5 h, 77%; (j) DDQ, H_2O, CH_2Cl_2, rt, 4 h, 73%; (k) TMSSEt, TMSOTf, CH_2Cl_2, -60 to -30 ^oC, 2 h, 72%; (l) $AgClO_4$, $NaHCO_3$, silica gel, MS4A, CH_3NO_2, THF, rt, 1 h, 13 to 30%; (m) *m*CPBA, CH_2Cl_2, rt, 1 h, then Me_3Al, -30 to -10 ^oC, 1.5 h; (n) TBAF, THF, rt, 3 h, 43% (two steps), **3** : **22** : **23** = 4 : 1 : 1.

strategy realized the expeditious synthesis of the heptacyclic ether (**3**) in only thirteen steps from the building blocks.

In conclusion, tetracyclic and heptacyclic ALPs (**2**) and (**3**) possessing a *cis*-fused 6/7 ring system have been synthesized through convergent assemblage of the building blocks via esterification, Takeda reaction, hydroxy dithioacetal cyclization, and introduction of angular methyl groups. The double reaction strategy, in which the above methodology was applied to two discrete reaction sites in the same molecule, enabled the expeditious synthesis of the heptacyclic ether (**3**) in only thirteen steps from the building blocks. Evaluation of the interaction between these ALPs and membrane-integral proteins is currently in progress in our laboratory.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Exploratory Research (No. 15655033), for Scientific Research on Priority Areas (No. 16073211) from MEXT.

REFERENCES AND NOTES

1. Y. Shimizu, *Chem. Rev*., 1993, **93**, 1685; T. Yasumoto and M. Murata, *Chem. Rev*., 1993, **93**, 1897; M. Murata and T. Yasumoto, *Nat. Prod. Rep*., 2000, **17**, 293; T. Yasumoto, *Chem. Rec*., 2001, **1**, 228.
2. Y.-Y. Lin, M. Risk, S. M. Ray, D. V. Engen, J. Clardy, J. Golik, J. C. James, and K. Nakanishi, *J. Am. Chem. Soc*., 1981, **103**, 6773.
3. P. J. Scheuer, W. Takahashi, J. Tsutsumi, and T. Yoshida, *Science*, 1967, **155**, 1267; M. Murata, A. -M. Legrand, Y. Ishibashi, M. Fukui, and T. Yasumoto, *J. Am. Chem. Soc*., 1990, **112**, 4380; M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hirama, N. Harada, and T. Yasumoto, *J. Am. Chem. Soc*., 1997, **119**, 11325.
4. W. A. Catterall and M. Risk, *Mol. Pharmacol*., 1981, **19**, 345; V. L. Trainer, D. G. Baden, and W. A. Catterall, *J. Biol. Chem*., 1994, **269**, 19904; M.-Y. Dechraoui, J. Naar, S. Pauillac, and A.-M. Legrand, *Toxicon*, 1999, **37**, 125.
5. Reviews on the total synthesis of ladder-shaped polyethers, see: T. Nakata, *Chem. Rev.*, 2005, **105**, 4314; M. Inoue, *Chem. Rev.*, 2005, **105**, 4379; I. Kadota and Y. Yamamoto, *Acc. Chem. Res.*, 2005, **38**, 423; M. Sasaki and H. Fuwa, *Synlett*, 2004, 1851; M. Inoue, *Org. Biomol. Chem*., 2004, **2**, 1811; F. P. Marmsäter and F. G. West, *Chem. Eur. J*., 2002, **8**, 4346; P. A. Evans and B. Delouvrie, *Curr. Opin. Drug Discovery Dev*., 2002, **5**, 986; Y. Mori, *Chem. Eur. J*., 1997, **3**, 849; E. Alvarez, M.-L. Candenas, R. Pérez, J. L. Ravelo, and J. D. Martín, *Chem. Rev*., 1995, **95**, 1953.

6. M. Mori, T. Oishi, S. Matsuoka, S. Ujihara, N. Matsumori, M. Murata, M. Satake, Y. Oshima, N. Matsushita, and S. Aimoto, *Bioorg. Med. Chem*., 2005, **13**, 5099.
7. K. Torikai, H. Yari, M. Mori, S. Ujihara, N. Matsumori, M. Murata, and T. Oishi, *Bioorg. Med. Chem. Lett*., 2006, **16**, 6355.
8. There are few naturally occurring *cis*-fused cyclic ethers, e.g. dactomelynes, elatenyne, and the LM and NO ring system of maitotoxin. Y. Gopichand, F. J. Schmitz, J. Shelley, A. Rahman, and D.Van der Helm, *J. Org. Chem.*, 1981, **46**, 5192; J. G. Hall, and J. A. Reiss, *Aust. J. Chem.*, 1986, **39**, 1401; M. Murata, H. Naoki, S. Matsunaga, M. Satake, and T. Yasumoto, *J. Am. Chem. Soc.*, 1994, **116**, 7098.
9. Convergent synthesis of 7/7 and 6/7 *cis*-fused ring system by means of hydroxy ketone cyclization, see: K. C. Nicolaou, K. R. Reddy, G. Skokotas, F. Sato, X.-Y. Xiao, and C.-K. Hwang, *J. Am. Chem. Soc.*, 1993, **115**, 3558; E. Alvarez, R. Pérez, M. Rico, R. M. Rodríguez, and J. D. Martín, *J. Org. Chem.*, 1996, **61**, 3003.
10. Spectral data of **2**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.20-7.33 (10H, m, Ph), 4.57 (3H, m, Bn), 4.38 (1H, d, *J* = 11.5 Hz, Bn), 3.89 (2H, m, H1, H13), 3.77 (1H, dd, *J* = 11.5, 5.5 Hz, H1), 3.73 (1H, dd, *J* = 11.0, 1.0 Hz, H17), 3.70 (1H, ddd, *J* = 11.0, 9.5, 5.0 Hz, H3), 3.60 (1H, dd, *J* = 11.0, 5.0 Hz, H17), 3.56 (1H, d, *J* = 6.5 Hz, H9), 3.43 (1H, ddd, *J* = 11.0, 11.0, 4.0 Hz, H15), 3.37 (1H, ddd, *J* = 12.0, 9.5, 5.0 Hz, H6), 3.31 (2H, m, H2, H16), 3.01 (2H, m, H5, H12), 2.47 (1H, ddd, *J* = 11.5, 5.5, 4.0 Hz, H14eq), 2.40 (1H, ddd, *J* = 11.5, 5.0, 4.0 Hz, H4eq), 2.20 (1H, dd, *J* = 13.5, 5.0 Hz, H7eq), 1.81-1.93 (4H, m, H10, H11), 1.60 (2H, m, H4ax, H7ax), 1.40 (1H, ddd, *J* = 13.5, 11.5, 11.0 Hz, H14ax), 1.12 (3H, s, Me); ESI-MS *m*/*z* 577 ($M+Na^+$).
11. G. Matsuo, K. Kawamura, N. Hori, H. Matsukura, and T. Nakata, *J. Am. Chem. Soc*., 2004, **126**, 14374; J. S. Clark, M. C. Kimber, J. Robertson, C. S. P. McErlean, and C. Wilson, *Angew. Chem. Int. Ed.*, 2005, **44**, 6157; J. S. Clark and O. Hamelin, *Angew. Chem. Int. Ed.*, 2000, **39**, 372; J. L. Ravelo, A. Regueiro, and J. D. Martin, *Tetrahedron Lett.*, 1992, **33**, 3389; K. C. Nicolaou, D. G. McGarry, and P. K. Sommers, *J. Am. Chem. Soc.*, 1990, **112**, 3696.
12. G. L. Simpson, T. P. Heffron, E. Merino, and T. F. Jamison, *J. Am. Chem. Soc*., 2006, **128**, 1056; J. C. Valentine, F. E. McDonald, W. A. Neiwert, and K. I. Hardcastle, *J. Am. Chem. Soc*., 2005, **127**, 4586; T. Tokiwano, K. Fujiwara, and A. Murai, *Synlett*, 2000, 335.
13. The building block (**10**) was derived from corresponding TBS ether of **9**;[7] i) DIBAL, CH_2Cl_2; ii) I_2, PPh_3, imidazole, THF, 89% (two steps); iii) LDA, CH_3CO_2t-Bu, THF, HMPA; iv) aq. KOH, MeOH, THF, 76% (two steps).
14. E. P. Boden and G. E. Keck, *J. Org. Chem.*, 1985, **50**, 2394.
15. M. D. Rahim, T. Fujiwara, and T. Takeda, *Tetrahedron*, 2000, **56**, 763.

16. H. Uehara, T. Oishi, M. Inoue, M. Shoji, Y. Nagumo, M. Kosaka, J.-Y. Le Brazidec, and M. Hirama, *Tetraheadron*, 2002, **58**, 6493; T. Oishi, H. Uehara, Y. Nagumo, M. Shoji, J. -Y. Le Brazidec, and M. Hirama, *Chem. Commun*., 2001, 381.
17. Other related carbonyl olefination, see: H. W. B. Johnson, U. Majumder, and J. D. Rainier, *J. Am. Chem. Soc.*, 2005, **127**, 848.
18. The effect of temperature on the diastereoselectivity is significant and hydroboration at 0 °C gave **17** as a major product. Hydroboration using thexylborane did not improve the selectivity. M. Sasaki, H. Fuwa, M. Inoue, and K. Tachibana, *Tetrahedron Lett.*, 1998, **39**, 9027.
19. K. C. Nicolaou, M. E. Duggan, and C.-K. Hwang, *J. Am. Chem. Soc*., 1986, **108**, 2468; K. C. Nicolaou, C. V. C. Prasad, C.-K. Hwang, M. E. Duggan, and C. A. Veale, *J. Am. Chem. Soc*., 1989, **111**, 5321; K. C. Nicolaou, M. E. Duggan, and C.-K. Hwang, *Chem. Eur. J*., 1999, 599.
20. Other reaction conditions, e.g. $AgNO_3$-NCS, $NaHCO_3$ or pyridine, did not provide **21**.
21. H. Fuwa, M. Sasaki, and K. Tachibana, *Tetrahedron*, 2001, **57**, 3019.
22. Spectral data of **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-7.34 (10H, m, Ph), 4.53-4.60 (3H, m, Bn), 4.35 (1H, d, *J* = 11.0 Hz, Bn), 4.01 (1H, m), 3.89 (1H, m), 3.83 (1H, d, *J* = 4.0 Hz), 3.83 (1H, d, *J* = 4.5 Hz), 3.72-3.77 (2H, m), 3.58 (1H, d, *J* = 7.0 Hz, H9 or H19), 3.56 (1H, m), 3.54 (1H, d, *J* = 6.5 Hz, H9 or H19), 3.30-3.50 (3H, m), 3.25 (2H, m), 3.13 (1H, m), 3.00 (3H, m), 2.42 (2H, m), 2.28 (1H, m), 2.23 (1H, dd, *J* = 14.5, 4.5 Hz), 2.17 (1H, dd, *J* = 14.0, 5.0 Hz) 1.89-2.00 (2H, m), 1.77-1.86 (4H, m), 1.47-1.66 (6H, m), 1.38 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz) 1.13 (3H, s, Me), 1.11 (3H, s, Me); ESI-MS *m*/*z* 751 ($M+H^+$).
23. Chemical shifts of angular methyl groups of 6/7 *cis*-fused systems are ca. 1.1 ppm, while those of *trans*-fused ones are ca. 1.2 ppm. ^{1}H NMR (500 MHz, $CDCl_3$) δ **22**: 1.26 and 1.10; **23**: 1.22 and 1.10; for reference **1**: 1.23; **2**: 1.12; **3**: 1.13 and 1.11.