Synthetic Study of Pinnatoxin A: Intramolecular Diels-Alder Approach to the AG-ring

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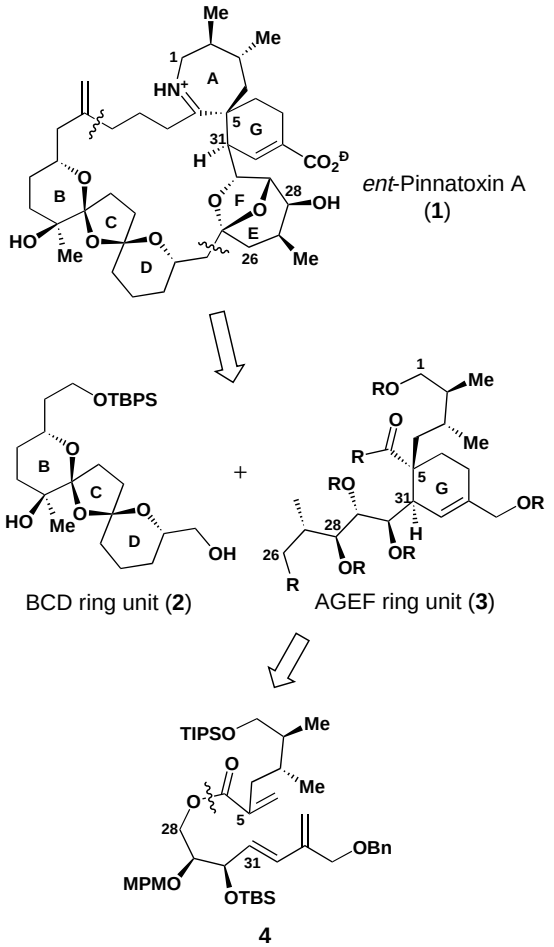
Abstract: A chiral quaternary carbon (C5) with the G-ring of pinnatoxin A has been diastereoselectively constructed via an intramolecular Diels-Alder reaction.

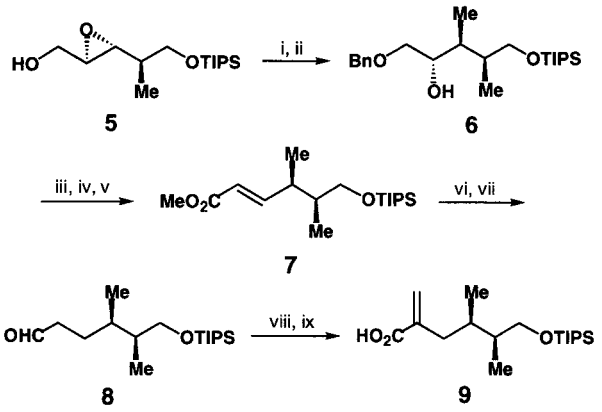
Key words: pinnatoxin A, diastereoselectivity, Ca^{2+}channel, intramolecular Diels-Alder reaction, convergent synthesis



TBPS = *tert*-butyldiphenylsilyl; TIPS = triisopropylsilyl; TBS = *tert*-butyldimethylsilyl; MPM = *p*-methoxyphenylmethyl

Scheme 1

Pinnatoxin A, recently isolated from the shellfish *Pinna muricata*,[1] is a member of the marine toxins which possess a spiro-linked cyclic imine within a carbocyclic macroring system.[2,3] The unique structure and potent biological activity as a Ca^{2+} channel activator[4] aroused our interest in a total synthesis. The total synthesis of *ent*-pinnatoxin A (**1**) recently reported by Kishi′s group has established the absolute stereochemistry.[5] The synthesis seems to be rather linear and the stereoselectivity in the penultimate intramolecular Diels-Alder reaction (IMDA) was not very high. A more convergent strategy that couples the two unique structural units, BCD-ring unit (**2**)[6,7] and AEGF-ring unit (**3**) (Scheme 1), is attractive, because it would allow the synthesis of a number of related analogs for a detailed study of the structure-activity relationship. We report here a diastereoselective IMDA approach to constructing the G-ring of **3** from triene (**4**).



Scheme 2. *Reagents and conditions* : (i) NaH (1.4 eq), BnBr (1.05 eq), Bu_4NI (0.1 eq), 0°C~rt, 2.5 h (94%); (ii) Me_3Al (3 eq), *n*-BuLi (0.3 eq), toluene, –78°C~rt, 2 d (85%); (iii) H_2 (1 atm), 10% Pd/C (cat.), AcOEt, rt, 2.5 h; (iv) $NaIO_4$ (2.0 eq), THF–H_2O, rt, 2.5 min; (v) $Ph_3P{=}CHCO_2Me$ (1.05 eq), toluene, rt, 16 h (85%, three steps); (vi) H_2 (1 atm), 10% Pd/C (cat.), EtOAc, 2 h (99%); (vii) DIBAL-H (2.5 eq), toluene, –78°C, 2 h (90%); (viii) $[Me_2N{=}CH_2]^+I^-$ (2 eq), Et_3N (10 eq), CH_2Cl_2, rt, 24 h (91%); (ix) $NaClO_2$ (3 eq), NaH_2PO_4 (3 eq), 2-methyl-2-butene (10 eq), *t*-BuOH–H_2O, 1 h (98%).

Scheme 2 illustrates the stereoselective synthesis of the dienophile (**9**). Protection of the α,β-epoxy alcohol (**5**)[8] as a benzyl ether followed by ring-opening under Pfalts′ conditions[9] provided the *syn*-dimethyl moiety (**6**) regioselectively. After hydrogenolysis of the benzyl ether, the resulting 1,2-diol was oxidatively cleaved and then treated with methyl (triphenylphosphoranylidene)acetate to give the α,β-unsaturated ester (**7**). The unsaturated ester (**7**) was converted to aldehyde (**8**) via hydrogenation and DIBAH-reduction. After α-methylenation of the aldehyde

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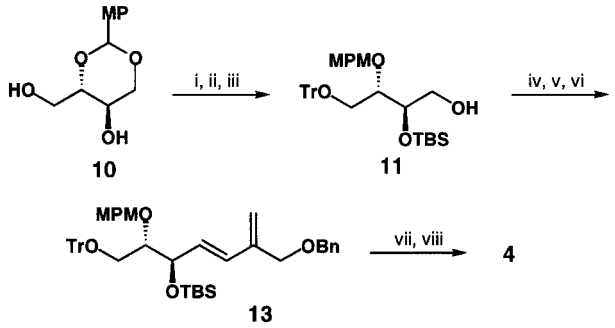
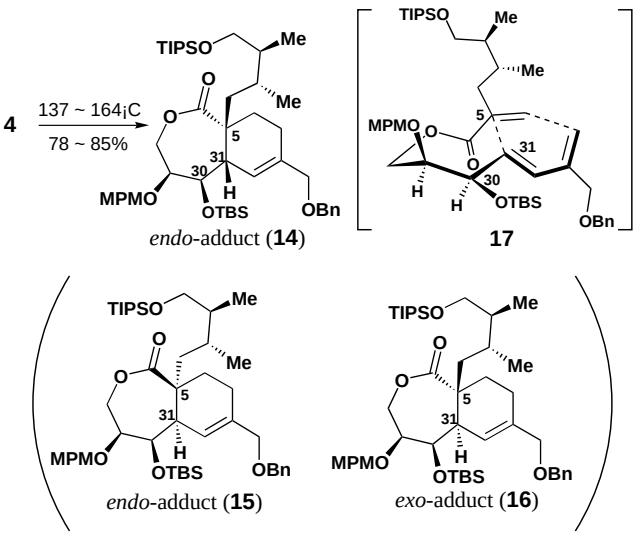
(**8**) using Eschenmoser reagent,[10] $NaClO_2$ oxidation gave dienophile (**9**) in good yield.



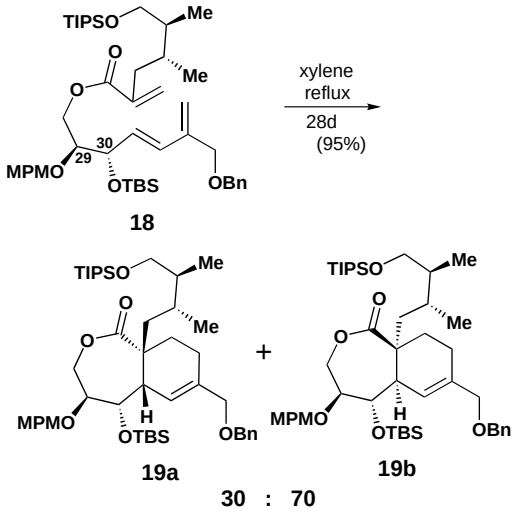
Scheme 3. *Reagents and conditions* : (i) TrCl (1.1 eq), Py–CH_2Cl_2, rt, 2 d (99%); (ii) *t*-$BuMe_2SiCl$ (1.3 eq), imidazole (2.6 eq), DMF, rt (99%); (iii) DIBAL-H (5 eq), CH_2Cl_2, –78~–30°C (70%); (iv) $(COCl)_2$ (1.5 eq), Et_3N (5 eq), DMSO (3 eq), –78~–40°C, 30 min; (v) $(MeO)_2P(O)CH_2COCH_2OBn$ (**12**) (1.1 eq), LiCl (2.5 eq), *i*-Pr_2NEt (2.5 eq), CH_3CN, rt, 30 h (64%, two steps); (vi) Ph_3PCH_3Br (2.1 eq), *n*-BuLi (2.0 eq), –20°C~rt, 12 h (79%); (vii) Et_2AlCl (4 eq), CH_2Cl_2, –78°C, 45 min (99%); (viii) **9** (1.05 eq), diethyl azodicarboxylate (4 eq), Ph_3P (4 eq), toluene, 0°C, 24 h (85%).

The chiral diol (**10**)[11] derived from *D*-glucose was converted to **11** via protection of the primary alcohol and the secondary alcohol as the trityl ether and TBS ether, respectively, followed by regioselective reductive ring cleavage of *p*-methoxybenzylidene acetal with DIBAL-H (Scheme 3).[12] The aldehyde obtained by Swern oxidation of **11** was subjected to Wadsworths-Emmons olefination with **12**[13] under mild conditions[14] and further Wittig olefination to give the diene (**13**). Esterification of the carboxylic acid (**9**) with the alcohol which was obtained by selective deprotection of the trityl ether of **13** with Et_2AlCl[15] proceeded successfully under Mitsunobu conditions[16] to give the Diels-Alder precursor (**4**) in 85% yield.

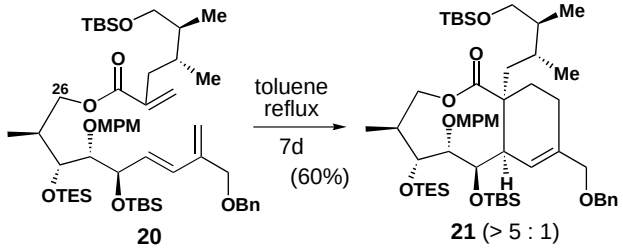


Scheme 4

IMDA of **4** was examined under various conditions: under reflux in toluene, **4** was recovered. At higher temperature in xylene (reflux, 28 days), IMDA of **4** proceeded slowly to give an *endo*-type cycloadduct (**14**) as the sole product in 85% yield; in mesitylene (reflux), the reaction was complete within 7 days (78%) (Scheme 4). None of the possible *endo*-type diastereomer (**15**)[17] nor any *exo*-type adducts such as **16** were detected. Lewis acid catalysts, such as MAD[18a] and $Eu(fod)_3$,[18b] did not affect the *endo* preference. The stereochemistry of **14** was assigned in a NOE experiment.[19] The exclusive formation of **14**, which has a correct stereochemistry at the C5 quaternary carbon, was attributable to the C30 bulky substituent: the enoate moiety approaches *anti* to the C30-OTBS group in the transition state model (**17**).[17] IMDA reaction of the epimer (**18**) of **4**, therefore, showed a low diastereoselectivity (**19a** : **19b** = 30 : 70) (Scheme 5). Furthermore, the triene (**20**), which has the two-carbon longer chain, was subjected to IMDA reaction. The major product was also an *endo* adduct (**21**) but the diastereoselectivity was completely reversed (Scheme 6).



Scheme 5



Scheme 6

In conclusion, we have demonstrated that the IMDA approach via **4** leads to the correct stereochemistry at the C5 chiral quaternary carbon of the G-ring of **3**, which is one of the most challenging problems in the synthesis of **1**.

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Further study directed toward total synthesis of **1** including the epimerization at C31 is currently underway in our laboratory.

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(8) Prepared from methyl (R)-(-)-hydroxy-2-methylpropionate as follows: 1) TIPSCl, imidazole, DMF (83%); 2) DIBAL-H, CH_2Cl_2 (92%); 3) $Ph_3P{=}CHCO_2Me$, toluene (95%); 4) DIBAL-H, CH_2Cl_2 (83%); 5) Ti(O*i*-Pr)$_4$ (cat.), (-)-diethyl tartrate (cat.), *t*-BuOOH, molecular sieves 4A, CH_2Cl_2 (95%).

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(11) Prepared from D-glucose as follows: 1) D-glucose, p-anisaldehyde (2 eq), *p*-TsOH (cat.), DMF; 2) $NaIO_4$ (3 eq), MeOH; 3) $NaBH_4$ (2 eq), MeOH in 25% yield (3 steps).

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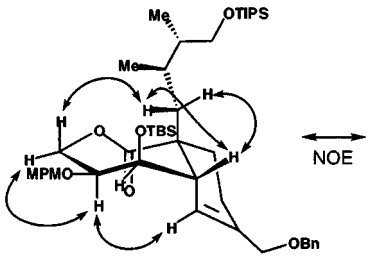
(19) **14** ($[\alpha]_D^{25}$ 18.8° (*c* 0.80, $CHCl_3$)): IR(film) 2954, 2866, 1723, 1613, 1516, 1464, 1251, 1189, 1112, 1031, 884, 837, 758, 679 (cm^{-1}); ^{1}H NMR ($(CD_3)_2CO$, 600 MHz) δ 7.28 (5 H, m, **Ph**CH2O), 7.23 (2 H, m, M**P**M), 6.85 (2 H, d, J = 8.6 Hz, M**P**M), 5.39 (1 H, brs, H32), 4.67 (1 H, brd, J = 12.0, 8.0 Hz, H28), 4.69 (1 H, d, J = 11.2 Hz, MP**M**), 4.57 (1 H, d, J = 11.2 Hz, MP**M**), 4.35 (1 H, d, J = 11.9 Hz, PhC**H**$_2$O), 4.33 (1 H, d, J = 11.9 Hz, PhC**H**$_2$O), 4.09 (1 H, brs, H30), 4.00 (1 H, brd, J = 12.0 Hz, H28), 3.82 (1 H, d, J = 12.0 Hz, H34), 3.79 (1 H, d, J = 12.0 Hz, H34), 3.72 (3 H, s, **M**PM), 3.56 (1 H, dd, J = 9.8, 7.5 Hz, H1), 3.52 (1 H, bt, J = 7.5, 1.5 Hz, H29), 3.46 (1 H, dd, J = 9.8, 6.4 Hz, H1), 2.64 (1 H, brs, H31), 2.47 (1 H, m, H4), 2.29 (2 H, m, H35, H39), 1.97 (1 H, m, H3), 1.92 (1 H, m, H35), 1.58 (1 H, qdd, J = 7.0, 7.0, 3.2 Hz, H2), 1.45 (2 H, m, H4, H39), 1.10–1.00 (21 H, m, SiC**H**(C**H**$_3$)$_2$), 0.88 (9 H, m, SiC(C**H**$_3$)$_3$), 0.77 (3 H, d, J = 7.0 Hz, C2(C**H**$_3$)), 0.74 (3 H, d, J = 7.0 Hz, C3(C**H**$_3$)), 0.07 (3 H, s, SiC**H**$_3$), 0.05 (3 H, s, SiC**H**$_3$). ^{13}C NMR ((CD3)2CO, 150 MHz) δ >150 (C6=O, MPM), 139.75 (Bn), 137.72 (C33), 131.14 (MPM), 130.36 (MPM), 128.99 (Bn), 128.46 (Bn), 128.13 (Bn), 124.22 (C32), 114.42 (MPM), 78.08 (C29), 77.36 (C30), 74.35 (C34), 74.29 (MPM), 72.09 (Bn), 67.28 (C1), 64.70 (C28), 55.44 (MeO), 50.90 (C5), 47.36 (C31), 43.82 (C4), 43.46 (C2), 43.38 (C3), 33.06 (C35), 28.48 (SiC(**C**H$_3$)$_3$), 26.44 (SiC(**C**H$_3$)$_3$), 24.66 (C39), 18.79 (Si**C**(CH$_3$)$_3$), 18.41 (SiCH(**C**H$_3$)$_2$), 15.21 (C3-**C**H$_3$), 12.76 (Si**C**H(CH$_3$)$_2$), 11.82 (C2-**C**H$_3$), –4.45 (Si**C**H$_3$).



NOE correlation of **4**

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