Tetrahedron: *Asymmetry* 27 (2016) 603–607

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereoselective synthesis of (*R*)-(−) and (*S*)-(+)-phoracantholide I from (*R*)-(+)-γ-valerolactone

Rajender Datrika [a,b], Srinivasa Reddy Kallam [a], Sandip R. Khobare [a], Vikas S. Gajare [a], Muralikrishna Kommi [a], Rama Mohan H. [a], Siddaiah Vidavalur [b], Pratap T. V. [a,*]

[a] *Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Hyderabad 500049, India*
[b] *Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India*

ARTICLE INFO

Article history:
Received 22 April 2016
Accepted 27 May 2016
Available online 25 June 2016

This article is dedicated to the memory of Dr. Kallam Anji Reddy, the founder of Dr. Reddy's Laboratories Ltd.

ABSTRACT

A concise total synthesis of (*R*)-(−)-phoracantholide I **1** and (*S*)-(+)-phoracantholide I **2** has been developed from (*R*)-(+)-γ-valerolactone **6**. The key steps in the synthesis of these macrolides involved enzymatic reduction of Levulinic ester **4** by asymmetric dehydrogenase, *Z*-selective Wittig reaction of (4-carboxybutyl)triphenylphosphonium ylide **11** with lactol **7**, and cyclization of *seco*-acid **8** using either a Yamaguchi lactonization protocol or a Mitsunobu protocol to afford (*R*)-(−)-phoracantholide I and (*S*)-(+)-phoracantholide I respectively.

1. Introduction

γ-Lactones are important structural entities and valuable building blocks in the synthesis of natural products and biologically active molecules such as pheromones, polyketides and prostaglandins.[1] Considering the high stereoselectivity during Wittig reactions of the corresponding lactol of enantiomerically pure γ-valerolactone, the latter become very good chiral synthons in the synthesis of natural products.[2] A variety of methods are used for the synthesis of enantiomerically pure γ-lactones that either use stoichiometric or catalytic chiral reagent systems[3] or enzymes as part of a greener approach for the asymmetric hydrogenation[4] of γ-keto esters. With so much progress being made in the field of asymmetric reductions of γ-keto esters using enzymes,[5] it has now become quite easy to obtain the chiral alcohols that afford enantiomerically pure γ-valerolactones in large quantities starting from γ-keto esters. The biological activity of macrolides stems from the presence of a macrocyclic ring that is either medium-sized (7- to 11-membered) or large-sized (12-membered and larger).[6] These lactones are important structural motifs in a wide range of biologically active natural products.[7] A few examples of simple monocyclic macrolides include Recifeioltide, Diplodialide A and B, Lasiodiplodin, Phoracantholide I and Phoracantholide J, and Patulolide A and C (Fig. 1).

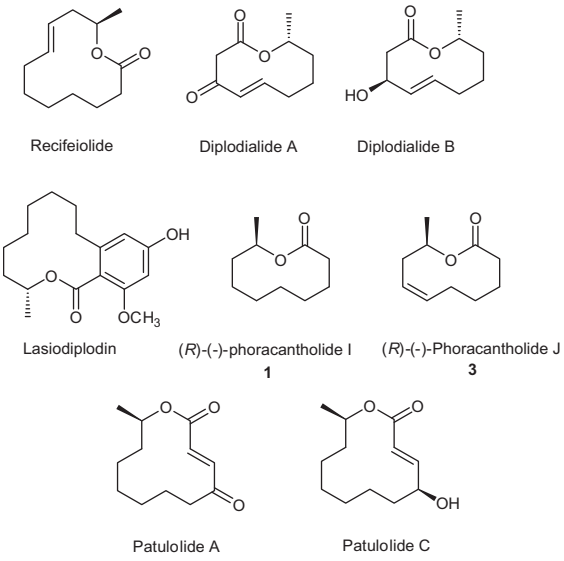


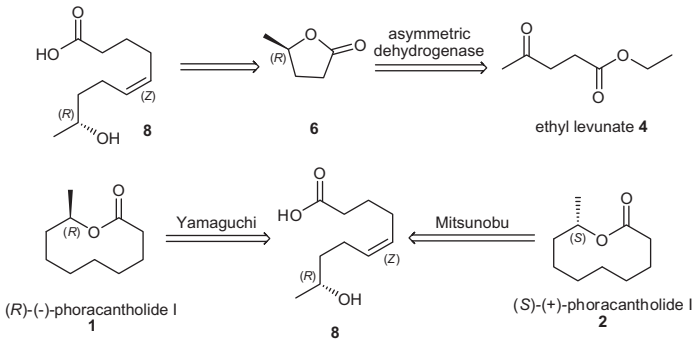
Figure 1. Monocyclic macrolides.

Mantillidae is a family of small frogs of Madagascar which are characterized by the presence of femoral glands on the ventral sides of the shanks of the males. These glands were found to secrete the pheromones that attract female frogs.

Phoracantholide J was identified as one of the pheromones secreted by these glands.[8] Thus phoracantholides have gained the attention of synthetic chemists. Several syntheses of (*R*)-(−)- and

* Corresponding author. Fax: +91 (40) 44658699.
E-mail address: tvpratap@drreddys.com (T.V. Pratap).

http://dx.doi.org/10.1016/j.tetasy.2016.05.008
0957-4166/



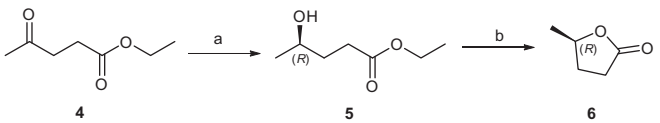
Scheme 1. Retrosynthetic analysis of (*R*)-(−)- and (*S*)-(+)-phoracantholide I.

(*S*)-(+)-phoracantholide I **1** and **2**, have been reported in the literature.[9] Although these syntheses afforded the desired products in high yield, they required the use of complex reagents, critical reaction conditions and lengthy multistep synthetic sequences. Thus a simple and scalable approach for their synthesis was sought.

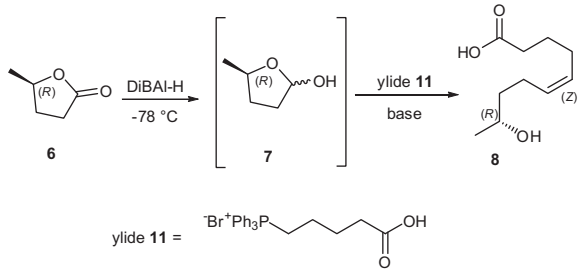
As part of our efforts to synthesize macrolides of biological significance using enantiomerically pure γ-valerolactone as a chiral synthon, we herein report a facile approach for the selective total synthesis of both (*R*)-(−) and (*S*)-(+)-phoracantholide I (**1** and **2**). The retrosynthetic approach for synthesis of **1** and **2** is described in Scheme 1. Thus **1** and **2** can be obtained either by Yamaguchi lactonization or by Mitsunobu esterification of the *seco*-acid intermediate (*Z*)-9-hydroxydec-5-enoic acid **8**, a common. The intermediate *seco*-acid **8** has a *Z*-double bond crafted to facilitate the intramolecular lactonization. The latter is synthesized with high stereoselectivity via Wittig reaction of lactol **7** with (4-carboxybutyl)triphenyl phosphonium ylide **11**. The lactol **7** intermediate involved in the Wittig reaction can be obtained by DIBAL-H reduction of corresponding (*R*)-(+)-γ-valerolactone **6**. Synthesis of (*R*)-(+)-γ-valerolactone **6** can be traced to ethyl levulinate. Ethyl levulinate on enzymatic reduction with asymmetric dehydrogenase affords the corresponding enantiomerically pure alcohol **5**.

2. Results and discussion

Our synthesis commenced with the enzymatic asymmetric reduction of ethyl levulinate using asymmetric dehydrogenase in presence of $NADPH_4$ to provide alcohol **5**[10] with high enantiomeric excess (98.14% *ee* by GC).[11] Lactonization of hydroxyl ester **5** using methanolic HCl gave a lower yield, but obtained a good yield of (*R*)-(+)-γ-valerolactone **6** with either the use of catalytic PTSA or Amberlyst IR-120 H^+ resin (Scheme 2). The obtained enantiomerically pure (*R*)-(+)-γ-valerolactone was reduced with DIBAL-H to the corresponding lactol **7**. Lactol **7** upon Wittig reaction with (4-carboxybutyl)triphenyl phosphonium ylide **11**[12] afforded the *Z*-olefin with high stereoselectivity (*Z*:*E* = 99:1)[13] and yield (Scheme 3). The *Z*-selectivity and yield were studied with different organic bases and molar equivalents of ylide (Table 1). Although all of the bases mentioned in Table 1 afforded almost identical selectivity, KHMDS afforded a higher yield when used in 4.0 equiv against 2.0 equiv of ylide **11**.

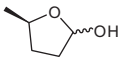


Scheme 2. Reagents and conditions: (a) asymmetric dehydrogenase enzyme, $NaDPH_4$, rt, pH: 6.8–7.2; 24 h, 74%; (b) PTSA/MeOH, rt, 20 h, 92% or Amberlyst IR-120 resin, MeOH, rt, 40 h, 90%.



Scheme 3. Reagents and conditions: (a) DIBAL-H, DCM, −78 °C, 0.5 h, 91%; (b) **11**, Base, 0 °C, 82%.

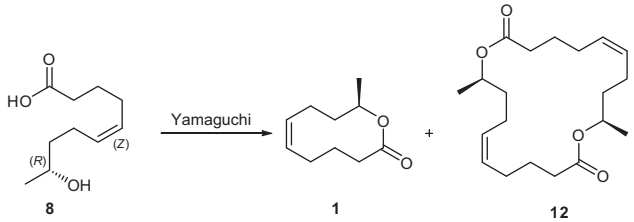
Table 1
Z-Selective Wittig reaction condition

Lactol	Ylide **11** mol equiv	*seco*-acid **8** Yield (%)	Base (4.0 mol equiv)
	1.0	65	KHMDS
	1.0	61	NaHMDS
	1.0	59	LiHMDS
	2.0	82	KHMDS
	2.0	74	NaHMDS
	2.0	69	LiHMDS
	1.2	56	*t*-BuOK

7

The *Z*-configuration of olefin **8** facilitates the lactonization process by bringing the reactive sites together. The stage was now set for the construction of macrocyclic ring. Yamaguchi lactonization protocol[14] on olefin **8** afforded lactone **9** with retention of configuration of the secondary hydroxyl group while the Mitsunobu protocol[15] would afford corresponding antipod **10** with inversion of the stereogenic center.

In the Yamaguchi lactonization (Scheme 4), dilution was found to be one of the key factors to control the formation of dimer **12**. Therefore, studies were conducted to find appropriate dilution as mentioned (Table 2). The dilution of 100:800 was found to give a better ratio of monomer to dimer.



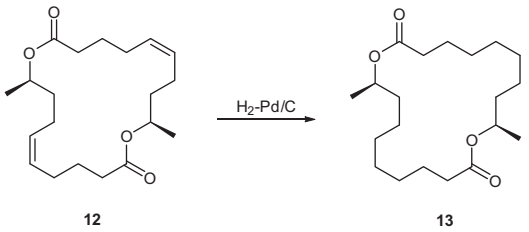
Scheme 4. Yamaguchi lactonization.

Table 2
Yamaguchi cyclization

seco-Acid	Dilution* (vol)	Monomer **1** (%)	Dimer **12** (%)
8	100:100	15	85
8	100:400	65	35
8	100:800	95	5

* DMAP/toluene dilution versus mixed anhydride dilution.

Accordingly Yamaguchi lactonization was performed in 100:800 dilution in the presence of 2,4,6-trichlorobenzoyl chloride, triethylamine and DMAP to afford the unsaturated lactone **9** with an (*R*)-configuration. On the other hand, lactonization in the presence of DIAD (diisopropyl azodicarboxylate) and triphenylphosphine afforded the corresponding unsaturated lactone **10**, with an (*S*)-configuration in good yield. Intermediates **9** and **10** individually when subjected to hydrogen pressure on Pd/C in ethyl acetate furnished the title compounds (*R*)-(−)-phoracantholide I **1** and (*S*)-(+)-phoracantholide I **2** respectively in good yield (Scheme 5). Under these conditions, the corresponding dimeric impurity **12** is also saturated to afford the dimeric by-product **13** (Scheme 6). The latter was identified and characterized by spectroscopic data.



Scheme 6. Macrocyclic dimer of (*R*)-(−)-phoracantholide I; Reagents and conditions: 10% Pd/C, H_2, ethyl acetate, rt, 25 psi, 2 h, 82%.

3. Conclusion

In conclusion, a highly stereoselective synthesis of (*R*)-(−)-phoracantholide I **1** and (*S*)-(+)-phoracantholide I **2** has been achieved in good yields. Cyclization of *seco*-acid **8** according to the Yamaguchi lactonization furnished (*R*)-(−)-phoracantholide I with retention of configuration while cyclization of *seco*-acid **8** according to the Mitsunobu lactonization furnished (*S*)-(+)-phoracantholide I with inversion of configuration. This synthesis for these macrolides utilizes fairly inexpensive reagents and is an environmentally friendly process. The application of this strategy of using enantiomerically pure γ-valerolactone in the synthesis of complex macrolides is currently underway.

4. Experimental

4.1. General

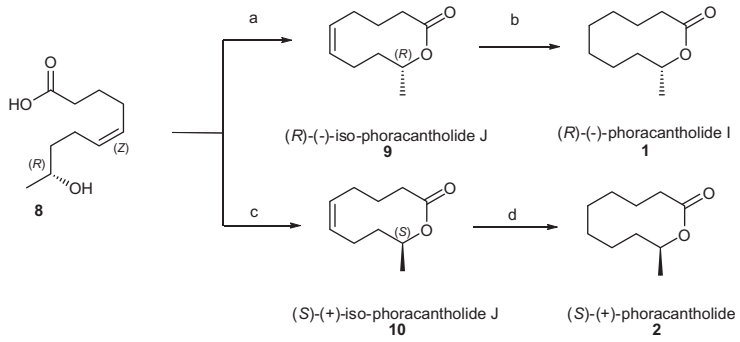
Reactions were conducted under N_2 in anhydrous solvents such as DCM, THF, DMSO, CH_3CN, Et_2O, Toluene, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualized under UV light, in case of non UV-active intermediates used suitable charring solution). Yields refer to the isolation of compounds after chromatography and spectroscopic (^1H and ^{13}C NMR) analysis of homogeneous material. Air-sensitive reagents were transferred by syringe or a double-ended needle. Evaporation of the solvents was performed at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300 spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were obtained on MS-EI, MS-ESI, HRMS mass spectrometers of Agilent Technologies 1100 Series. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. IR (FT-IR) spectra were recorded either on KBr pellets or neat as thin film or in $CHCl_3$. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter.

4.2. Ethyl (*R*)-hydroxypentanoate 5

Synthesized from 50 g of Levulinic ester **4**.[10] Compound **5** was obtained (37 g, 74%) as a pale yellow oil, enantiomer purity by GC: 98.14% *ee*; $[\alpha]_D^{24} = -12.2$ (*c* 2.0, $CHCl_3$); IR (Neat, cm^{-1}): ν_{max} 3417, 2972, 2933, 1733, 1299, 1267, 1094, 962; ^1H NMR (400 MHz, $CDCl_3$): δ 4.11 (q, 2H), 3.83 (d, 1H), 2.42 (t, 2H), 1.64 (m, 3H), 1.2 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 23.47, 30.76, 33.83, 60.45, 67.31, 174.12; HRMS Calcd for $C_7H_{15}O_3$ ($M+H^+$): 147.1021, found: 147.1026.

4.3. (*R*)-(+)-γ-Valerolactone 6

Ethyl (*R*)-hydroxypentanoate **5** (20 g, 0.137 mol) was treated with PTSA (0.02 g) in anhydrous methanol (200 mL) at room temperature for 20 h. The reaction mass was quenched with TEA (3.0 mL) and the solvent was evaporated. The crude residue obtained was diluted with MTBE (240 mL) and washed with satd $NaHCO_3$ (240 mL). The solvent was removed under reduced pressure and the crude residue was further purified by fraction distillation to afford compound **6** (13 g, 92%) as a colorless oil; $[\alpha]_D^{22}$ = +37.05 (*c* 1.0, MeOH); IR (Neat, cm^{-1}); ν_{max} 2980, 1771; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, *J* = 6.4 Hz, 3H), 1.78–1.88 (m, 1H), 2.09–2.40 (m, 1H), 2.53–2.57 (m, 2H), 4.62 (q, *J* = 6.4 Hz, 1H); ^{13}C



Scheme 5. Reagents and conditions: (a) Yamaguchi lactonization: 2,4,6-trichlorobenzoyl chloride, TEA, DMAP, toluene, 16 h, rt, 69%; (b) 10% Pd/C, H_2, ethyl acetate, rt, 25 psi, 2 h, 85%; (c) Mitsunobu reaction: DIAD/TPP, 0 °C, 14 h, 63%; (d) 10% Pd/C, H_2, ethyl acetate, rt, 25 psi, 2 h, 80%.

NMR (100 MHz, $CDCl_3$): δ 20.79, 28.85, 29.44, 77.09, 177.14; GC–MS: (100, M+).

4.4. (*R*,*Z*)-9-Hydroxydec-5-enoic acid 8

To a solution of lactone **6** (1.2 g. 0.012 mol) in DCM (24 mL) was added 1.6 M DIBAL-H (9.6 mL, 0.014 mol) at −78 °C and reaction mixture was stirred for 0.5 h. After completion of the reaction, the reaction was quenched with methanol. The reaction mass was treated with a saturated solution of sodium potassium tartrate solution (24 mL) and stirred for 2 h at room temperature. The product was extracted in DCM (24 mL), the combined organic layers washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford lactol **7** (1.1 g, 91%) as a colorless oil. It was used in the next stage without further purification.

To a solution of ylide **11** (8.69 g, 0.019 mol) in THF (15 mL) at 0–5 °C was added 20% KHMDS (39 mL, 0.0294 mol) under an inert atmosphere. After maintaining the temperature of the reaction at 0 °C for 10–15 min, the temperature of the reaction mass was allowed to return to room temperature, and stirred for 15–30 min. The reaction mass was cooled to 0 °C after which was added lactol **7** (1.0 g, 0.01 mol) as a solution in THF (15 mL) under an inert atmosphere. After completion of reaction, the reaction mass was quenched with ice cold water (30 mL), and washed with MTBE (2 × 25 mL). The pH of the obtained aqueous layer was adjusted to 2–3 using 3 M HCl and the product was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by flash chromatography to afford **8** (1.5 g, 82%) as a colorless oil, $[\alpha]_D^{23} = -7.4$ (*c* 0.53, $CHCl_3$); IR (Neat, cm^{-1}); ν_{max} 3384, 3005, 2932, 1709, 1452, 1241, 1082, 854; ^1H NMR (400 MHz, $CDCl_3$): δ 5.34–5.46 (m, 2H), 3.80 (m, 1H), 2.34 (m, 2H), 2.07 (m, 4H), 1.66 (m, 2H), 1.47–1.53 (m, 2H), 1.19 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.34, 23.53, 24.51, 26.31, 33.20, 38.86, 67.79, 128.95, 130.42, 179.03; HRMS Calcd for $C_{10}H_{19}O_3$ ($M+H^+$) 187.1334, found: 187.1343.

4.5. (*R*,*Z*)-10-Methyl-4,5,9,10-tetrahydro-3*H*-oxecin-2(8*H*)-one 9

To a solution of *seco*-acid **8** (0.25 g, 0.0013 mol) in dry THF (12.5 mL) were added TEA (1.35 g, 0.013 mol) and 2,4,6-trichloro benzoylchloride (1.95 g, 0.008 mol) at 0 °C under inert conditions and stirred for 2 h at 0 °C. The solid suspension was removed by filtration, further diluted with 200 mL of dry toluene, transferred to an addition vessel under inert atmosphere and then added slowly to a solution of DMAP (1.64 g, 0.013 mol) and toluene (25 mL) in a separate reaction flask at 25 °C over a period of 16 h. After completion of the reaction, it was diluted with ethyl acetate (50 mL) and washed with 1 M HCl (250 mL) and brine. The organic layer obtained was evaporated and then purified by flash chromatography to afford **9** (0.15 g, 69%) as colorless oil; $[\alpha]_D^{23} = -56.3$ (*c* 0.53, $CHCl_3$); IR (Neat, cm^{-1}); ν_{max} 2999, 2966, 2934, 2914, 2873, 1724, 1658, 1224, 868; ^1H NMR (400 MHz, $CDCl_3$): δ 5.33 (m, 2H), 4.80–4.85 (m, 1H), 1.61–2.35 (m, 10H), 1.21 (d, J = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.02, 129.60, 129.41, 70.17, 35.88, 33.63, 26.45, 24.43, 23.25, 20.27; HRMS Calcd for $C_{10}H_{17}O_2$ ($M+H^+$) 169.1229 found: 169.1237.

4.6. (*S*,*Z*)-10-Methyl-4,5,9,10-tetrahydro-3*H*-oxecin-2(8*H*)-one 10

To a solution of triphenylphosphine (1.7 g, 6.4 mmol) in toluene (60 mL) at 0 °C was added DIAD (1.3 g, 6.4 mmol) dropwise under an inert atmosphere. The resultant mixture was stirred for 2 h at 0 °C, after which *seco*-acid **8** (0.3 g, 1.6 mmol) was added as a dilute solution in toluene (180 mL) over a period of 14 h. After completion of the reaction, the reaction mass was washed with water (50 mL), and the solvent was evaporated under reduced pressure and purified by flash chromatography to afford **10** (0.17 g, 63%): Colorless oil; $[\alpha]_D^{22} = +94.2$ (*c* 0.8, $CHCl_3$); IR (Neat, cm^{-1}); ν_{max} 2999, 2966, 2934, 2914, 2873, 1724, 1658, 1224, 868; ^1H NMR (400 MHz, $CDCl_3$): δ 5.33 (m, 2H), 4.80–4.85 (m, 1H), 1.61–2.35 (m, 10H), 1.21 (d, J = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.02, 129.60, 129.41, 70.17, 35.88, 33.63, 26.45, 24.43, 23.25, 20.27; HRMS Calcd for $C_{10}H_{17}O_2$ ($M+H^+$) 169.1229 found: 169.1224.

4.7. (*R*)-(−)-Phoracantholide I 1

To a solution of **9** (0.1 g, 0.0005 mol) in ethyl acetate (15 mL) was added 10% Pd/C and hydrogenated at 25 psi pressure for 2 h at room temperature. After completion of the reaction, the reaction mass was filtered and the solvent was removed under reduced pressure to afford pure **1** (0.085 g, 85%) as a colorless oil; $[\alpha]_D^{22} = -40.1$ (*c* 0.5, $CHCl_3$); [Lit.[16] $[\alpha]_D^{24} = -37.3$ (*c* 0.6, $CHCl_3$)]; IR (Neat, cm^{-1}); ν_{max} 2954, 2926, 1727, 1468, 1256, 1166, 1078, 1049; ^1H NMR (400 MHz, $CDCl_3$): δ 4.98–5.02 (m, 1H), 2.45–2.51 (m, 1H), 1.91–2.20 (m, 3H), 1.71–1.79 (m, 1H), 1.35–1.60 (m, 8H), 1.26 (d, J = 6.4 Hz, 3H), 1.02–1.57 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$):19.41, 20.62, 23.39, 23.96, 24.21, 27.09, 31.33, 35.17, 72.58, 173.97; HRMS Calcd for $C_{10}H_{19}O_2$ ($M+H^+$) 171.1385 found: 171.1378.

4.8. (*S*)-(+)-Phoracantholide I 2

To a solution of **10** (0.1 g, 0.0005 mol) in ethyl acetate (15 mL) was added 10% Pd/C and hydrogenated with 25 psi for 2 h at room temperature. After completion of the reaction, the reaction mass was filtered and the solvent was removed under reduced pressure to afford pure **2** (0.08 g, 80%) as a colorless oil; $[\alpha]_D^{22} = +31.8$ (*c* 0.6, $CHCl_3$); {Lit.[17] $[\alpha]_D^{22} = +34.8$ (*c* 0.68, $CHCl_3$)}; IR (Neat, cm^{-1}); ν_{max} 2954, 2926, 1727, 1468, 1256, 1166, 1078, 1049; ^1H NMR (400 MHz, $CDCl_3$): δ 4.98–5.02 (m, 1H), 2.45–2.51 (m, 1H), 1.91–2.20 (m, 3H), 1.71–1.79 (m, 1H), 1.35–1.60 (m, 8H), 1.26 (d, J = 6.4 Hz, 3H), 1.02–1.57 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$):19.41, 20.62, 23.39, 23.96, 24.21, 27.09, 31.33, 35.17, 72.58, 173.97; HRMS Calcd for $C_{10}H_{19}O_2$ ($M+H^+$) 171.1384 found: 171.1379.

4.9. (4*Z*,8*R*,14*Z*,18*R*)-8,18-Dimethyl-1,9-dioxacyclooctadeca-4,14-diene-2,10-dione 12

Pale yellow colored solid: Mp: 42.9 °C; IR (KBr, cm^{-1}); ν_{max} 2999, 2966, 2934, 2914, 2873, 1724, 1658, 1224, 868; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, J = 6.4 Hz, 6H), 1.50–1.77 (m, 8H), 2.02–2.36 (m, 12H), 4.85–4.91 (m, 2H), 5.32–5.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.05, 129.64, 129.44, 70.20, 35.92, 33.68, 26.49, 24.47, 23.28, 20.29; HRMS Calcd for $C_{20}H_{33}O_4$ ($M+H^+$): 337.2379 found: 337.2374.

4.10. (8*R*,18*R*)-8,18-Dimethyl-1,9-dioxacyclooctadecane-2,10-dione 13

Pale yellow colored solid: Mp: 40.7 °C; IR (KBr, cm^{-1}); ν_{max} 2930, 2856, 1729, 1253, 1015; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, J = 6.3 Hz, 6H), 1.26–1.69 (m, 24H), 2.22–2.36 (m, 4H), 4.90–4.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.33, 24.99, 25.11, 28.48, 29.25, 29.32, 34.62, 35.91, 70.30, 173.36; HRMS Calcd for $C_{20}H_{37}O_4$ ($M+H^+$) 341.2692 found: 341.2698.

Acknowledgments

The authors would like to thank Dr. Vilas Dahanukar and Dr. Reddy's Laboratories for continued support. We also thank the Analytical Department of Dr. Reddy's Laboratories, for providing the analytical support.

DRL IPD communication No: IPDO IPM-00501.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.05.008.

References and notes

1. (a) Mandrioli, R.; Mercolini, L.; Saracino, M. A.; Raggi, M. A. *Curr. Med. Chem.* **2012**, *19*, 1846–1863; (b) Ghosh, A. K.; Swanson, L. *J. Org. Chem.* **2003**, *68*, 9823–9826; (c) Lipshutz, B. H.; Lower, A.; Kucejko, R. J.; Noson, K. *Org. Lett.* **2006**, *8*, 2969–2972; (d) Stangeland, E. L.; Sammakia, T. *J. Org. Chem.* **2004**, *69*, 2381–2385; (e) Hilbon, J. W.; Lu, Z. H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919–8921.
2. (a) Resul, B.; Stjernschantz, J.; No, K.; Liljebris, C.; Selen, G.; Astin, M.; Karlsson, M.; Bito, L. Z. *J. Med. Chem.* **1993**, *36*, 243–248; (b) Poth, D.; Peram, P. S.; Vences, M.; Schulz, S. *J. Nat. Prod.* **2013**, *76*, 1548–1558; (c) Patel, P.; Lee, G.-J.; Kim, S.; Grant, G. E.; Powell, W. S.; Rokach, J. *J. Org. Chem.* **2008**, *73*, 7213–7218.
3. Ramachandran, P. V.; Pitre, S.; Brown, H. C. *J. Org. Chem.* **2002**, *67*, 5315–5319.
4. Starodubtseva, Eugenia V.; Turova, Olga V.; Vinogradov, Maxim G.; Gorshkova, Lilia S.; Ferapontov, Vladimir A.; Struchkova, Marina I. *Tetrahedron* **2008**, *64*, 11713–11717.
5. (a) Sugai, T.; Hamada, K.; Akeboshi, T.; Ikeda, H.; Ohta, H. *Synlett* **1997**, 983–985; (b) Forzato, C.; Gandolfi, R.; Molinari, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2001**, *12*, 1039–1046; (c) Nanduri, V. B.; Hanson, R. L.; Goswami, A.; Wasylyk, J. M.; LaPorte, T. L.; Katipally, K.; Chung, H. J.; Patel, R. N. *Enzyme Microb. Technol.* **2011**, *28*, 632–636.
6. (a) Radha Krishna, P.; Sreeshailam, A. *Synlett* **2008**, 2795–2798; (b) Raji Reddy, Ch.; Narsimha Rao, N. *Tetrahedron Lett.* **2009**, *50*, 2478–2480; (c) Lukesh Julie, M.; Donaldson William, A. *Tetrahedron: Asymmetry* **2003**, *14*, 757–762; (d) Yadav, J. S.; Pratap, T. V.; Rajender, V. *J. Org. Chem* **2007**, *72*, 5882–5885.
7. (a) Tsoukatou, M.; Siapi, H.; Vagias, C.; Roussis, V. *J. Nat. Prod.* **2003**, *66*, 444–446; (b) Sang, S.; Cheng, X.; Fu, H. Y.; Shieh, D. E.; Bai, N.; Lapsley, K.; Stark, R. E.; Rosen, R. T.; Ho, C. T. *Tetrahedron Lett.* **2002**, *43*, 2547–2549; (c) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777–2849; (d) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J. M. *Chem. Rev.* **2013**, *113*; (e) Kleinke, A. S.; Webb, D.; Jamison, T. F. *Tetrahedron* **2012**, *68*, 6999–7018; (f) Shiina, I. *Chem. Rev.* **2007**, *107*, 239–273.
8. Poth, D.; Wollenberg, K. C.; Vences, M.; Schulz, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2187–2190.
9. (a) Gerlach, H.; Kunzler, P.; Oertle, K. *Helv. Chem. Acta* **1978**, *61*, 1226–1231; (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1595–1597; (c) Sugimone, H.; Yamada, S. *Tetrahedron Lett.* **1985**, *26*, 3715–3718; (d) Ohnuma, T.; Hata, N.; Miyachi, N.; Wakamatsu, T.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 219–222.
10. Alba, Díaz-Rodríguez; Wioleta, Borzęcka; Iván, Lavandera; Vicente, Gotor *ACS Catal.* **2014**, *4*, 386–393.
11. *GC conditions:* Column Betadex (30 m, 0.25 mm, 0.25 μm); Temp program: 100 °C (5 min Hold) to 200 °C then Ramp 5 °C/min; Injector temp: 200 °C, Detector temp: 210 °C, Carrier gas: Helium 2.0 mL (constant flow); Injection volume: 1.0 μL, Split ratio: 50:1; Diluent: DCM.
12. (4-Carboxybutyl)triphenylphosphonium ylide **11** was prepared using reference: Wube, A.; Hufner, A.; Thomaschitz, C.; Blunder, M.; Kollroser, M.; Bauer, R.; Bucar, F. *Bioorg. Med. Chem.* **2011**, *19*, 567–579.
13. Matsumura, Y.; Mori, N.; Nakano, T.; Sasakura, H.; Matsugi, T.; Hara, H.; Morizawa, Y. *Tetrahedron Lett.* **2004**, *45*, 1527–1529.
14. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
15. Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, *17*, 2455–2458.
16. Hamada, T.; Daikai, K.; Irie, R.; Katsuki, T. *Tetrahedron: Asymmetry* **1995**, *6*, 2441–2451.
17. Kitahara, Takeshi; Koseki, Koshi; Mori, Kenji *Agric. Biol. Chem.* **1983**, *47*, 389–394.