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First total synthesis of (−)-diospongin B☆

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Abstract—The first total synthesis of (−)-diospongin B has been achieved starting from benzaldehyde using chiral allylation, a base catalyzed conjugate addition of an α,β-unsaturated ester and an intramolecular oxy-Michael reaction as the key steps in 16% overall yield.

The 2,4,6-trisubstituted tetrahydropyran core is found in a number of natural products.[1] Many examples possess a tetrahydropyran core, and show excellent biological properties. Recently identified trisubstituted pyran natural products include leucascandrolide A[2] **1**, phorboxazole A[3] **2**, and diospongins **3** and **4**.[4] We have been interested in the total synthesis of bioactive natural products, which contain substituted tetrahydropyran rings (Fig. 1).

Diospongin B (**4**) is one such example isolated in 2003 from the rhizomes of *Dioscorea spongiosa* and was reported to have anti-osteoporotic activity.[4]

As part of our research programme on the synthesis of substituted tetrahydropyran-containing molecules,[5] we report herein, the first total synthesis of (−)-diospongin B starting from benzaldehyde using a Keck asymmetric allylation, a base catalyzed conjugate addition of an α,β-unsaturated ester and an intramolecular oxy-Michael reaction as the key steps (Scheme 1).

The chiral allyl phenyl carbinol **5**, easily obtained by Keck allylation[6] of benzaldehyde was subjected to one-pot ozonolysis-Wittig olefination[7] with the stable ylide, ethoxycarbonylmethylene triphenylphosphorane to furnish the α,β-unsaturated ester **6** in 79% yield. The protected *syn* 1,3-diol derivative **7** was prepared in 61% yield by base catalyzed intramolecular conjugate addition using PhCHO, *t*-BuOK in THF.[8] Next, the reduction of the ester group in compound **7** with lithium aluminium hydride in THF gave compound **8** in 77% yield. The primary alcohol in **8** was oxidized[9] to the aldehyde using IBX in THF/DMSO at room temperature and the corresponding crude aldehyde immediately

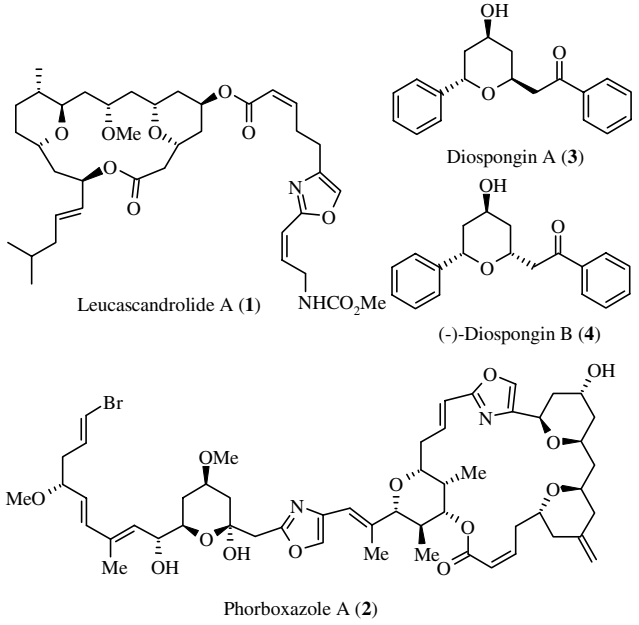

Figure 1.

Keywords: Keck allylation; Base catalyzed conjugate addition; Intramolecular oxy-Michael reaction; Diospongin B; Substituted tetrahydropyran.
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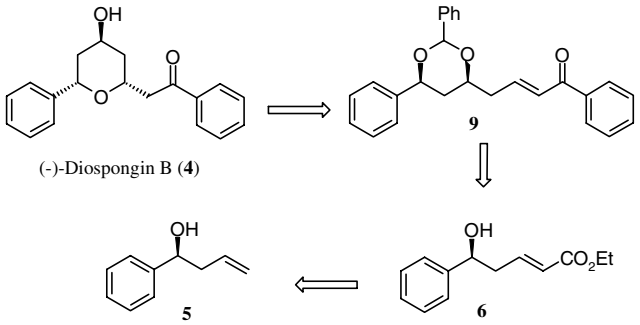
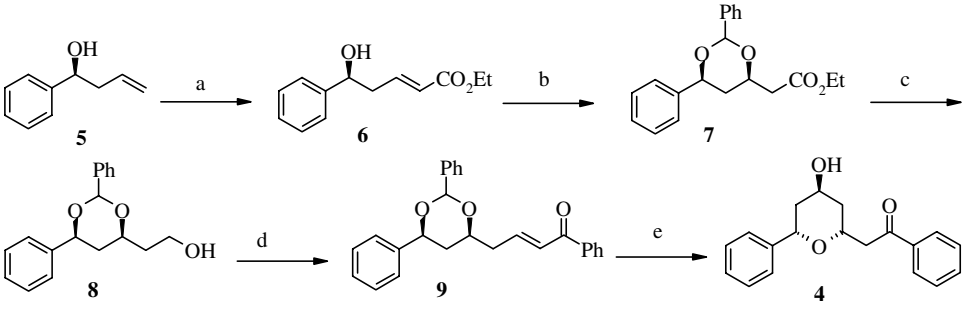


Scheme 1. Retrosynthetic analysis.

treated under normal Wittig[10] conditions with phenacyl triphenylphosphonium bromide and *t*-BuOK in THF to give the required *E*-enone derivative **9** in 77% yield over two steps.

Finally, hydrolysis of the benzylidene acetal group as well as intramolecular oxy-Michael addition was successfully achieved in one-pot[5a,11] with 50% TFA in CH_2Cl_2 to furnish the target molecule **4** {$[\alpha]_D^{25}$ −18.4 (*c* 0.5, $CHCl_3$),[12] HRMS: $m/z = 297.1483$ $[M+H]^+$} as a single isomer in 69% yield (Scheme 2). To confirm the stereochemical outcome of the oxy-Michael reaction, extensive NMR studies were conducted on (−)-diospongin B. The assignment of the structure and stereochemistry of compound **4** was achieved by incisive and detailed two-dimensional NMR studies, DQFCOSY, NOESY, HSQC and HMBC. The ^{1}H NMR and ^{13}C spectral assignments are given in Table 1. The HSQC data clearly established the different carbons.

The position of the carbonyl carbon (C-1) could be assigned by the HMBC correlation between the phenyl protons (Ha and He) and carbonyl carbon (C-1). The two phenyl groups were distinguished from each other by HMBC cross-peaks between H6/C-g and H5/C-l and also through NOE cross-peaks between H2/H4 and H2′/H4′. The HMBC cross-peaks between H3/C-7 and H7/C-3 indicate the presence of an ether linkage between C-3 and C-7. The large coupling between H3/H4′ (11.8 Hz), H5/H6′ (11.7 Hz), indicated that H3 and H6 are in equatorial and that H4′ and H6′ are in axial positions whereas the small couplings between H5/H6, H5/H4′ and H7/H6, H6′ indicated that H4, H6 and H7 are also in equatorial positions. NOE cross-peaks between H3/H6 and H4′/Hh, and the above described



Scheme 2. Reagents and conditions: (a) (i) O_3, CH_2Cl_2, −78 °C, 30 min, then PPh_3; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 2 h, 79% (for two steps); (b) PhCHO, *t*-BuOK, THF, 0 °C, 30 min, 61%; (c) LAH, THF, 0 °C to rt, 4 h, 77%; (d) (i) IBX, THF, DMSO, rt, 2 h; (ii) $PhCOCH_2P^+PH_3Br$, *t*-BuOK, THF, 0 °C to rt, 6 h, 77% (for two steps); (e) 50% TFA/CH_2Cl_2, 0 °C to rt, 8 h 69%.

Table 1.

No.	^{1}H chemical shift	^{13}C chemical shift
1	—	198.0
2	3.38 (dd) $J_{2,2'} = 16.2$, $J_{2,3} = 6.03.00$, (dd) $J_{2,2'} = 16.2, J_{2',3} = 6.4$	44.7
3	4.50 (dddd) $J_{2,3} = 6.0$, $J_{2',3} = 6.4, J_{3,4'} = 11.8$, $J_{3,4} = 2.8$	69.5
4	2.12 (ddd) $J_{3,4} = 2.8$, $J_{4,4'} = 14.5$, $J_{4,5} = 1.8$	34.6
4′	1.74 (ddd) $J_{4,4'} = 14.5, J_{3,4'} = 11.8, J_{4',5} = 1.0$	—
5	4.75 (ddd) $J_{5,6} = 2.5$, $J_{5,6'} = 11.7, J_{4',5} = 1.0$	74.0
6	2.08 (ddd) $J_{6,7} = 2.8$, $J_{6,6'} = 14.5$, $J_{5,6} = 2.5$	36.5
6′	1.84 (ddd) $J_{6',7} = 2.8, J_{6,6'} = 14.5, J_{5,6'} = 11.8$	—
7	5.46 (t) $J = 2.8$	73.1
a, e	7.90 (m)	128.2
b, d	7.40 (m)	128.6
c	7.47 (m)	133.3
h, j	7.24 (m)	128.3
g, k	7.22 (m)	125.8
i	7.20 (m)	127.9
f	—	141.2
l	—	128.9

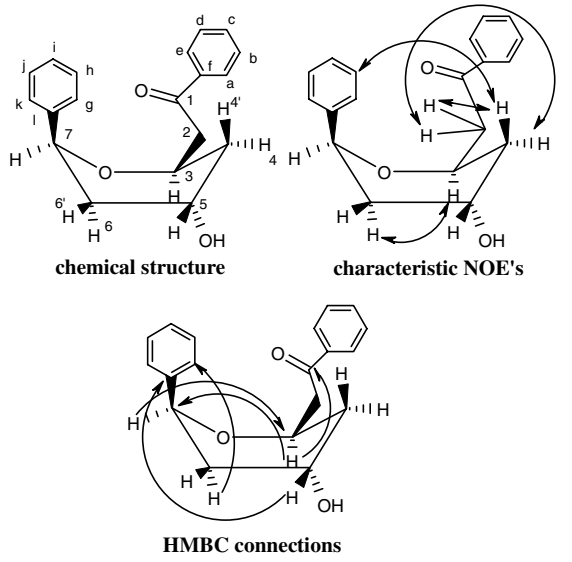


Figure 2.

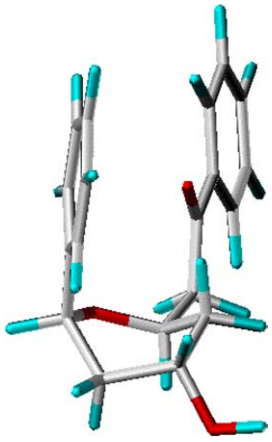


Figure 3. Energy minimized structure of (−)-diospongin B.

coupling constants support the boat conformation for the pyran ring as shown in Figure 2. The structure determined through molecular mechanics studies on **4** is in agreement with the experimental data (Fig. 3).[13]

In conclusion, the first total synthesis of (−)-diospongin B has been realized. The syntheses of related substituted tetrahydropyran molecules are under progress.

Acknowledgements

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12. The optical rotation $[\alpha]_D^{25}$ −23.4 (*c* 0.6, $CHCl_3$) as reported by Kadota and co-workers,[4] was not observed by us. This prompted us to conduct extensive NMR studies to confirm the stereochemical assignments.
13. The energy minimization was carried out using SIBYL 6.8 with default Tripose force field parameters. Minimization was performed first with steepest descent followed by conjugate gradient methods for a maximum of 2000 iterations each or RMS deviation of 0.005 kcal/mol, whichever was earlier.