Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(3):134-139
(http://derpharmachemica.com/archive.html)

Synthetic approach towards the stereoisomers of Diospongin family

Bollipalli Nagarjuna[a], Namburi Suresh[b], M. V. Basaveswara Rao[b*] and C. Venkata Rao[a*]

[a]*Department of Chemistry, Sri Venkateswara University, Tirupati, A.P, India*
[b]*Department of Chemistry, Krishna University, Machilipatnam, A.P, India*

ABSTRACT

Eight stereoisomers of diospongin family, have been planned to achieve in an efficient manner over 8–9 linear steps starting from economical and commercially available benzaldehyde following keck allylation protocol, cross-metathesis (CM), and tandem isomerization followed by C–O and C–C bond formation reaction and then Grignard reaction.

Key words: keck allylation, diospongin, Tetrahydropyran ring, Cross-metathesis Tandem isomerization followed by C–O and C–C bond formation reaction.

INTRODUCTION

In general diarylheptanoids are present in a wide variety of natural products which possess interesting biological[1] and pharmacological activities such as antioxidant[2], anticancer[3], and inhibitory activity on nitric oxide production[4], and anti-inflammatory[5] and antileishmanial activity[6]. Both Diospongins A (**3**) and B (**2**) are naturally occurring heterocyclic compounds possess 2,4,6-trisubstituted tetrahydropyran cyclic ether core with two aromatic side chains. Diospongin A and B isolated in 2003 from the rhizomes of *Dioscorea spongiosa* [7]. Rhizomes of *Dioscorea spongiosa* (*dioscoreaceae*) are used for the treatment of rheumatism, urethra, and renal infection in Chinese traditional medicine. Diospongins A (**3**) shows *syn* stereochemistry in the alkyl substituents on both carbons flanking the ether linkage, whereas its epimer Diospongins B (**2**) shows *trans* stereochemistry.

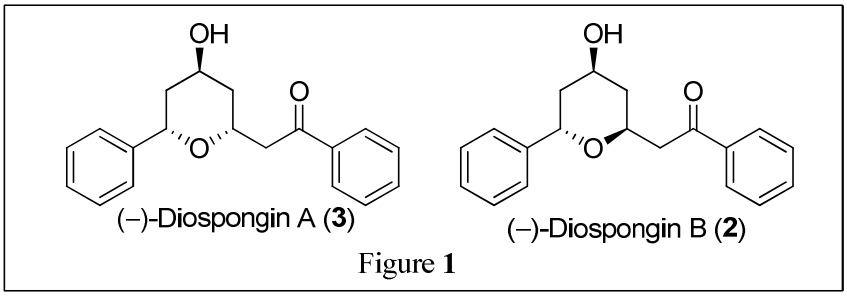


Figure **1**

Only Diospongin B (**2**) displays potent inhibitory activity on bone resorption induced by parathyroid hormone, which is comparable to that of elcitionin, a drug used clinically for osteoporosis, a skeletal disease. Therefore, diospongin B is considered as a promising lead for the discovery of novel antiosteoporotic drugs. Diospongin A (**3**) does not show any anti-osteoporotic activity.

MATERIALS AND METHODS

General Remarks: Chemicals were purchased from Sigma-Aldrich, Merck and Alfa Aesar, used as such without further purification. All solvents used for spectroscopy and other physical studies were reagent grade and were further purified by literature methods. Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven or flame-dried glassware. All anhydrous solvents were distilled and dried prior to use. Tetrahydrofuran, benzene, toluene, diethylether are dried over sodium using benzophenone; dichloromethane, N,N-Diemethylsulphoxide, N,N- Diemthylformamide, hexane from calcium hydrid, methanol and ethanol were dried over magnesium cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} degcm^{2}g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). TOF analyzer type was used for the HRMS measurement. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(*S*)-1-phenyl-3-en-1-ol (*S*)-10:
To a solution of Benzaldehyde **9** (1 gm, 9.4 mmol) in dry dichloromethane (10 mL) was added to a mixture of *S*-(+)-l, l-Bi-2-naphthol (405 mg, 1.4 mmol), 1M Ti(^{i}OPr)$_4$ in dichloromethane (1.4 mL, 1.4 mmol) and oven-dried powdered 4Aº sieves (1 gm). After being stirred for 10 min, the contents were cooled to -78ºC using ehtylacetate and liquid Nitrogen. At -78ºC allyltri-*n*-butylstannane (3.4 mL, 11.3 mmol) was added to the reaction mixture. The reaction was stirred for 10 min and then placed in a -20ºC freezer for 70 h. The reaction mixture was treated with saturated sodium bicarbonate (50 mL) and the contents were stirred for 1h and then poured over sodium sulphate and filtered through a pad of celite. The crude material was purified by chromatography over silica gel eluting with (ethyl acetate/hexane 1:20) to give (*S*)-1-phenyl-3-en-1-ol (*S*)-**10** (1.19 gm, 93% yield) which is characterized by its spectral and analytical data.

$[\alpha]^D_{25}$: −40 (c = 1.0, $CHCl_3$, 97% *ee*); IR (neat): ν_{max} 3420, 3074, 3002, 2934, 2907, 2836, 1734, 1640, 1611, 1513, 1462, 1374, 1301, 1176, 1035, 917, 832, 547 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.37-7.35 (m, 5H), 5.82 (m, 1H), 5.21-5.12 (m, 2H), 4.75 (m, 1H), 2.56-2.44 (m, 2H), 2.05 (bs, 1H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ 143.7, 134.3, 128.3, 127.4, 118.1, 73.2, 43.6 ppm. ESI-HRMS: calcd for $C_{10}H_{12}O$ [M$^+$] : 148.0888. Found: 148.0899.

(*R*)-1-phenylbut-3-en-1-ol (*R*)-10:
The title compound was obtained from **9** (500 mg, 4.7 mmol) by following the procedure described for the (*S*)-**10**. Yield: (580 mg, 92%), $[\alpha]^D_{25}$ = +41.3 (c = 0.9, $CHCl_3$); other analytical data are identical to those observed for (*S*)-**10**.

(*S*,*E*)-5-Hydroxy-5-phenylpent-2-enal (*S*,*E*)-11:
To a stirred solution of homoallyl alcohol (*S*)-**10** (1.0 g, 20.8 mmol) in dichloromethane argon gas was purged through it for 10 min then added acrolein (3.7 gm, 67.5 mmol) and Hoveyda-Grubbs' 2nd generation catalyst (420 mg, 0.67 mmol) at room temperature and again degassed for 10 min. The reaction mixture was allowed to stir for overnight. After completion of the reaction (monitored by TLC), solvent was removed under reduced pressure and directly purified by column

chromatography over silica gel (ethyl acetate/hexane = 1: 9) to afford *δ*-hydroxy *α*,*β*-unsaturated aldehyde (*S*,*E*)-**11** (1.0 gm, 84% yield).

^{1}H NMR (300MHz, $CDCl_3$): δ 9.38 (d, *J* = 7.9 Hz, 1H), 7.38-7.24 (m, 5H), 6.82 (m, 1H), 6.09 (m, 1H), 4.82 (m, 1H), 2.99 (bs, 1H), 2.82-2.64 (m, 2H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ 194.1, 154.4, 143.1, 134.6, 128.5, 127.8, 125.5, 72.6, 41.8 ppm. ESI-HRMS: Calcd for $C_{11}H_{12}O_2$ [M-H]$^+$: 175.07568, found: 175.07536.

(*R*,*E*)-5-hydroxy-5-phenylpent-2-enal (*R*,*E*)-11:
The title compound was obtained from (*R*)-**10** (400 mg, 3.7 mmol) by following the procedure described for the (*S*,*E*)-**11**. Yield: (400 mg, 83%); other analytical data are identical to those observed for (*S*,*E*)-**11**.

(2*S*,6*S*)-6-allyl-2-phenyl-3,6-dihydro-2*H*-pyran (2*S*,6*R*)-12:
To a solution of *δ*-hydroxy *α*,*β*-unsaturated aldehyde (*S*,*E*)-**11** (900 mg, 5.11 mmol) in dry tetrahydrofuran (10 mL), allyltrimethylsilane (1.2 mL, 7.6 mmol) was added dropwise at room temperature. After complete addition tt was cooled to 0ºC and then iondine (257 mg, 10.2 mmol) was slowly added to it at the same temperature. It was allowed to room temperature with stirring and then stirring was continued for further 2 h and then quenched with saturated solution of $Na_2S_2O_3$ (60 mL) to get a colorless mixture. It was diluted with ethyl acetate (50 mL) and two layers

were separated. The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic extracts were washed with brine solution (20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude product which on purification by flash column chromatography over silica gel (ethyl acetate/hexane = 1:49) furnished the desired cyclic product (2*S*,6*R*)-**12** (950 mg, 93% yield.) as a colorless liquid.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.42-7.22 (m, 5H), 5.99-5.77 (m, 3H), 5.15-5.04 (m, 2H), 4.75 (m, 1H), 4.32 (m, 1H), 2.52 (m, 1H), 2.42-2.29 (m, 3H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ 142.2, 134.8, 129.3, 128.2, 127.3, 124.4, 117.0, 72.9, 39.0, 31.4 ppm. ESI-HRMS: calcd for $C_{14}H_{16}O$ $[M+H]^+$: 201.12772, found: 201.12739.

(2*S*,6*R*)-6-allyl-2-phenyl-3,6-dihydro-2*H*-pyran (2*R*,6*S*)-12:
The title compound was obtained from (*R*,*E*)-**11** (300 mg, 2.8 mmol) by following the procedure described for the (2*S*,6*R*)-**12**. Yield: (310 mg, 91%); other analytical data are identical to those observed for (2*S*,6*R*)-**12**.

2-((2*R*,6*S*)-6-phenyl-5,6-dihydro-2*H*-pyran-2-yl)acetaldehyde (2*R*,6*S*)-13:
To a stirred solution of compound (2*S*,6*R)*-**12** (500 mg, 2.5 mmol) in dioxane-water (3:1, 16 mL) added 2,6-lutidine (0.58mL, 5.0 mmol), Osmium tetroxide (0.0196M in 2-methyl-2-propanol, 2.5 mL, 0.05 mmol), and Sodium periodate (2.13 gm, 10.0 mmol). The reaction was stirred at 25°C and monitored by thin layer chromatography. After the completion of the reaction water (10 mL) and dichloromethane (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted by dichloromethane (3X10 mL). The combined organic extracts were washed with brine solution and was dried over anhydrous sodium sulphate. The reaction mixture was concentrated and the crude product obtained was purified with silica gel column chromatography (ethyl acetate/ hexane = 1:19) to yield aldehyde (2*R*,6*S*)–**13** (410 mg, 81%) as a colorless oil, which is characterized by its spectral and analytical data given below.

^{1}H NMR (300MHz, $CDCl_3$): δ 9.83-9.81 (t, 1H), 7.40-7.24 (m, 5H), 6.02 (m, 1H), 5.78 (m, 1H), 4.86 (m, 1H), 4.72 (t, 1H), 2.86 (m, 1H), 2.63 (m, 1H), 2.39-2.32 (m, 2H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ 200.8, 141.4, 128.3, 128.0, 127.5, 126.2, 125.4, 69.9, 68.4, 47.9, 30.9 ppm.

2-((2S,6R)-6-phenyl-5,6-dihydro-2*H*-pyran-2-yl)acetaldehyde (2*S*,6*R*)-13:
The title compound was obtained from (2*S*,6*R)*-**12** (100 mg, 0.5 mmol) by following the procedure described for the (2*R*,6*S*)-**13**. Yield: (82 mg, 81%); other analytical data are identical to those observed for (2*R*,6*S*)-**13**.

1-phenyl-2-((2*R*,6*S*)-6-phenyl-5,6-dihydro-2*H*-pyran-2-yl)ethanol (2*R*,6*S*)-14:
To the freshly prepared (0.5 M solution in tetrahydrofuran) solution of phenylmagnesium bromide (8.91 mL, 4.45 mmol) under argon atmosphere at room temperature aldehyde (2*R*,6*S*)–**13** (300 mg, 1.4 mmol) in tetrahydrofuran (50 mL) was added drop wise over a period of 0.5 h and the resulting solution was stirred for 3h at room temperature till the complete conversion of the reaction followed by the thin layer chromatographys. The reaction mixture was extracted with diethylether (15 ml). The combined organic extracts were washed with aqueous sodium bicarbonate solution (10 ml) followed by brine solution (10 ml). The organic layer was dried over anhydrous sodium sulphate, concentrated and subjected to column chromatography (AcOEt/ hexane = 1:4), yielding (2*R*,6*S*)-**14** as colorless liquid (370 mg, 81%, nearly eqimolar mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.19 (m, 10H), 5.94 (m, 1H), 5.68 (m, 1H), 4.99 (m, 1H), 4.79(m, 1H), 4.51 (m, 1H), 3.26 (m, 1H), 2.38-2.31 (m, 2H), 2.20 (m, 1H), 1.86 (m, 1H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ 144.4, 141.5, 129.5, 128.30, 128.37, 127.6, 127.0, 126.4, 125.5, 124.4, 71.2, 70.3, 70.0, 41.5, 31.1 ppm. ESI-HRMS: calcd for $C_{19}H_{20}O_2$ $[M+Na]^+$: 303.1466, found: 303.1465.

1-phenyl-2-((2*S*,6*R*)-6-phenyl-5,6-dihydro-2*H*-pyran-2-yl)ethanol (2*S*,6*R*)-14:
The title compound was obtained from (2*R*,6*S*)–**13** (50 mg, 0.247 mmol) by following the procedure described for the (2*R*,6*S*)-**14**. Yield: (63 mg, 80%); other analytical data are identical to those observed for (2*R*,6*S*)-**14**.

RESULT AND DISCUSSION

Over the years, much effort has been directed toward the development of new strategies for the construction of tetrahydropyran rings. Recently developed methodology,[47] using iodocyclization is proved to be a potent protocol for the synthesis of tetrahydropyran rings by using low cost reagents with a quantitative yield. We present a unique synthetic solution for naturally available diospongin A and B and eight stereoisomers by using iodocyclization as key step.

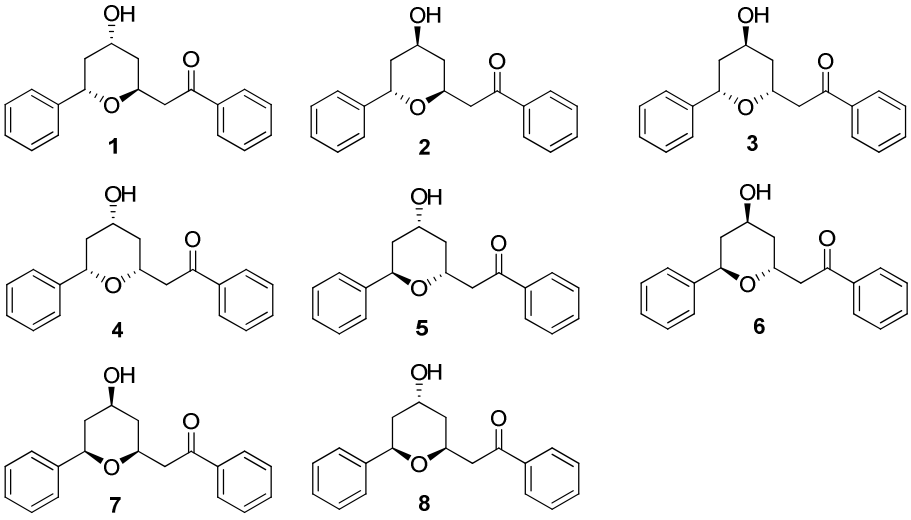
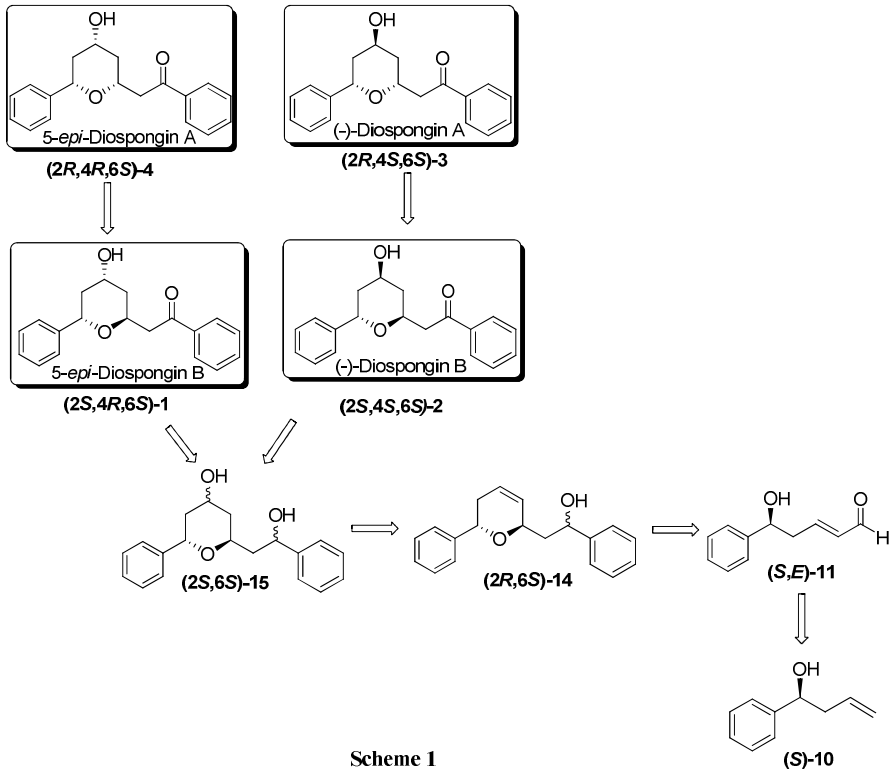


Fig.1. Structures of eight stereoisomers of diospongin family

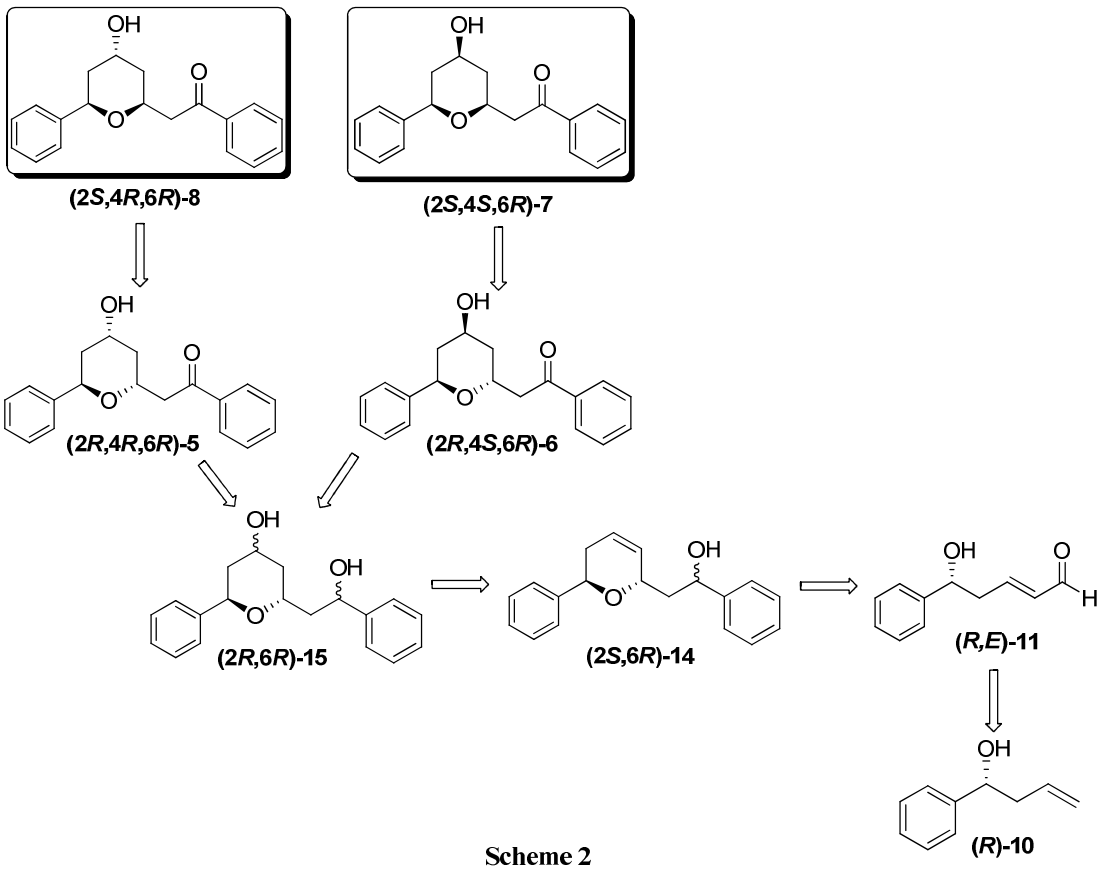
Retrosynthetic analysis:

According to our retrosynthetic approach as shown in the scheme **1** and **2**. The synthesis has started with commercially available cheaper starting material benzaldehyde **9**. The key intermediate involved in the synthesis is (2*S*,6*S*)-**15**. 5-*epi*-Diospongin A (2*R*,4*R*,6*S*)-**4**, (-)-Diospongin A (2*R*,4*S*,6*S*)-**3**, could be opened from 5-*epi*-Diospongin B (2*S*,4*R*,6*S*)-**1** and (-)-Diospongin B (2*S*,4*S*,6*S*)-**2**, by following acid catalyzed isomerization reaction, both the compounds which in turn could be opened from the key intermediate (2*S*,6*S*)-**15**. The key intermediate (2*S*,6*S*)-**15** in turn could be obtained by oxymercuration followed by demercuration reaction of Grignard compound (2*R*,6*S*)-**14** Which could be prepared by domino isomerization followed by C–O and C–C bond formation reaction of *δ*-hydroxy *α*,*β*-unsaturated aldehyde (*S*,*E*)-**11** which could be prepared from homoallyl alcohol (*S*)-**10** by following cross-metathesis reaction.

The homoallyl alcohol (*S*)-**10** could be synthesized from benzaldehyde **9** through Keck allylation.

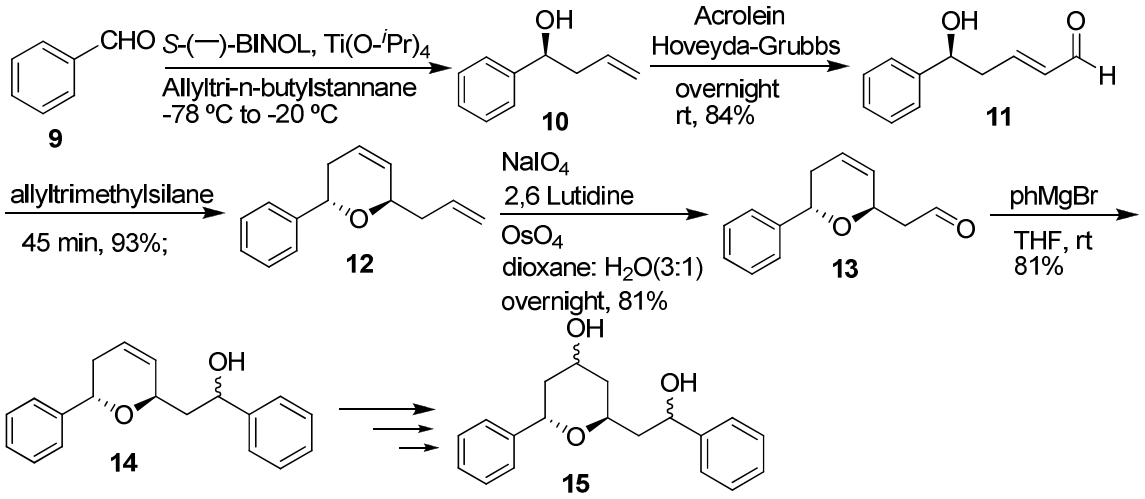


Scheme 1



Scheme 2

We initiated the synthesis of homoallyl alcohol (*S*)-**10**, through asymmetric allylation of cheaper, commercially available benzaldehyde by using a mixture of *S*-(–)-BINOL, titanium (IV) isopropoxide and allyl-tri-*n*-butylstannane at -78 ºC and stirred for 3 days at -20ºC in 93% yield in 96% *ee* under conditions originally developed by Keck, G. E.; Enholm.[8] The product was characterized by its ^{1}H NMR, ^{13}C NMR, ESI-MS and were in well accordance with the previous report. In order to obtain the *α,β*-unsaturated aldehyde (*S,E*)-**11**, a cross-metathesis (CM)[9] between (*S*)-**10** and acrolein was first carried out with Grubbs second generation catalyst. Unfortunately, the reaction was very sluggish in this case and didn't proceed to completion even after prolonged time (48 h) and thus ended with low yield. Even, use of excess aldehyde and catalyst proved to be unfruitful in this case. We then turned our attention to Hoveyda-Grubbs catalyst which is known to be an efficient catalyst for cross metathesis. After extensive experimentation, best result was obtained in CH_2Cl_2 using 6.0 equiv of acrolein and 10 mol% of catalyst. The desired *α,β*-unsaturated aldehyde (*S,E*)-**11** was afforded in 84% yield in 24 h under this condition. Now, the stage is set to conduct our own developed tandem isomerization followed by **C–O** and C–C bond formation reaction.[10] Accordingly, *δ*-hydroxy *α,β*-unsaturated aldehyde (*S,E*)-**11** was treated with allyltrimethylsilane and catalytic amount (10 mol %) of iodine in THF to furnish *trans*-2,6-disubstituted-3,4-dihydropyran (2*S*,6*R*)-**12** in 93% yield. Conversion of terminal olefin to aldehyde (2*R*,6*S*)-**13** was achieved by modified dihydroxylation-oxidation protocol[11] by using OsO_4, 2,6-Lutidine, $NaIO_4$ in 1,4 dioxane-H_2O (3:1) in 81% yield. The aldehyde was exposed for a Grignard reaction with phenylmagnesium bromide[12] giving the secondary alcohol (2*R*,6*S*)-**14** in 81% yeild.



Scheme 3

CONCLUSION

In order to show the diversity of iodocyclization strategy we have started a synthetic program for the total synthesis of all stereoisomers of Diospongin family. We have achieved the synthesis of Diospongin advanced intermediate *i.e* (2*R*,6*S*)-**14** through the following key steps, Keck allylation, cross metathesis, iodocyclization, and Grignard reaction and this intermediate can be utilized for the further work is under progress for the completion of total synthesis of Diospongin family.

REFERENCES

[1] S. Kadota, Y. Tezuka, J. K. Prasain, M. S. Ali, A. H. Banskota, *Curr. Top. Med. Chem.* **2003**, *3*, 203; J. Zhu, G. Islas-Gonzalez, M. Bois-Choussy, *Org. Prep. Proced. Int.* **2000**, *32*, 505; P. Claeson, U. P. Claeson, P. Tuchinda, V. Reutrakul, in _Studies in Natural Product Chemistry, Ed. Atta-ur-Rahman, *Elsevier Science* B.V, Amsterdam, **2002**, *26*, 881.
[2] H. Mohamad, N. H. Lajis, F. Abas, A. M. Ali, M. A. Sukari, H. Kikuzaki, N. Nakatani, *J. Nat. Prod*. **2005**, *68*, 285; K. Akiyama, H. Kikuzaki, T. Aoki, A. Okuda, N. H. Lajis, N. Nakatani, *J. Nat. Prod*. **2006**, *69*, 1637.
[3] M. S. Ali, Y. Tezuka, S. Awale, A. H. Banskota, S. Kadota, J. Nat. Prod. **2001**, 64, 289; J. Ishida, M. Kozuka, H. Tokuda, H. Nishino, S. Nagumo, K.-H. Lee, M. Nagai, *Bioorg. Med. Chem*. **2002**, *10*, 3361; K.-S. Chun, K.-K. Park, J. Lee, M. Kang, Y. J. Surh, *Oncol. Res*. **2002**, *13*, 37.
[4] H. Matsuda, S. Ando, T. Kato, T. Morikawa, M. Yoshikawa, *Bioorg. Med. Chem*. **2006**, *14*, 138; H.-J. Kim, S.-H. Yeom, M.-K. Kim, J.-G. Shim, I.-N. Paek, M.-W. Lee, *Arch. Pharm. Res*. **2005**, *28*, 177.
[5] P. N. Yadav, Z. Liu, M. M. Rafi, *J. Pharmacol. Exp. Ther*. **2003**, *305*, 925.
[6] M. Takahashi, H. Fuchino, S. Sekita, M. Satake, *Phytother. Res*. **2004**, *18*, 573.
[7] Yin, J.; Kouda, K.; Tezuka, Y.; Le Tran, Q.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med*. **2004**, *70*, 54.
[8] Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.
[9] (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 8168. (b) Dinh, M.-T.; Bouzbouz, S.; Peglion, J. L.; Cossy, J. *Tetrahedron.* **2008**, *64*, 5703.
[10] Mohapatra, D. K.; Bhimireddy, E.; Krishnarao, P. S.; Das, P. P.; Yadav, J. S. *Org. Lett*. **2011**, *13*, 744;
[11] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett*. **2004**, *6*, 3217.
[12] W. Chazadaj, R. Kowalczyk and J. Jurczak, *J. Org. Chem.*, **2010**, *75*, 1740.