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Enantiospecific total synthesis of phytoalexins, (+)-solanascone, (+)-dehydrosolanascone, and (+)-anhydro-β-rotunol

A. Srikrishna* and S. S. V. Ramasastry

Department of Organic Chemistry, Indian Institute of Science, C. V. Raman Avenue, Bangalore 560012, India

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Abstract—Enantiospecific total synthesis of the phytoalexins, solavetivone, anhydro-β-rotunol, solanascone, and dehydrosolanascone, starting from the readily available monoterpene, (*R*)-carvone has been accomplished.

Phytoalexins are low molecular weight secondary metabolites produced as a method of self-defense in plants. Phytoalexins are similar to antiviral proteins that inhibit protein synthesis in the event of pathogenic attack and therefore prevent growth of foreign agents by removing all possible avenues for invasion of the pathogen. Phytoalexins solavetivone **1** and anhydro-β-rotunol **2** were isolated,[1] as major stress metabolites, from potato tubers infected with the blight fungus *Phytophthora infestans* or with the soft-rot bacterium *Erwinia carotovora* var *atroseptica*. Solavetivone **1** was later isolated from a few other sources such as air-cured tobacco leaves and potato cell suspension cultures.[2] Isolation of the structurally complex phytoalexin (+)-solanascone **3** was first reported by Fujimori et al. from *Nicotiana tabacum* cv. Burley.[3] The stereostructure of solanascone **3** was elucidated by single crystal X-ray diffraction analysis of the oxime derivative. The structure was further confirmed by conversion of natural solavetivone **1** into solanascone **3**, which not only established solavetivone **1** as the biogenetic precursor of solanascone **3** but also confirmed the absolute configuration. Later, Nishikawaji et al. reported the isolation of dehydrosolanascone **4** from flue-cured tobacco leaves.[4] Subsequently, isolation of a few other members of solanascane family was reported (Fig. 1).[5] Solavetivone **1** inhibits germination, germ tube and mycelial growth, and essential enzymes of *Pseudomonas infestans*. It also possesses inhibitory activity against the *Pseudomonas syringae* pv. *tabaci*.[6] Strong antibacterial activity of solanascone **3**, solavetivone **1**, and 3-hydroxysolavetivone on *Pseudomonas solanacearum* is also well established.[7]

The unusual and novel tetracyclo[5.3.1.1^{1,4}.0^{5,11}]dodecane carbon framework incorporating three contiguous quaternary carbon atoms and six chiral centers, coupled with the biological activities, made solanascone **3** an interesting and challenging synthetic target. Herein, we describe enantiospecific syntheses of solanascone[8] **3** and dehydrosolanascone **4**, along with solavetivone[6,9] **1** and anhydro-β-rotunol[10] **2**.

Our retrosynthetic analysis of solanascone **3** is depicted in Scheme 1. Enone **5** was identified as the key intermediate, which could be elaborated into solanascones **3** and **4**, and also to solavetivone **1** and anhydro-β-rotunol **2**. The enone **5** could be obtained from dione **6** by an intramolecular aldol reaction. Diketone **7** was considered as an appropriate precursor for the dione **6** and but-3-enyl group was identified as the masked 3-oxobutyl group. It was thought that 2-acetyl-2-butenylcyclopentanone **7** could be obtained from carvone **8** via 3-butenylcarvone **9**.

The synthetic sequence starting from (*R*)-carvone **8** is depicted in Schemes 2 and 3. To begin, (*R*)-carvone **8** was converted into 3-(but-3-enyl)carvone **9**. Thus, a Barbier reaction between carvone **8** and 4-bromobut-1-ene, followed by oxidation of the resultant allylic tertiary alcohol[11] furnished the 1,3-transposed enone (*S*)-3-(but-3-enyl)carvone **9**, $[\alpha]_D^{23}$ +94.3 (*c* 1.4, $CHCl_3$). Nucleophilic epoxidation of the enone **9** with 30% aqueous hydrogen peroxide in the presence of sodium hydroxide furnished the *anti*-epoxide **10**, in 85% yield. Rearrangement of the epoxide **10** with amberlyst-15 in methylene chloride

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* Corresponding author. Tel.: +91 8022932215; fax: +91 8023600683; e-mail: ask@orgchem.iisc.ernet.in

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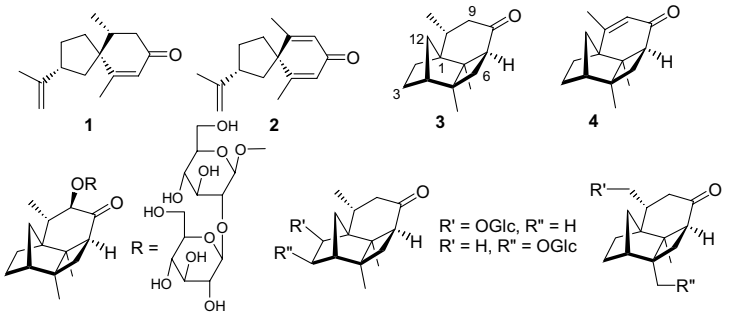
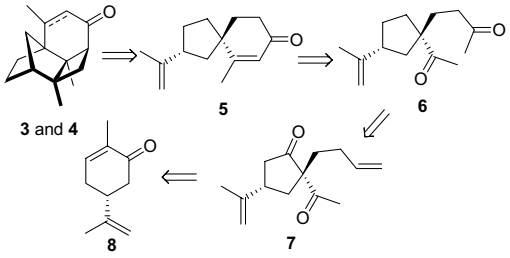


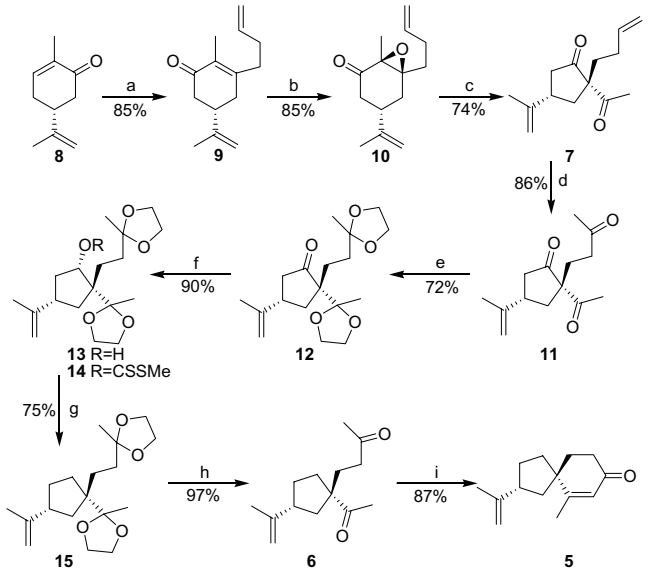
Figure 1.



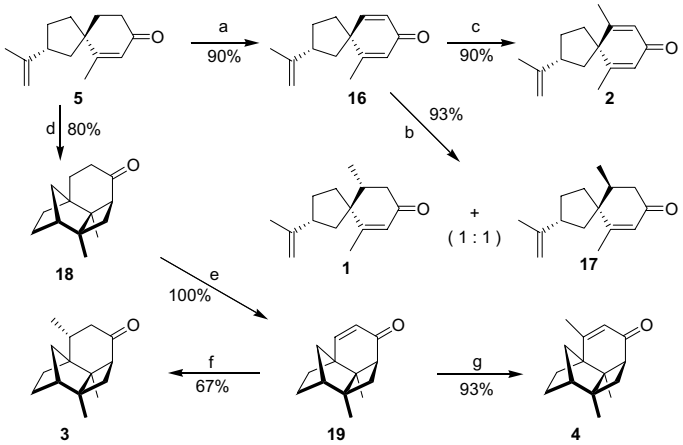
Scheme 1.

at room temperature then generated the ring-contracted product,[12] dione **7**, $[\alpha]_D^{23}$ −95.2 (*c* 1.26, $CHCl_3$), in 74% yield. The stereochemistry of the spiro center was assigned on the basis of the well established stereo control in the epoxide rearrangement.[12] A Wacker oxidation[13] of dione **7** with cuprous chloride and 0.1 equiv of palladium chloride in *N*,*N*-dimethylformamide (DMF) and water at room temperature under oxygen atmosphere (balloon) furnished the trione **11**, in 86% yield.

Our attention next turned to the reductive deoxygenation of the cyclic ketone and Barton's radical deoxygenation[14] was chosen. Since selective reduction of the ring ketone in **11** was unsuccessful, the two acetyl groups were protected as ketals in 72% yield by reacting with 1,2-ethanediol and *p*-toluenesulfonic acid (PTSA)



Scheme 2. Reagents and conditions: (a) i. Li, $BrCH_2CH_2CH{=}CH_2$, THF,))), 1 h; ii. PCC, silica gel, CH_2Cl_2, rt, 4 h; (b) 30% H_2O_2, 6 N aq NaOH, MeOH, 0 °C, 20 h; (c) amberlyst-15 (1:1 w/w), CH_2Cl_2 (0.1 M), rt, 24 h; (d) $PdCl_2$, CuCl, DMF, H_2O, O_2, rt, 20 h; (e) $(CH_2OH)_2$, PTSA, C_6H_6, reflux, 45 min; (f) LAH, Et_2O, 0 °C → rt, 1 h; (g) i. NaH, CS_2, MeI, imidazole, THF, reflux, 5 h; ii. Bu_3SnH, AIBN, C_6H_6, reflux, 3 h; (h) 1 N aq HCl, THF (1:2), 1 h, rt; (i) piperidine, AcOH, C_6H_6, reflux, 45 min.



Scheme 3. Reagents and conditions: (a) i. LHMDS, TMSCl, Et_3N, THF, −70 °C, 3 h; ii. $Pd(OAc)_2$, CH_3CN, rt, 4 h; (b) Me_2CuLi, Et_2O, −30 °C, 1 h; (c) i. Me_2CuLi, TMSCl, Et_3N, Et_2O, −70 °C, 2 h; ii. $Pd(OAc)_2$, CH_3CN, rt, 3 h; (d) hν, MeOH, 2 h; (e) i. LHMDS, TMSCl, Et_3N, THF, −70 °C, 3 h; ii. $Pd(OAc)_2$, CH_3CN, rt, 3.5 h; (f) Me_2CuLi, Et_2O, −70 °C → −30 °C, 1.5 h; (g) i. Me_2CuLi, TMSCl, Et_3N, −70 °C, 2 h; ii. $Pd(OAc)_2$, CH_3CN, rt, 24 h.

in benzene at reflux, using a Dean–Stark water trap. Reaction of the resulting bisketal **12** with lithium aluminum hydride (LAH) in ether at 0 °C furnished alcohol **13** in 90% yield. Treatment of the alcohol **13** with sodium hydride in the presence of 20 mol % of imidazole, followed by addition of dry carbon disulfide and methyl iodide, furnished the dithiocarbonate **14** in 88% yield. Thermal reaction of **14** with tributyltin hydride in the presence of 10 mol % of azobisisobutyronitrile (AIBN) in refluxing benzene furnished the bisketal **15** in 85% yield. Treatment of the bisketal **15** with aqueous hydrochloric acid in THF at room temperature for 1 h, then furnished the diketone **6**, $[\alpha]_D^{25}$ −24.2 (*c* 1.24, $CHCl_3$), in 97% yield. After exploring various conditions, piperidine and acetic acid was found to be the best reagent combination for the regioselective intramolecular aldol condensation of dione **6**. Thus, refluxing a benzene solution of the diketone **6** with piperidine and acetic acid for 1 h using a Dean–Stark water trap furnished the key intermediate, nor-solavetivone[†] **5** in 87% yield. The 15th carbon of solavetivone **1** was introduced via conjugate addition to the dienone **16**. Generation of the kinetic TMS enol ether of the enone **5** with lithium hexamethyldisilazide (LHMDS), trimethylsilyl chloride and triethylamine, followed by oxidative desilylation[15] with palladium acetate in acetonitrile generated the cross-conjugated dienone, nor-anhydro-β-rotunol[†] **16**, in 90% yield. Treatment of the dienone **16** with lithium dimethylcuprate in dry ether at −30 °C furnished, as expected, a 1:1 epimeric mixture of solavetivone **1** and 10-*epi*-solavetivone **17** in 93% yield. On the other hand, reaction of the dienone **16** with lithium dimethylcuprate, trimethylsilyl chloride and triethylamine, followed by oxidative desilylation[15] of the resultant TMS dienolate with palladium acetate in acetonitrile generated anhydro-β-rotunol **2**, $[\alpha]_D^{24}$ +53.3 (*c* 1.52, EtOH) [Lit.[1] +52.0 (*c* 0.7, EtOH)], in 90% yield, which exhibited spectral data identical to those of an authentic sample.[1,10]

Next, syntheses of solanascone **3** and dehydrosolanascone **4** were investigated. Since the introduction of the C-10 methyl group in solavetivone **1** resulted in an epimeric mixture (**16** → **1**+**17**), it was decided to introduce the secondary methyl group after construction of the tetracyclic carbon framework using the shape of the tetracyclic framework to direct addition of the methyl group from the *exo* face. Accordingly, photochemical irradiation of a degassed methanolic solution of the enone **5** with a 450 W Hanovia medium pressure mercury vapor lamp for 2 h furnished the tetracyclic ketone[†] **18** in 80% yield. Generation of the TMS enol ether of ketone **18** with LHMDS, trimethylsilyl chloride and triethylamine in THF at −70 °C, followed by treatment with palladium acetate in acetonitrile at room temperature furnished the enone[†] **19** in quantitative yield. Addition of lithium dimethylcuprate to dehydro-nor-solanascone **19** at −70 °C, followed by stirring at −30 °C for 1.5 h furnished solanascone **3** in 67% yield. The synthetic sample exhibited optical rotation {$[\alpha]_D^{24}$ +20.5 (*c* 0.78, $CHCl_3$) [lit.[3] +20.3 (*c* 1.97, $CDCl_3$)]} and ^1H and ^{13}C NMR spectral data identical to those of the natural compound. On the other hand, reaction of enone **19** with lithium dimethylcuprate, trimethylsilyl chloride, and triethylamine, followed by treatment of the resultant TMS enol ether with palladium acetate in acetonitrile furnished dehydrosolanascone **4**, $[\alpha]_D^{25}$ +117.8 (*c* 0.28, $CHCl_3$), in 93% yield, which exhibited the ^1H and ^{13}C NMR spectral data identical to those of a natural sample.[4]

In conclusion, we have accomplished enantiospecific total syntheses of the phytoalexins solavetivone **1** and *epi*-solavetivones **17**, anhydro-β-rotunol **2**, solanascone **3**, and dehydrosolanascone **4** in a highly regio- and stereoselective manner from (*R*)-carvone **8**. In the present synthesis, anhydro-β-rotunol **2** was obtained in thirteen steps in 15% overall yield, and solanascone **3** and dehydrosolanascone **4** were obtained in 14 steps in 10% and 14% overall yield, respectively. Investigations on the synthesis of higher oxygenated solanascones and solavetivones for evaluating their biological profile are in progress.

[†] Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR, and mass) consistent with their structures. Selected spectral data for (−)-(2*R*,5*R*)-2-isopropenyl-6-methylspiro[4.5]dec-6-en-8-one **5**: $[\alpha]_D^{25}$ −162.5 (*c* 0.24, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1673, 1614, 886. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.75 (1H, s), 4.73 (1H, s), 4.71 (1H, s), 2.70–2.55 (1H, m), 2.45–2.37 (2H, m), 2.05–1.92 (4H, m), 1.95 (3H, s), 1.87 (1H, dd, *J* 12.9 and 6.6 Hz), 1.75 (3H, s), 1.67–1.54 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 198.1 (C), 166.6 (C), 146.9 (C), 127.0 (CH), 109.3 (CH_2), 46.4 (C), 46.0 (CH_2), 40.0 (CH_2), 36.4 (CH_2), 36.0 (CH_2), 34.7 (CH_2), 31.4 (CH_2), 21.3 (CH_3), 20.1 (CH_3). Mass: 204 (M^+, 9), 189 (8), 176 (11), 161 (31), 148 (30), 147 (41), 133 (44), 123 (46), 121 (40), 108 (52), 105 (47), 91 (73). HRMS: *m*/*z* Calcd for $C_{14}H_{21}O$ (M+1): 205.1592. Found: 205.1592. For (+)-(2*R*,5*S*)-2-isopropenyl-6-methylspiro-[4.5]dec-6,9-dien-8-one **16**: $[\alpha]_D^{25}$ +31.8 (*c* 0.22, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1665, 1625, 881. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 (1H, d, *J* 9.9 Hz), 6.10 (1H, dd, *J* 9.9 and 1.8 Hz), 6.07 (1H, s), 4.76 (2H, br s), 2.90–2.74 (1H, m), 2.20–1.70 (6H, m), 2.03 (3H, s), 1.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 185.7 (C), 162.0 (C), 155.2 (CH), 146.0 (C), 127.8 (CH), 125.0 (CH), 110.0 (CH_2), 50.0 (C), 46.8 (CH), 41.8 (CH_2), 36.0 (CH_2), 32.2 (CH_2), 21.4 (CH_3), 19.7 (CH_3). Mass: 202 (M^+, 8), 187 (10), 174 (11), 159 (35), 146 (38), 131 (32), 121 (71), 105 (20), 91 (100). HRMS: *m*/*z* Calcd for $C_{14}H_{19}O$ (M+H): 203.1436. Found: 203.1442. For (+)-(1*R*,4*R*,5*S*,7*S*,11*S*)-5,11-dimethyltetracyclo[5.3.1.$1^{1,4}$.$0^{5,11}$]-dodecan-8-one **18**: $[\alpha]_D^{25}$ +24.1 (*c* 0.58, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1707. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 2.43 (1H, dd, *J* 12.0 and 6.3 Hz), 2.40–2.30 (1H, m), 2.32 (1H, d, *J* 7.5 Hz), 2.20–1.85 (5H, m), 1.74 (1H, br s), 1.55–1.35 (3H, m), 1.20–1.06 (2H, m), 1.13 (3H, s), 1.05 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 217.5 (C), 48.1 (CH), 47.72 (C), 47.69 (C), 44.7 (CH, C-4), 44.5 (C), 39.5 (CH_2), 36.8 (CH_2), 35.7 (CH_2), 29.1 (CH_2), 26.2 (CH_2), 23.7 (CH_2), 17.4 (CH_3), 16.0 (CH_3). Mass: 189 (M^+−CH_3, 1), 161 (4), 142 (5), 129 (11), 125 (5), 111 (5), 87 (100). HRMS: *m*/*z* Calcd for $C_{14}H_{21}O$ (M+1): 205.1592. Found: 205.1596. For (+)-(1*S*,4*R*,5*S*,7*S*,11*S*)-5,11-dimethyltetracyclo[5.3.1.$1^{1,4}$.$0^{5,11}$]dodec-9-en-8-one **19**: $[\alpha]_D^{25}$ +102.2 (*c* 0.46, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1671. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.02 (1H, d, *J* 9.9 Hz), 5.98 (1H, d, *J* 9.9 Hz), 2.57 (1H, dd, *J* 12.3 and 6.3 Hz), 2.12 (1H, t, *J* 12.6 Hz), 2.05 (1H, dd, *J* 12.6 and 6.3 Hz), 1.80–1.32 (7H, m), 1.12 (3H, s), 1.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 200.9 (C), 152.6 (CH), 131.0 (CH), 50.2 (C), 49.0 (CH_2), 47.6 (C), 46.9 (CH), 44.1 (C), 43.5 (CH), 36.4 (CH_2), 27.8 (CH_2), 24.1 (CH_2), 17.2 (2C, CH_3). Mass: 174 (M^+−CO, 2), 173 (15), 157 (14), 149 (40), 105 (21), 97 (32), 91 (34). HRMS: *m*/*z* Calcd for $C_{14}H_{19}O$ (M+1): 203.1436. Found: 203.1442.

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