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Total synthesis of (−)-Sachalinol A and evaluation of its cytotoxicity

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(−)-Sachalinol A, a group of monoterpenoids, oxygenated derivatives of rosinidol, has been synthesized employing a simple, eight step procedure. The compound demonstrates excellent cytotoxicity against MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26) and HeLa derived from human cervical cancer cells (ATCC No. CCL-2). Good activity is observed against A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185) and Neuro2a derived from mouse neuroblastoma cells (ATCC No. CCL-131). Moderate activity is also observed against MCF-7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22).

Keywords: Anticancer, (−)-Sachalinol A, cytotoxicity, monoterpenoids, Sharpless epoxidation, Riley oxidation anhyd.

Natural products play a very important role in drug delivery processes as they are less toxic and from a bioactivity perspective they exhibit anticancer, antifungal, antiprotozoal and antimicrobial activities[1,2]. With the increasing number of diseases and bacterial resistance towards antibiotics, the importance of natural products based medicines is growing day-by-day[3-5]. In a tropical country like India, where there is a constant threat to life with the emergence and re-emergence of several diseases like cancer, there is an urgent need to explore more and more newer resources to develop therapeutics along with the implementation of knowledge by carrying out more research on bioactive compounds.

Terpenoids constitute one of the largest groups of natural products which are known to exhibit good biological activities and find use in the treatment of human diseases. It is said that the world-wide sale of terpene-based pharmaceuticals in 2002 was approximately 12 billion US dollars. Most of the terpenoids are commonly classified as monoterpenoids which display a wide range of biological activities against cancer, malaria, inflammation and a variety of infectious diseases[6-8]. Sachalinols are a group of monoterpenoids, oxygenated derivatives of rosinidol, secondary metabolites from the medicinal plant *Rhodiola rosea* (Crassulaceae, roseroot). There is a paucity of information on the synthesis of sachalinols and further, it also involves several synthetic steps.

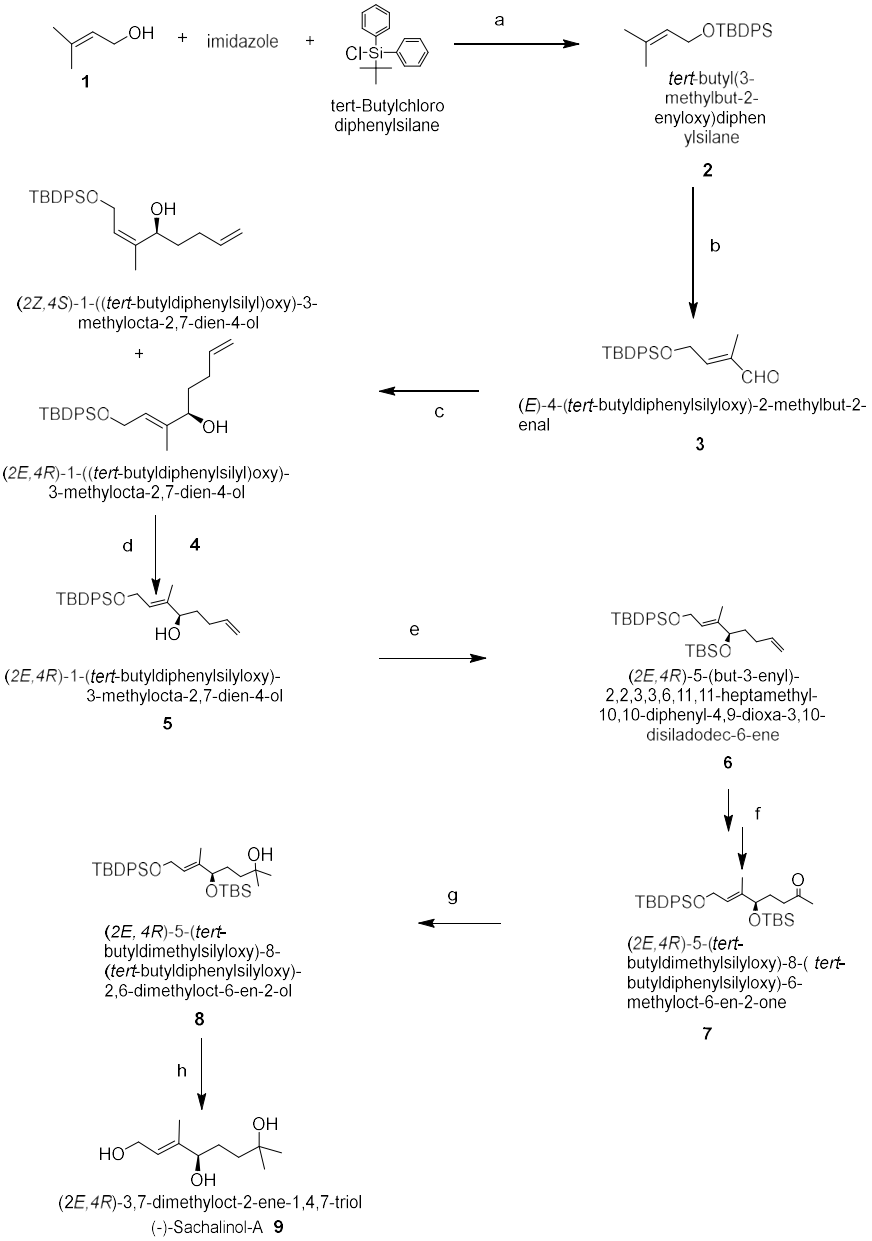
A series of new monoterpenoids, Sachalinols A-C_1 was isolated from *Rhodioloa sachalinensis* by Kadota *et al*.[9,10] and were found to exhibit non-competitive endopeptidase inhibition against *Flavobacterium* PEP with an IC_{50} value of 84 μM. Subsequently, Kristina *et al*.[11] developed a 12 step procedure for the synthesis of (−)-Sachalinol A. They initially synthesized (*E*)-1-(tert-butyldiphenylsilyloxy)-3,7-dimethylocta-2,6-dien-4-one following the method developed by Schottner *et al*.[9] followed by enantioselective reduction of ketone by the CBS reagent [(+)-(R)-2-methyl CBS-oxazoborolidine][11,12], which provided secondary alcohol. The secondary alcohol was subjected to epoxidation followed by reduction with $LiBEt_3H$ to afford the diol (77% yield). Desilylation of the diol afforded the natural product, (−)-Sachalinol A. Diez and coworkers reported the first total synthesis of (−)-Sachalinol A *via* α, β-unsaturated nitrile intermediate[13].

(−)-Sachalinol A belongs to the family of terpenoids, which are known to be excellent cytotoxic agents used for cancer therapy[14]. However, not much literature is available on the synthesis and biological activities of this compound. Moreover, the reported procedures involve more than 10 steps providing lower yields. Owing to its structural simplicity, efforts have been made to develop a shorter and more efficient total synthesis of the title compound, (−)-Sachalinol A, in the

present investigation. Considering the above facts, (−)-Sachalinol A was synthesized and evaluated for cytotoxicity against a panel of different cancer cell lines, namely, A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), HeLa derived from human cervical cancer cells (ATCC No. CCL-2), MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22).

Results and Discussion

(−)-Sachalinol A was synthesized employing a simple eight step procedure using the commercially available prenol and a series of standard oxidation reactions were performed (Scheme I). The first step involved the protection of the hydroxyl group of prenol, **1** using tert-butyldiphenylsilylchloride (TBDPSCl) and imidazole in the presence of DMAP to obtain tert-butyl-(3-methyl-but-2-enyloxy) diphenyl silane, **2**. Riley oxidation[15] with SeO_2/TBHB



Scheme I — Total synthesis of (−)-Sachalinol A: (a) DMAP, CH_2Cl_2, 0°C to RT, 5 h; (b) SeO_2, TBHP, CH_2Cl_2, 0°C to RT, 18 h; (c) THF, 0°C to RT, 1 h; (d) $Ti(iOPr)_4$, (+)-DIPT, t-BuOOH, 4 Å MS, CH_2Cl_2; (e) TBSOTf, 2,6-lutidine, DCM, 0°C to RT, 3 h; (f) DMF:H_2O, O_2, CuCl, $PdCl_2$; (g) THF, MeMgI; (h) TBAF, THF.

afforded a mixture of (*E*)-allylic alcohol and (*E*)-aldehyde. Further, the corresponding mixture was column purified to obtain *E*-4-(tert-butyl diphenyl siloxy)-2-methyl but-2-enal **3**.

An allylic alcohol contaning-1-(tert-butyldiphenyl-siloxy)-3-methyl-octa-2,7-dien-4-ol with a secondary hydroxyl functionality was obtained by the reaction of **3** with 3-butenylmagnesium bromide at 0°C for 1 h to afford isomers of *E*-1-(tert-butyldiphenylsiloxy)-3-methyl-octa-2,7-dien-4-ol, **4**. The product obtained is a mixture of isomers which were separated by Sharpless epoxidation[16] using $Ti(iopr)_4$ and (+)-DIPT followed by column purification to obtain the pure compound (*2E*, *4R*)-1-(tert-butyldiphenyl siloxy)-3-methyl octa 2, 7-dien-4-ol, **5**.

The secondary hydroxyl group of **5** was protected using (tert-butyl dimethylsilyl-triflouro sulfonate) TBSOTf in the presence of 2,6-lutidine in DCM. The reaction was quenched with water, dried and column purified to obtain protected **6**. Compound **6** was subjected to Keto-Wacker oxidation in the presence of $PdCl_2$ and $CuCl_2$ for 3 h at RT. The crude product was column purified to obtain compound **7**. The keto group of compound **7** was reduced to tertiary alcohol employing the Grignard reagent, MeMgI. The compound was column purified to obtain tertiary alcohol **8**. Deprotection of silylated compound **8** was carried out using TBAF at 0°C for 5 h. The crude product was column purified to afford the targeted colourless oil compound. The currently reported method is much simpler as compared to the earlier reported methods[8,10]. All the compounds were characterized using ^{1}H NMR, ^{13}C NMR and ESI-MS.

The compounds were further evaluated for anti-cancer activity against different cell lines. The synthesized (−)-Sachalinol A exhibited promising activity against MDA-MB-231 and HeLa and good activity against A549 and Neuro2a. Whereas, moderate activity was observed against MCF-7. From a structure-activity relationship perspective, it is observed that the most stable tertiary and the allylic hydroxyl groups which are electron donating in nature are responsible for the cytotoxic activity. The anti-tumor activity of (−)-Sachalinol A can be assigned as being similar to Camptothecin containing α-hydroxy lactone (*tert* alcohol) and its analogues topotecan and irinotecan which are today used in cancer chemotherapy. In this context, (−)-Sachalinol A with good anti-tumor activity can be a promising candidate which can be further explored in a number of pharmaceutical formulations similar to other mono- and tri-terpenoids reported[17-24] (Table I).

Experimental Section

All reagents used were of analytical grade and were used as obtained from different commercially sources without any further purification. All dry reactions were carried out under nitrogen environment in oven-dried glassware using standard gas-tight syringes, cannulas and septa. Reactions were carried out using anhydrous solvents and were monitored on silica gel TLC plates (coated with TLC grade silica gel, obtained from Merck) employing iodine vapors for detection of spots. Column chromatography was performed over silica gel (100-200 mesh) procured from Qualigens (India) using freshly distilled solvents. Mass spectra were recorded using electron spray ionization-mass spectrometry (ESI-MS). ^{1}H and ^{13}C NMR spectra were recorded on Brucker UXNMR (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C NMR) spectrometer using $CDCl_3$. Chemical shifts δ are reported relative to TMS (δ = 0.0) as an internal standard. All spectra were recorded at 25°C. The following abbreviations were used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Coupling constants (*J* values) are given in Hertz (Hz).

Synthetic protocols for the preparation of (−)-Sachalinol A

Step 1: Synthesis of tert-butyl (3-methylbut-2-enyloxy) diphenylsilane, 2

To a solution of **1** (4.0 g, 46.45 mmol) in CH_2Cl_2 (75 mL) were added imidazole (4.74 g, 69.67 mmol),

Table I — (−)-Sachalinol A anti-tumour activity against a panel of five cancer cell lines

Test Compd	IC_{50} values (μM)				
	HeLa Human cervical cancer cells (ATCC No. CCL-2)	A549 Human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185)	MDA-MB-231 Human breast adenocarcinoma cells (ATCC No. HTB-26)	MCF-7 Human breast adenocarcinoma cells (ATCC No. HTB-22)	Neuro 2a Mouse neuroblastoma cells (ATCC No. CCL-131)
(−)-Sachalinol A	1.0 ± 0.04	12 ± 0.04	5.8 ± 0.05	50.2 ± 0.02	15.57± 0.03
Doxorubicin	0.50 ± 0.01	0.45 ± 0.02	0.91 ± 0.02	1.0 7± 0.02	1.0 4± 0.04

tert-butylchlorodiphenylsilane (14.04 g, 51.09 mmol), and a catalytic amount of DMAP at 0°C. Thereafter, the solution was stirred for 5 h at RT and quenched with H_2O (50 mL), and the reaction mixture was extracted with DCM (50 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and purified by column chromatography to provide olefin **2** (14.3g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, J = 6.8 Hz, 2H), 7.42 – 7.36 (m, 3H), 4.49 – 4.43 (m, 1H), 1.70 (d, J = 1.3 Hz, 3H), 1.06 (s, 5H); ^{13}C NMR (125 MHz): δ 138.29, 135.55, 133.85, 129.97, 128.81, 121.27, 62.01, 26.8, 25.59, 19.14, 18.16; ESI-MS: *m/z* 325.19 [M^+].

Step 2: Synthesis of (*E*)-4-(tert-butyldiphenylsilyloxy)-2-methylbut-2-enal, 3

To a stirred solution of SeO_2 (1.43g, mmol) in DCM at 0°C, TBHP (21.6 mL, 108 mmol) was added and the reaction mixture was stirred for 0.5 h at 0°C. Compound **2** (14.0g 43.2 mmol) dissolved in DCM was added slowly at 0°C to above reaction mixture. Stirring was continued for 18 h and quenched with saturated $NaHCO_3$ and the organic layer extracted with DCM. Solvent was evaporated and purified by column chromatography to give aldehyde **3** (9.93g, 68%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (d, J = 1.0 Hz, 1H), 7.67 (m, J = 5.7 Hz, 4H), 7.42 – 7.36 (m, 6H), 6.64 (tt, J = 6.1 Hz, 1H), 4.46 (dt, J = 6.1 Hz, 2H), 1.83 (d, J = 1.0 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz): δ 193.84, 138.92, 136.39, 135.55, 133.85, 129.97, 128.81, 62.74, 26.84, 19.14, 9.63; ESI-MS: *m/z* 339.17 [M^+].

Step 3: Synthesis of (*E*)-1-(tert-butyldiphenylsilyloxy)-3-methylocta-2,7-dien-4-ol, 4

To a stirred solution of aldehyde **3** (9.5g, 28.06 mmol) in THF was added 3-butenyl magnesium bromide (33.6 mL, 1M solution in THF) at 0°C and stirring continued for 1 h and quenched with aqueous NH_4Cl solution. Organic layer was separated and dried over anhyd. Na_2SO_4. Evaporation of solvent under reduced pressure and purification by column chromatography gave allyl alcohol **4** (8.3g,75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, J = 5.7Hz, 4H), 7.42 – 7.36 (m, 6H), 5.85 (m, J = 16.8 Hz, 1H), 5.61 – 5.54 (m, 1H), 5.02 – 4.92 (m, 2H), 4.94 – 4.88 (m, 2H), 4.18 (m, J = 10.9 Hz, 1H), 3.91 (m, J = 12.3 Hz, 1H), 2.33 (tt, J = 12.8 Hz, 1H), 2.02 (m, J = 12.5 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.70 – 1.56 (m, 5H), 1.06 (s, 10H); ^{13}C NMR (125 MHz): δ 138.09, 135.55, 133.85, 129.97, 128.81, 124.45, 115.19, 75.29, 61.80, 32.60, 31.47, 26.84, 12.32; ESI-MS: *m/z* 395.24 [M^+].

Step 4: Synthesis of isomers of 1-(tert-butyldiphenylsilyloxy)-3-methylocta-2,7-dien-4-ol, 5

To a suspension of activated 4Å (102 mg) molecular sieve powder in CH_2Cl_2 (4 mL), $Ti(O^iPr)_4$ (1.12 mL, 3.8 mmol) and (+)-DIPT (0.8 mL, 3.8 mmol) were added sequentially at –20°C. After being stirred for 15 min, compound **4** (7.5g, 19.0 mmol) in CH_2Cl_2 (4 mL) was added and stirring continued for another 0.5 h at the same temperature. TBHP (5.0 M in toluene, 2.85 mL) was added to it and stirring was continued for another 40 min at the same temperature. The reaction was quenched with water (1.6 mL). Then it was allowed to attain to RT and stirred for 1 h. After re-cooling it to 0°C, an aqueous solution of NaOH (30% w/v, 0.30 mL, saturated with brine) was added to it and stirred at 0°C for 30 min. CH_2Cl_2 was removed under reduced pressure and the residue was extracted with EtOAc (60 mL), washed with water (20 mL), brine (10 mL), dried (anhyd. Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7% Et_2O in petroleum ether eluant) afforded pure compound **5** (3.75g, 45%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, J = 5.7 Hz, 4H), 7.42 – 7.36 (m, 6H), 5.85 (m, J = 16.7 Hz, 1H), 5.61 – 5.54 (m, 1H), 5.02 – 4.92 (m, 2H), 4.91 (dt, J = 10.6 Hz, 2H), 4.20 (m, J = 11 Hz, 1H), 3.91 (m, J = 12.1Hz, 1H), 2.32 (tt, J = 12.8 Hz, 1H), 2.02 (m, J = 12.6 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.69 – 1.57 (m, 5H), 1.06 (s, 9H); ^{13}C NMR (125 MHz): δ 138.09, 135.55, 133.85, 129.97, 128.81, 124.45, 115.19, 75.29, 61.80, 32.60, 31.47, 26.84, 12.32; ESI-MS: *m/z* 395.24 [M^+].

Step 5: Synthesis of (2*E*,4*R*)-2,2,3,3,6,11,11-heptamethyl-5-((*Z*)-pent-3-enyl)-10,10-diphenyl-4,9-dioxa-3,10-disiladodec-6-ene, 6

OTBS protection: To a stirred solution of alcohol **5** (3.1 g, 7.85 mmol) in DCM at 0°C was added 2,6-lutidine (1.37 mL) and after 10 min TBSOTf (1.98mL,8.64mmol) was added slowly. Reaction was quenched by addition of H_2O (1.6 mL) and the reaction mass extracted with DCM (2 × 20 mL) and dried over anhyd. Na_2SO_4. Crude product was then purified by column chromatography over silica gel to get compound **6** (3.4g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, J = 5.7 Hz, 4H), 7.42 – 7.36 (m, 6H), 5.82 (m, J = 17.8 Hz, 1H), 5.65 (m, J = 9.9 Hz, 1H), 5.02 – 4.90 (m, 2H), 4.86 (m, J = 12.2 Hz, 1H), 4.23 – 4.15 (m, 1H), 4.01 (m, J = 12.1 Hz, 1H), 2.05 – 1.91 (m, 2H), 1.63 – 1.53 (m, 4H), 1.08 (d, J = 17.6 Hz, 18H), 0.08 (s, 6H); ^{13}C NMR (125 MHz): δ 138.09, 135.55, 133.85, 129.9, 128.81, 125.54, 115.19, 77.70,

61.80, 32.32, 31.76, 26.84, 25.82, 13.02, -4.34; ESI-MS: *m/z* 509.32 [M^+].

Step 6: Synthesis of (2*E*,4*R*)-5-(tert-butyldimethyl-silyloxy)-8-(tert-butyldiphenylsilyloxy)-6-methyloct-6-en-2-one, 7

To a stirred solution of olefin **6** (2.0 g, 3.93 mmol) in DMF and H_2O (7:1) at 0°C were added $PdCl_2$ (0.21 g, 1.18 mmol) and CuCl (0.116 g, 1.18 mmol) successively. After 5 min O_2 filled balloon was placed over the neck of round bottom flask and reaction stirred for 3 h at RT. Reaction was quenched by addition of 3N HCl, extracted in ether (2×20 mL) and dried over anhyd. Na_2SO_4. Crude product was then purified by column chromatography over silica gel to get compound **7** (2.45 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, *J* = 6.7 Hz, 4H), 7.42 – 7.36 (m, 6H), 5.54 (m, *J* = 9.9 Hz, 1H), 4.86 (dd, *J* = 12.5Hz, 1H), 4.18 (dt, *J* = 11.3Hz, 1H), 4.08 – 4.00 (m, 1H), 2.94 (td, *J* = 12.7 Hz, 1H), 2.29 (td, *J* = 12.7 Hz, 1H), 2.10 (s, 3H), 1.88 (tt, *J* = 12.7Hz, 1H), 1.51 (d, *J* = 1.3 Hz, 3H), 1.38 – 1.26 (m, 1H), 1.06 (d, *J* = 1.8 Hz, 18H), 0.08 (s, 6H); ^{13}C NMR (125 MHz): δ 135.55, 133.85, 129.97, 128.81, 125.54, 77.68, 61.80, 38.98, 30.53, 30.02, 26.84, 25.82, 13.0, 4.34; ESI-MS: *m/z* 525.32 [M^+].

Step 7: Synthesis of (2*E*,4*R*)-8-(tert-butyldiphenyl-silyloxy)-2, 6-dimethyl-5-(2,3,3-trimethylbutan-2-yloxy)oct-6-en-2-ol, 8

Convertion of ketone to 3-alcohol by Grignard reagent

To the stirred solution of above ketone (2.0 g, 3.81 mmol) at 0°C was added CH_3MgI (5.7 mL, 5.71 mmol, 1M solution in THF) slowly. After 1 h, the reaction was quenched by addition of water and sat. aq. NH_4Cl solution and extracted into ethyl acetate. The organic layer was dried over anhyd. Na_2SO_4 and the crude product was purified by column chromatography to give tertiary alcohol **11** (1.4g,68%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.8 (ddq, *J* = 6.7Hz, 6H), 7.56 – 7.49 (m, 4H), 5.7 (t, 1H), 4.64 (S, OH), 4.39 – 4.37 (m, 2H), 1.56 – 1.39 (m, 2H), 1.34 (s, 1H), 1.32 – 1.28 (m, 3H), 1.82 (s, 3H), 1.18 (dd, 2H), 0.99 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz): δ 138.43, 135.38, 133.75, 129.29, 127.42, 124.84, 76.82, 70.51, 60.67, 39.13, 29.61, 29.53, 26.84, 24.82, 19.22, 17.24; ESI-MS: *m/z* 541.35 [M^+].

Step 8: (2*E*,4*R*)-3,7-dimethyloct-2-ene-1,4,7-triol ((−)-Sachalinol –A), 9

Reaction with TBAF

To a stirred solution of silyl compound **8** (1.0 g, 1.84 mmol) was added TBAF (7.4 mL,1M solution in THF) at 0°C and the mixture was stirred at RT for 5 h. Thereafter, the reaction mass was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (2×50 mL). Combined organic extracts were washed with water (30 mL), saturated aqueous NaCl (30 mL), dried (anhyd. Na_2SO_4) and concentrated *in vacuo*. Crude product was then purified by chromatography over silica gel to get the target molecule (0.208 g, 60%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (t, *J* = 6.5Hz, 1H), 5.55 (t, 3*J* = 6.5 Hz, 1 H,), 4.13 (d, 3*J* = 6.5 Hz, 2 H,), 3.91 (t, *J* = 6.5 Hz, 1 H,), 1.63 (s, 3 H,), 1.61–1.49 (m, 3 H,), 1.41–1.32 (m, 1H,), 1.18 (s, 3 H), 1.17 (s, 3 H) (Figure 1, Supplementary Information); ^{13}C NMR (125 MHz): δ 140.9, 126.2, 78.6, 71.1, 59.2, 40.8, 30.6, 29.31, 29.2, 11.6 (Figure 2, Supplementary Information); ESI-MS: *m/z* 189.14 [M^+].

Anti-cancer activity

Cytotoxicity of (−)-Sachalinol A was determined on the basis of measurement of *in vitro* growth inhibition of tumor cell lines in 96-well plates by cell-mediated reduction of tetrazolium salt to water insoluble formazan crystals using doxorubicin as a standard. The cytotoxicity as assessed against a panel of five different human tumor cell lines: A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), HeLa derived from human cervical cancer cells (ATCC No. CCL-2), MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26), MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22) and Neuro2a derived from mouse neuroblastoma cells (ATCC No. CCL-131) using the MTT assay[25]. The IC_{50} values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose-response curves. IC_{50} values (in lM) are expressed as the average of two independent experiments.

Conclusions

The study involves development of a simple novel synthetic method for the preparation of (−)-Sachalinol A. The method involves an eight step procedure, where the title compound is synthesized in good yield. Riley oxidation and Sharpless epoxidation are the key steps in the synthesis, where an aldehyde and allylic functionalities are generated which on further series of oxidations result in (−)-Sachalinol A. The synthesized compound when evaluated for cytotoxicity exhibited excellent cytotoxicity against MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26) and HeLa derived from human cervical cancer

cells (ATCC No. CCL-2). Good activity could be observed against A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185) and Neuro2a derived from mouse neuroblastoma cells (ATCC No. CCL-131). Moderate activity was observed against MCF-7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22). Overall (−)-Sachalinol A proved to be a promising anti-cancer agent similar to other mono-and triterpenoids.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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