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A rapid enantiospecific synthesis of the (6,6,5)-tricyclic ring system of the elisabethane diterpenes

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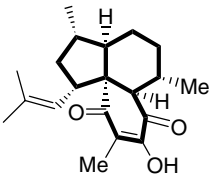
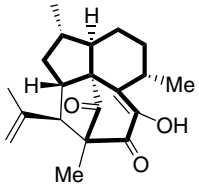
Abstract—A rapid enantiospecific stereoselective synthesis of the 6,6,5-ring system of the novel tricyclic elisabethin diterpenes, starting from (*R*)-carvone, employing a ROM-RCM sequence as the key step, has been accomplished.

Gorgonian corals have attracted considerable attention as a result of their wealth of bioactive secondary metabolites.[1] Specifically, the West Indian sea whip *Pseudopterogorgia elisabethae*, collected in deep waters near San Andreas Island (Colombia), has been a goldmine for novel diterpenoids with unusual carbon-skeleton architectures. The structural variety found among the many terpenoid natural products isolated from *P. elisabethae*, as well as the ample spectrum of biological activities exhibited by many of these compounds, is indeed quite remarkable. Rodriguez and co-workers have reported the isolation of a series of structurally related novel metabolites, elisabethins, colombiasins, cumbiasins and elisapterosins, for example **1**–**4**, from *P. elisabethae*, collected from the waters near San Andreas Island, Colombia.[2] Many members of this super family display anti-inflammatory, anticancer and antitubercular activities, and/or general antibacterial properties. Elisabethanes stand out among these diterpenoids for their interesting anti-inflammatory, antibacterial, analgesic and cytotoxic activities. The more intricate members of the family, elisapterosins, cumbiasins and colombiasins, were suggested to be biosynthesized from elisabethin A, which in turn arises from geranylgeranyl pyrophosphate via a serrulatane precursor. It was also shown that colombiasin A **4** readily isomerises to elisapterosin B **2**.

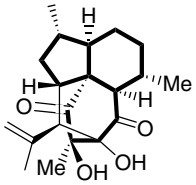
The 6,6,5-ring system (tricyclo[7.4.0.0^{1,5}]tridecane) of elisabethin A **1** embodies a fully substituted enedione functionality and six contiguous stereogenic centres, of which one, at the junction of the three rings, is quaternary. The structural complexity and interesting biological activity has made these terpenes interesting and novel targets for chemical synthesis.[3,4] To date, only two research groups have tackled the total synthesis of elisabethin A **1** with limited success.[4] In continuation of our interest in the enantiospecific synthesis of polycyclic sesquiterpenes and diterpenoids from the readily and abundantly available monoterpene (*R*)-carvone,[5] herein we report a rapid and efficient enantiospecific approach to the 6,6,5-tricyclic ring system (comprising the C 1–9 and C 14–19 carbons of elisabethanes) of the elisabethin diterpenoids, which is also present as part of the



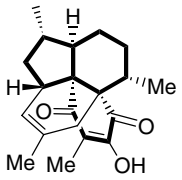
Elisabethin A (**1**)



Elisapterosin B (**2**)



cumbiasin A (**3**)



Colombiasin A (**4**)

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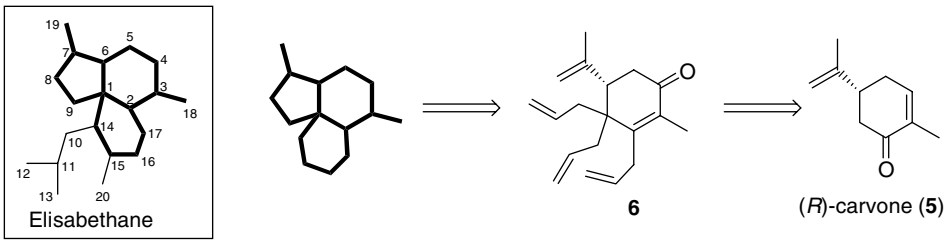
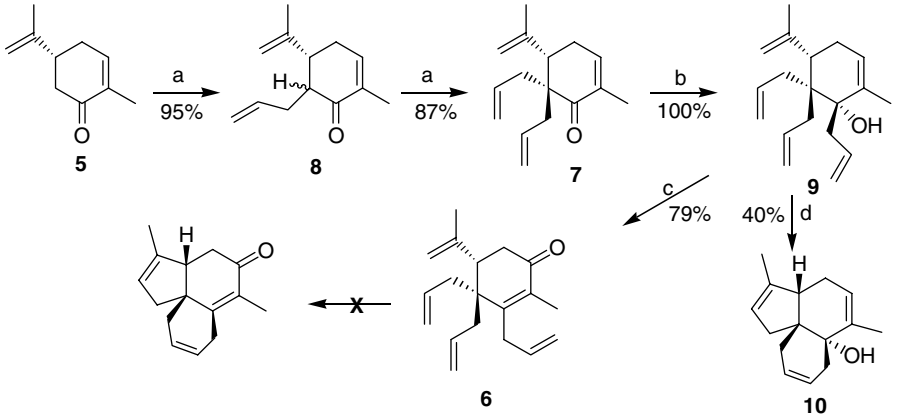


Scheme 1.

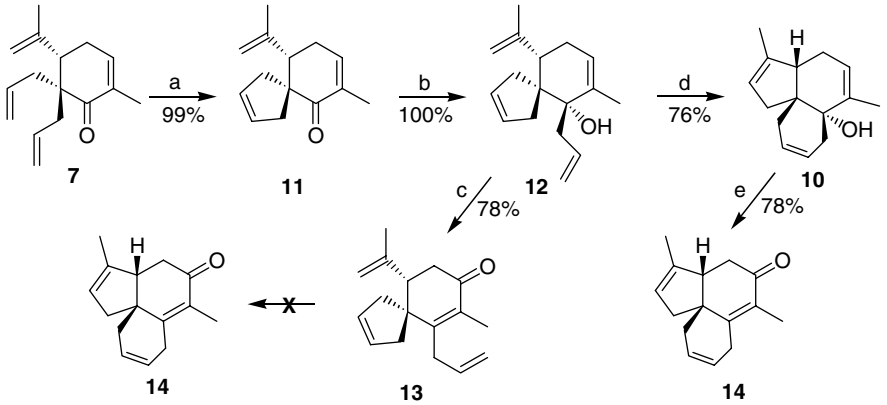
structure of the tetracyclic diterpenes colombiasins, cumbiasins and elisapterosins, employing a ROM-RCM reaction as the key step.

Carvone **5** was identified as the A-ring precursor of elisabethins, Scheme 1. Initially two simultaneous RCM reactions[6] in a single step were contemplated for the construction of the B- and C-rings, and pentaenone **6** was identified as a suitable precursor, which could be obtained from carvone **5** via 6,6-bisallylcarvone **7**.

Thus, kinetic allylation of carvone **5** with lithium diisopropylamide and allyl bromide[7] generated a 1:5 *cis–trans* mixture of 6-allylcarvone **8** in 95% yield, which on second allylation using the same conditions furnished 6,6-bisallylcarvone **7** in 87% yield. An alkylative 1,3-enone transposition[8] was adopted for the introduction of the third allyl group. Thus, sonochemically accelerated Barbier reaction with zinc and allyl bromide transformed bisallylcarvone **7** into trisallylcarveol **9** in quantitative yield, which on oxidation with pyridinium



Scheme 2. Reagents and conditions: (a) LDA, THF, −15 °C, 45 min, CH_2=$CHCH_2Br$, rt, 12 h; (b) Zn, CH_2=$CHCH_2Br$, THF,))), 45 min; (c) PCC, silica gel, CH_2Cl_2, rt, 24 h; (d) $Cl_2Ru(PCy_3)_2$=CHPh (5 mol %), CH_2Cl_2, reflux, 24 h.



Scheme 3. Reagents and conditions: (a) $Cl_2Ru(PCy_3)_2$=CHPh (5 mol %), CH_2Cl_2, reflux, 4 h. (b) Zn, CH_2=$CHCH_2Br$, THF,))), 45 min; (c) PCC, silica gel, CH_2Cl_2, rt, 24 h; (d) $Cl_2Ru(PCy_3)_2$=CHPh (10 mol %), CH_2Cl_2, reflux, 12 h; (e) PCC, silica gel, CH_2Cl_2, rt, 1 h.

chlorochromate (PCC) and silica gel in methylene chloride furnished 3,4,4-trisallylcarvone[†] **6** in 79% yield. Attempted RCM reaction of trisallylcarvone **6** with the first generation Grubbs' catalyst, contrary to our expectation, furnished a complex mixture. On the other hand, RCM reaction of trisallylcarveol **9** with Grubbs' first generation catalyst furnished the targeted tricyclic system **10**, albeit in low yield, whose structure was established from spectral data (Scheme 2).[†]

It was then conceived that a two stage metathesis sequence might control the reaction and improve the formation of the tricyclic compound **10**. Accordingly, a ROM-RCM strategy was explored via spiroenone **11**. Thus, RCM reaction of bisallylcarvone **7** with Grubbs' first generation catalyst furnished spiroenone[†] **11** in 99% yield. Sonochemically accelerated Barbier reaction of spiroenone **11** with zinc and allyl bromide generated *tert*-alcohol[†] **12**, in quantitative yield, which on oxidation with PCC and silica gel furnished enone **13**. Although reaction of enone **13** was found to be unsuccessful, alcohol **12** underwent a smooth ROM-RCM reaction. Thus, refluxing a 0.01 M methylene chloride solution of alcohol **12** and 10 mol % of the Grubbs' first generation catalyst for 12 h furnished the targeted tricyclic system **10** in 76% yield. Oxidation with PCC and silica gel transformed alcohol **10** into enone[†] **14** in 78% yield, whose structure was established from spectral data (Scheme 3).

In summary, we have developed an efficient enantiospecific methodology for the synthesis of the tricyclic ring system present in the elisabethin diterpenes (which is also present in colombiasins, cumbiasins and elisapterosins), starting from the readily and abundantly available monoterpene (*R*)-carvone. A ROM-RCM sequence was employed for the simultaneous generation of the B- and C-rings. Currently, we are investigating the extension of the methodology for the total synthesis of the elisabethin natural products and their analogues for evaluating their biological potential.

[†] Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^{1}H and ^{13}C NMR and HRMS) consistent with their structures. Selected spectral data for (5*R*)-3,4,4-trisallyl-5-isopropenyl-2-methylcyclohex-2-enone **6**: $[\alpha]_D^{26}$ +91.2 (*c* 2.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1668, 1635, 1606, 912; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4) δ 5.88–5.57 (3H, m), 5.20–5.00 (6H, m), 4.93 (1H, br s), 4.85 (1H, br s), 3.20–3.00 (2H, m), 2.79 (1H, dd, *J* 9.0 and 6.0 Hz), 2.65–2.30 (6H, m), 1.85 (3H, s), 1.74 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 197.6 (C), 157.3 (C), 145.1 (C), 135.3 (C), 135.0 (CH), 134.6 (CH), 134.3 (CH), 118.4 (CH_2), 117.8 (CH_2), 117.5 (CH_2), 115.9 (CH_2), 47.2 (CH), 46.6 (C), 42.5 (CH_2), 39.7 (CH_2), 39.2 (CH_2), 35.7 (CH_2), 23.2 (CH_3), 12.1 (CH_3); HRMS: *m*/*z* calcd for $C_{19}H_{26}ONa$ (M+Na): 293.1881; found, 293.1873. (10*R*)-10-Isopropenyl-7-methylspiro[4.5]dec-2,7-dien-6-one **11**: $[\alpha]_D^{25}$ −179.2 (*c* 1.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1670, 895; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.52 (1H, br s), 5.60 and 5.49 (2H, 2 × dt, *J* 6.0 and 2.1 Hz), 4.76 (1H, s), 4.62 (1H, s), 2.90–2.25 (7H, m), 1.79 (3H, s), 1.64 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 200.9 (C), 146.4 (C), 140.8 (CH), 134.0 (C), 129.4 (CH), 127.0 (CH), 114.0 (CH_2), 54.5 (C), 51.8 (CH), 41.8 (CH_2), 37.8 (CH_2), 29.0 (CH_2), 22.0 (CH_3), 16.9 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{18}ONa$ (M+Na): 225.1255; found, 225.1257. (6*S*,10*R*)-6-Allyl-10-isopropenyl-7-methylspiro[4.5]deca-2,7-dien-6-ol **12**: $[\alpha]_D^{24}$ +2.96 (*c* 2.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3573, 1633, 893; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.93 (1H, ddt, *J* 16.8, 9.0 and 7.2 Hz), 5.68–5.60 (1H, m), 5.60–5.50 (1H, m), 5.34 (1H, br s), 5.17–5.10 (2H, m), 4.72 (1H, s), 4.70 (1H, s), 2.77 (1H, dd, *J* 11.1 and 6.6 Hz), 2.60–2.20 (8H, m), 2.05–1.94 (1H, m), 1.71 (3H, s), 1.69 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 147.2 (C), 139.8 (C), 135.7 (CH), 130.9 (CH), 129.9 (CH), 121.9 (CH), 117.9 (CH_2), 114.3 (CH_2), 78.0 (C), 52.6 (C), 47.3 (CH), 44.6 (CH_2), 37.9 (CH_2), 36.5 (CH_2), 28.6 (CH_2), 20.6 (CH_3), 20.0 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{24}ONa$ (M+Na): 267.1725; found, 267.1721. (1*R*,5*S*,9*S*)-4,8-Dimethyltricyclo[7.4.0.0^{1,5}]trideca-3,7,11-trien-9-ol **10**: $[\alpha]_D^{24}$ −124.0 (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3490, 1660, 889; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.65 (2H, br s), 5.45 (1H, m), 5.18 (1H, s), 2.55–1.78 (10H, m), 1.77 (3H, s), 1.64 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 143.4 (C), 143.1 (C), 125.8 (CH), 124.4 (CH), 122.9 (CH), 121.4 (CH), 74.7 (C), 51.1 (C), 50.1 (CH), 44.7 (CH_2), 37.0 (CH_2), 35.9 (CH_2), 26.4 (CH_2), 19.0 (CH_3), 15.5 (CH_3); HRMS: *m*/*z* calcd For $C_{15}H_{20}ONa$ (M+Na): 239.1412; found, 239.1404. (1*R*,5*S*)-4,8-Dimethyltricyclo[7.4.0.0^{1,5}]trideca-3,8,11-trien-7-one **14**: $[\alpha]_D^{26}$ −168.3 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1670, 1622; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.90–5.60 (2H, m, H-11 and 12), 5.21 (1H, br s, H-3), 3.11 and 2.91 (2H, 2 × d, *J* 21 Hz), 2.56–2.16 (7H, m), 1.75 (3H, s) and 1.68 (3H, s) [2 × olefinic-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 197.8 (C), 154.5 (C), 141.4 (C), 129.2 (C), 126.0 (CH), 124.7 (CH), 122.1 (CH), 51.8 (CH), 46.7 (C), 43.1 (CH_2), 39.1 (CH_2), 38.0 (CH_2), 30.0 (CH_2), 14.9 (CH_3), 11.4 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{18}ONa$ (M+Na): 237.1255; found, 237.1250.

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