Synthesis of the B,C,D,E,F-Ring Fragment of Pinnatoxins

Tetsuya Sugimoto, Jun Ishihara, Akio Murai*

Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo, 060-0810, Japan
Fax 81-11-706-2714; E-mail: amurai@sci.hokudai.ac.jp

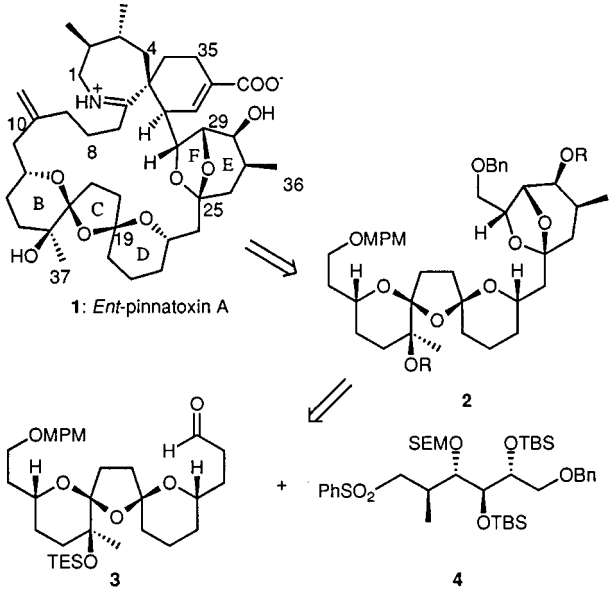
Received 24 February 1999

Abstract: Construction of the B,C,D,E,F-ring of pinnatoxins is disclosed. Julia coupling reaction between the E,F-ring fragment (C_{26}-C_{31}) as the sulfone and the B,C,D-ring fragment (C_{10}-C_{25}) as the aldehyde proceeded smoothly to afford the B,C,D,E,F-ring system via acetalization.

Key words: pinnatoxin, dispiroacetal, trioxadispiro[5.1.5.2]pentadecane dioxabicyclo[3.2.1]octane

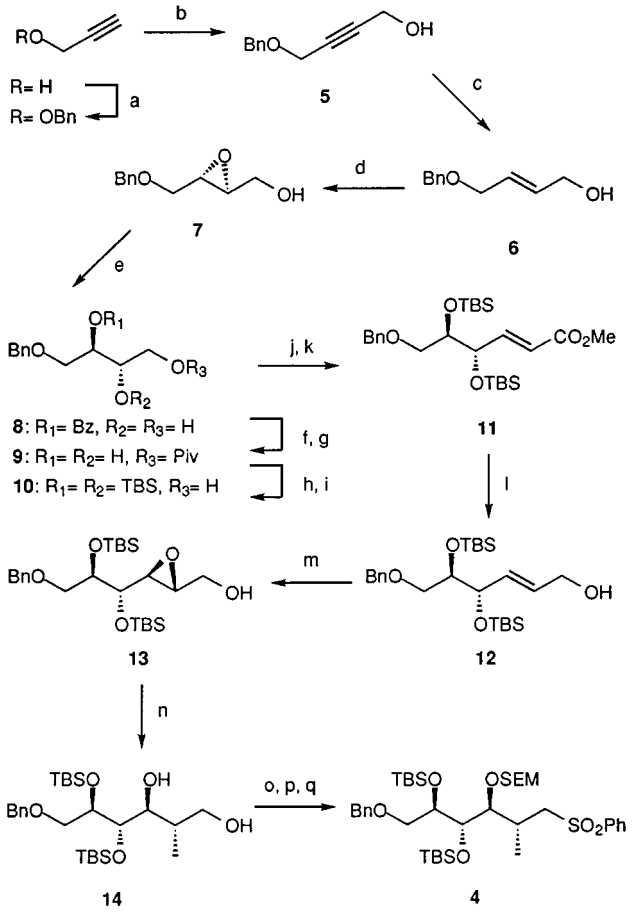
Pinnatoxins are potent shellfish toxins isolated from *Pinna muricata*,[1] and their unique structures and biological properties have attracted the attention of scientists.[2] Recently, we reported the stereoselective construction of the dispiroacetal core (C_{10}-C_{24} fragment) of pinnatoxins.[3] In this report, the synthesis of the B,C,D,E,F-ring system **2** is described.

Our retrosynthetic pathway is shown in Scheme 1. The coupling of the E,F-ring part and the dispiroacetal core **3**[4, 5] would be effected by Julia coupling reaction. All the chiral centers in sulfone **4** could be introduced by Sharpless asymmetric epoxidation (AE).



Scheme 1

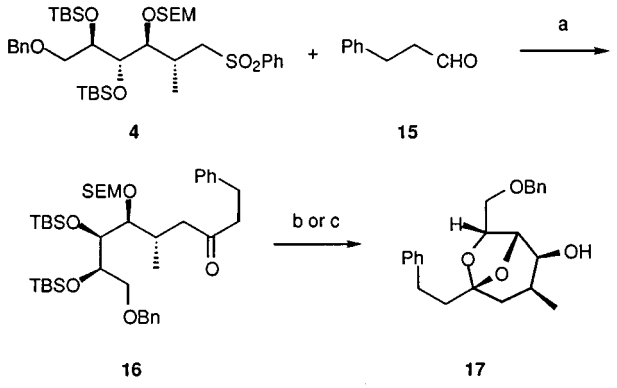
Propargyl alcohol was protected as its benzyl ether which, upon addition to the *p*-formaldehyde, gave the primary alcohol **5** in 82% yield for 2 steps (Scheme 2). The triple bond was reduced with LAH in THF at low temperature to afford **6** in 73% yield. When the reaction was carried out at rt, elimination of the benzyloxy group took place to give the allene compound. Sharpless AE of **6** provided epoxide **7** in 93% yield in 92% ee.[6] The epoxide was opened regioselectively with $Ti(O^iPr)_4$ and benzoic acid to afford **8** in 94% yield. The benzoyl group in **8** was cleaved with NaOH aq in MeOH (94% yield) and the primary hydroxyl group of the resulting triol compound was protected as a



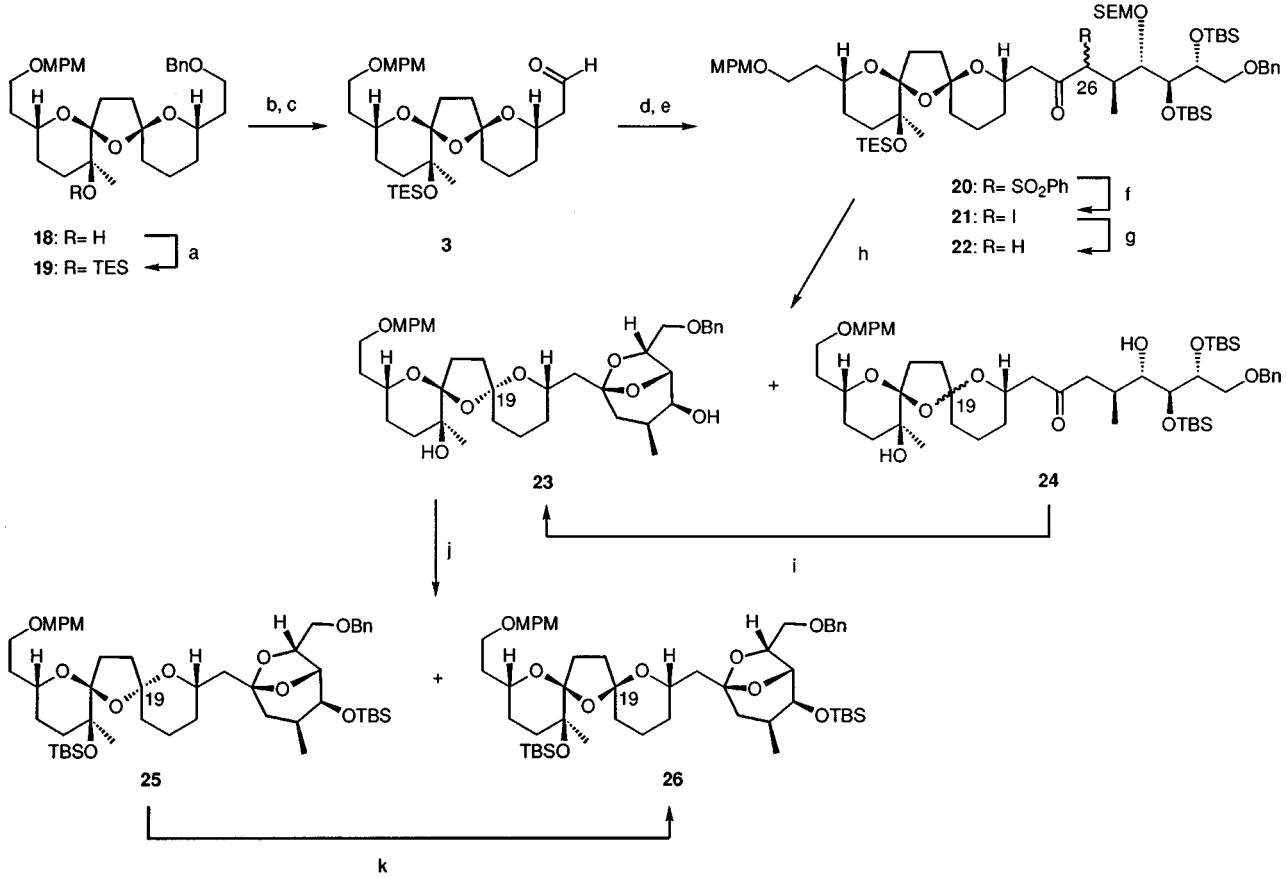
Scheme 2. *Reagents and conditions*: a) NaH, BnBr, TBAI, THF, rt, 7.5 h, 93%; b) BuLi, $(CH_2O)_n$, THF, -78 °C → 0 °C, 50 min, 88%; c) LAH, THF, -78 °C → 0 °C, 7.5 h, 73%; d) L-(+)-DET, $Ti(O^iPr)_4$, TBHP, MS4A, CH_2Cl_2, -25 °C, 21 h, 93%, >92% ee; e) $Ti(O^iPr)_4$, $PhCO_2H$, CH_2Cl_2, rt, 2 h, 94%; f) 4M aq. NaOH, MeOH, rt, 45 min, 94%; g) PivCl, CH_2Cl_2, Py, 0 °C, 18 h, 76%; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 25 min, 100%; i) DIBAL, CH_2Cl_2, -78 °C, 20 min, 98%; j) DMPI, CH_2Cl_2, 2 d; k) $Ph_3P{=}CHCO_2Me$, PhH, rt, 21 h, 86% for 2 steps; l) DIBAL, CH_2Cl_2, -78 °C, 20 min, 99%; m) D-(-)-DET, $Ti(O^iPr)_4$, TBHP, MS4A, CH_2Cl_2, -25 °C, 21 h, 93%; n) Me_2CuLi, ether, -30 °C, 23 h, 96%; o) *N*-(phenylthio)phthalimide, Bu_3P, CH_2Cl_2, rt, 4 h, 76%; p) SEMCl, $^iPr_2NEt$, TBAI, $(ClCH_2)_2$, reflux, 6 h, ~100%; q) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, rt, 25 min, 95%.

pivaloate ester to obtain **9** in 76% yield. Silylation of two secondary hydroxyl groups with TBSOTf and detachment of the primary pivaloyl group gave **10** in 98% yield for 2 steps. Oxidation of **10** with Dess-Martin periodinane and the following Wittig reaction provided the ester **11** (86% yield, 2 steps), which was reduced with DIBAL to allyl alcohol **12** in 99% yield. Sharpless AE of **12** proceeded with excellent selectivity; when the substrate of 92% ee was treated under the standard conditions, the epoxide **13** was obtained in >98% ee as a result of kinetic resolution.[7] On the other hand, when **12** was exposed to *m*-CPBA, the opposite and high stereoselectivity was observed according to the literature.[8] Regioselective opening of the epoxide was effected by Me_2CuLi in ether at -30 °C to give **14** in 96% yield. The primary hydroxyl group of **14** was converted to phenyl sulfide in 76% yield with *N*-(phenylthio)phthalimide and Bu_3P in CH_2Cl_2. The remaining secondary hydroxyl group was protected as SEM ether in a quantitative yield. Finally, the sulfide group was oxidized with *m*-CPBA to provide sulfone **4** in 95% yield.

In order to construct the E,F-ring fragment, we examined the coupling of **4** and the acetalization reaction as model studies (Scheme 3). The coupling reaction of **4** and hydrocinnamaldehyde **15** proceeded under the standard Julia coupling conditions and the resulting diastereomeric mixture was oxidized with Dess-Martin periodinane to ketosulfone. The subsequent desulfonylation reaction with Al(Hg) was somewhat troublesome, e.g., the reaction often stopped without completion. Eventually, the coupled product **16** was provided in 53% overall yield. Under both aqueous and non-aqueous conditions (46% HF aq in MeCN and SiF_4 in MeCN, respectively), the deprotection



Scheme 3. *Reagents and conditions*: a) i) BuLi, THF, -78 °C, 30 min, then **15**, -78 °C, 15 min, ii) DMPI, CH_2Cl_2, rt, 50 min, iii) Al(Hg), THF-H_2O (10:1), rt, 3.5 d, 53% from **29**; b) 46% aq. HF-MeCN (1:20), rt, 23 h, 77%; c) SiF_4, MeCN, rt, 25 min, 74%.

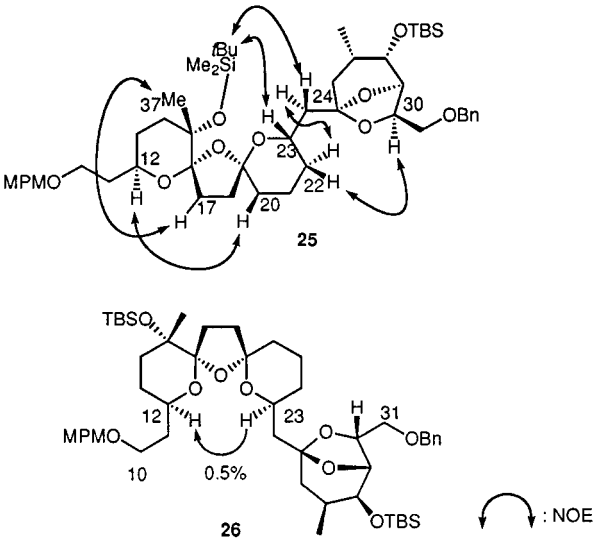


Scheme 4. *Reagents and conditions*: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 95%; b) Raney Ni (W2), H_2, EtOH, rt, 4 h, 81%; c) DMPI, CH_2Cl_2, rt, 5 h, 100%; d) **4**, BuLi, THF, -78 °C, 30 min, then **3**, -78 °C, 1.5 h; e) DMPI, CH_2Cl_2, rt, 3 h; f) SmI_2, THF-MeOH (7:1), -95 ~ -80 °C, 1 h, **21a**: 21%, **21b**: 34%, from **3**; g) Zn-Cu couple, sat. NH_4Cl in MeOH, rt, 10 min, 79% from **21a**, 90% from **21b**; h) 46% aq. HF-MeCN-THF (1:10:2), rt, 11 h, **23**: 60%, **22**: 32%; i) HF·Py, THF, rt, 67 h, 53%; j) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 20 h, **25**: 49%, **26**: 34%; k) CSA, CH_2Cl_2, rt, 5 h, 100% (**25**:**26**, 4.3:1).

and the following acetalization reaction occurred to produce predominantly bicyclo compound **17** having the natural relative configuration, albeit the C_{28} SEM group was cleaved under the reaction conditions. These results revealed that the bicyclo system of **17** was more favored than the other isomers, which finding was in good agreement with the results of MM2 calculations.[9] Keeping these results in mind, we aimed to construct the B,C,D,E,F-ring fragment **2**.

Compound **18** was prepared by our previous procedure[4] and its tertiary hydroxyl group was protected as TES ether to afford **19** in 95% yield (Scheme 4). The benzyl group was detached selectively with Raney nickel and the resulting primary hydroxyl group was oxidized to aldehyde **3**. The Julia coupling between **3** and **4** proceeded smoothly and the subsequent oxidation reaction gave keto-sulfone **20**. The desulfonylation reaction was performed with SmI_2 in THF/MeOH at -95 ~ -80 °C. The product was an unexpected diastereomeric mixture of α-iodo-ketones **21a** and **21b**. Although the stereochemistry at C26 was not determined, **21a** and **21b** were obtained in 21% and 34% yields from aldehyde **3**, respectively, along with the recovery of unreacted sulfone **4** (58% yield). The α-iodo-ketones **21a** and **21b** were reduced easily with a Zn-Cu couple to the corresponding ketone **22** in 79% and 90% yields, respectively. The final acetalization reaction was first examined with 46% aq. HF-MeCN. When the reaction mixture was stirred at rt for 6 h, all silicon protecting groups were removed, and the isolated yield of penta-cyclic compound **23** resulted only in 40%. When a mixture of 46% aq. HF-MeCN-THF (1:10:2) was used,[10] the reaction proceeded sluggishly, and after 11 h, **23** was obtained in 60% yield along with a mixture of the compounds **24** in 32% yield which had two TBS groups and no TES and SEM groups. The latter was further treated with HF·Py in THF at rt for 67 h to afford 53% of **23**. As a result, the yield of **23** amounted to 78% from **22**. When **22** was directly reacted with HF·Py in THF at rt for 24 h, the yield of **23** was only 48%.

Then, the isomerization of **23** to the compound having the natural relative stereochemistry was attempted. In order to cleave the intramolecular hydrogen-bonding, two hydroxyl groups were protected as TBS ethers. When the diol **23** was reacted with TBSOTf-2,6-lutidine (1:2) in CH_2Cl_2 at rt for 4 h, the products **25**[11] and **26**[12] were obtained in 49% and 34% yields, respectively. Further treatment effected no change. It is to be noted that the isomerization at C19 was not completed under standard silylation conditions, in contrast with the results of Kishi's report.[1d] When each sample of pure **25** or **26** was stirred with TBSOTf-2,6-lutidine (1:2) and MeOH in CH_2Cl_2, no reaction was observed. These results indicate that the isomerization in question occurred before the two hydroxyl groups were silylated. Once the two hydroxyl groups had been silylated, the TfOH-2,6-lutidine system no longer promoted the isomerization. When **25** was exposed to more acidic conditions (cat. CSA in CH_2Cl_2), the isomerization to **26** occurred. The reaction appeared to be in equilibrium within 10 min judging from TLC and further treatment (up to 4.5 h) was not effective. The product consisted of a 4.3:1 mixture of **25** and **26** in 100% total yield on the basis of NMR analysis.



Figure

The structures of **25** and **26** were confirmed by HMBC, HSQC, and NOE experiments (Figure). The characteristic NOE's correlations between H12 and H23 were observed in **26**, which exactly corresponded to the B,C,D,E,F-ring part of pinnatoxins A, B, and C. These results could open an alternate route to providing the compound **26** preferentially having the desired configuration on several recycles of **25**.

In conclusion, we have demonstrated the construction of all acetal rings of pinnatoxins. Further efforts toward the total synthesis of pinnatoxins are underway in our laboratory.

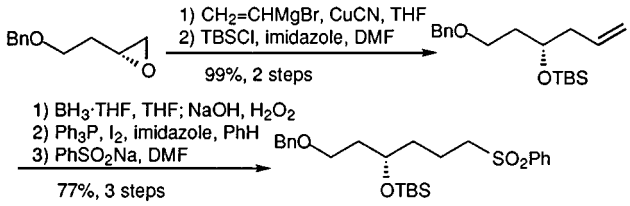
References and Notes

(1) (a) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A; Fukuzawa, S.; Zeng, S. Z.; Chen, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 1155. (b) Chou, T.; Kamo, O.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023. (c) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4027; (d) The absolute configuration of natural pinnatoxin A was determined synthetically as enantiomer of **1**: McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.

(2) Synthetic studies on pinnatoxins: (a) Noda, T; Ishiwata, A.; Uemura, S.; Sakamoto, S.; Hirama, M. *Synlett* **1998**, 298. (b) Suthers, B. D.; Jacobs, M. F.; Kiching, W. *Tetrahedron Lett.* **1998**, *39*, 2621. Total synthesis of *ent*-pinnatoxin A (**1**): ref. 1d.

(3) (a) Sugimoto, T.; Ishihara, J.; Murai, A. *Tetrahedron Lett.* **1997**, *38*, 7379. (b) Ishihara, J.; Sugimoto, T.; Murai, A. *Synlett* **1998**, 603.

(4) The B,C,D-ring part was prepared according to our previous report, except for the sulfone segment which was prepared from the known epoxide[5] as follows:



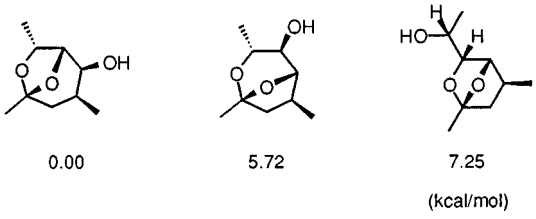
(5) Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, 621.

(6) Katsuki, T.; Lee, A. W. N.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.

(7) (a) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221. (b) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Org. Chem.* **1984**, *49*, 3517.

(8) Maruyama, K.; Ueda, M.; Sasaki, S.; Iwata, Y.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 4517.

(9) The relative energy differences among the model compounds are shown below: The calculation was performed by Cache Mechanics 3.6.



(10) Since the solubility of **22** in MeCN was very low, THF was required as a co-solvent for larger scale reaction.

(11) **25**: $[\alpha]_D^{18}$ -61.7 (*c* 0.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$), δ 0.02 (3H, s), 0.04 (3H, s), 0.08 (6H, s), 0.82 (3H, d, *J* = 6.6 Hz, H36), 0.88 (9H, s), 0.90 (9H, s), 1.19 (1H, dq, *J* = 3.0, 12.7 Hz, H22ax), 1.28 (3H, s, H37), 1.41 (1H, brt, *J* = 13.5 Hz, H26ax), 1.42 (1H, m, H13ax), 1.50 (1H, dd, *J* = 5.8, 13.5 Hz, H26eq), 1.55 (1H, m, H20a), 1.56 (1H, m, H17a), 1.56 (1H, m, H21ax), 1.57 (1H, m, H13eq), 1.57 (1H, m, H14eq), 1.64 (1H, m, H20b), 1.68 (2H, m, H11), 1.74 (1H, dd, *J* = 10.8, 14.0 Hz, H24a), 1.87 (1H, m, H18a), 1.88 (1H, m, H21eq), 1.95 (1H, m, H18b), 1.96 (1H, m, H22eq), 2.19 (1H, m, H27), 2.20 (1H, dd, *J* = 3.0, 14.0 Hz, H24b), 2.21 (1H, dt, *J* = 4.2, 13.2 Hz, H14ax), 2.28 (1H, dt, *J* = 9.3, 11.6 Hz, H17b), 3.47 (1H, m, H28), 3.49 (2H, t, *J* = 6.3 Hz, H10), 3.61 (1H, dd, *J* = 7.3, 10.0 Hz, H31a), 3.76 (1H, dd, *J* = 6.4, 10.0 Hz, H31b), 3.80 (3H, s, MPM), 3.95 (1H, m, H12), 4.12 (1H, m, H30), 4.13 (1H, m, H23), 4.21 (1H, dd, *J* = 2.0, 4.4 Hz, H29), 4.36 (1H, d, *J* = 11.5 Hz, MPM), 4.41 (1H, d, *J* = 11.5 Hz, MPM), 4.49 (1H, d, *J* = 12.4 Hz, Bn), 4.63 (1H, d, *J* = 12.4 Hz, Bn), 6.86 (2H, d, *J* = 8.8 Hz, MPM), 7.24 (2H, d, *J* = 8.8 Hz, MPM), 7.29-7.37 (5H, m, Bn).

(12) **26**: $[\alpha]_D^{20}$ -85 (*c* 0.02, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6), δ 0.05 (3H, s), 0.06 (3H, s), 0.10 (3H, s), 0.16 (3H, s), 0.97 (3H, d, *J* = 6.9 Hz, H36), 0.99 (9H, s), 1.00 (9H, s), 1.314 (3H, s, H37), 1.33-1.36 (1H, m), 1.38-1.42 (1H, m), 1.47-1.52 (1H, m), 1.61-1.93 (10H, m), 2.06 (1H, dt, *J* = 7.8, 13.8 Hz, H26ax), 2.10-2.20 (3H, m, H27, H11), 2.16 (1H, dd, *J* = 6.6, 14.5 Hz, H24a), 2.25-2.33 (2H, m), 2.44 (1H, dd, *J* = 5.0, 14.5 Hz, H24b), 3.32 (3H, s, MPM), 3.54 (1H, dd, *J* = 7.8, 9.4 Hz, H31a), 3.59 (1H, dd, *J* = 1.8, 4.0 Hz, H28), 3.69 (1H, dd, *J* = 5.5, 9.4 Hz, H31b), 3.76 (1H, m, H30), 3.97 (1H, m, H23), 4.19 (1H, d, *J* = 12.0 Hz), 4.32 (1H, d, *J* = 12.0 Hz), 4.32-4.42 (4H, m, H10, H12, H29), 4.47 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 11.9 Hz), 6.85 (2H, d, *J* = 8.8 Hz, MPM), 7.10 (2H, m, Bn), 7.18-7.22 (3H, m, Bn), 7.37 (2H, d, *J* = 8.8 Hz, MPM).

Article Identifier:
1437-2096,E;1999,0,05,0541,0544,ftx,en;Y02699ST.pdf