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Rapid assembly of the functionalized tricyclic core of umbellactal through domino metathesis involving ROM-RCM of a norbornene derivative

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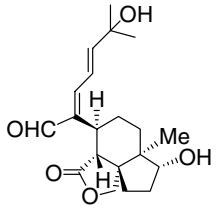
Abstract

A novel approach to the construction of the functionalized core structure of the anticancer diterpene umbellactal is described using a domino metathesis protocol involving ROM-RCM of an appropriately constructed norbornene derivative.

Keywords: Anti-tumour compounds; Metathesis; Spiro lactones; Terpenes

Umbellactal **1** is a novel diterpenoid with an unprecedented tricyclic ring system. It was isolated[1] from the soft coral *Xenia umbellata* Lamarck. It exhibits cytotoxicity against the P-388 cell line with an ED_{50} of 3.6 μg/ml. Due to its novel structure coupled with its interesting biological activity, we became interested in developing a route for the synthesis of **1**.



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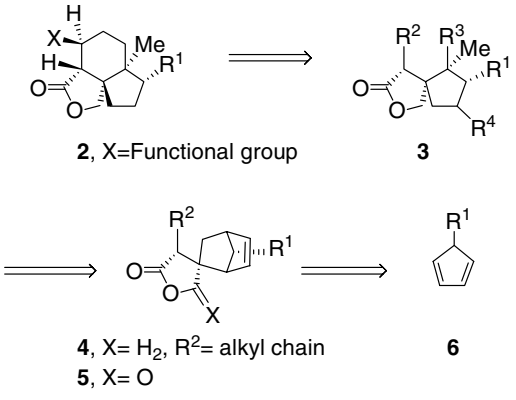
Structurally, umbellactal **1** is an angularly fused tricycle with a high degree of molecular complexity having five contiguous stereogenic centres. Synthesis of this molecule is thus a formidable task. Our projected synthetic plan (Scheme 1) requires construction of the functionalized tricyclic core **2** so as to enable introduction of the side chain at a late stage of the synthesis. It was anticipated that ring closure involving the substituents R^2 and R^3 in spirocycle **3** would lead to tricycle **2**. The substituent R^3 in spiro lactone **3** would be generated by ring opening of the norbornene derivative **4** along with substituent R^4 that would be removed at an appropriate stage. Diels–Alder cycloaddition of the substituted cyclopentadiene **6** with itaconic anhydride followed by structural manipulation of the



Scheme 1.

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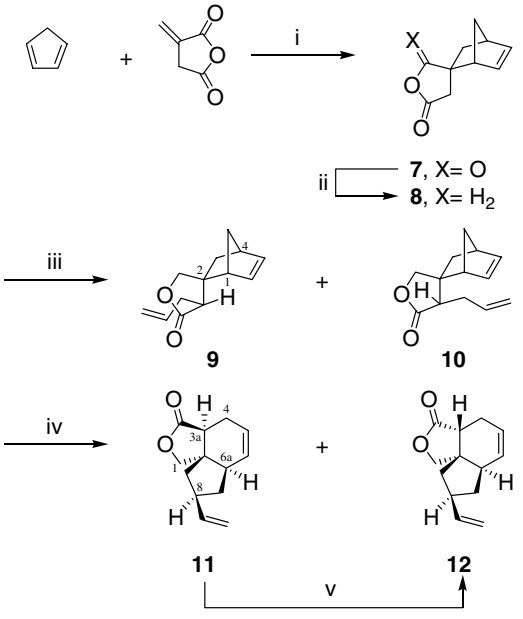
resulting adduct **5** would provide the norbornene derivative **4**. Substituent R^1 on cyclopentadiene **6** would serve as a latent hydroxyl group which would be delivered at a suitable stage.

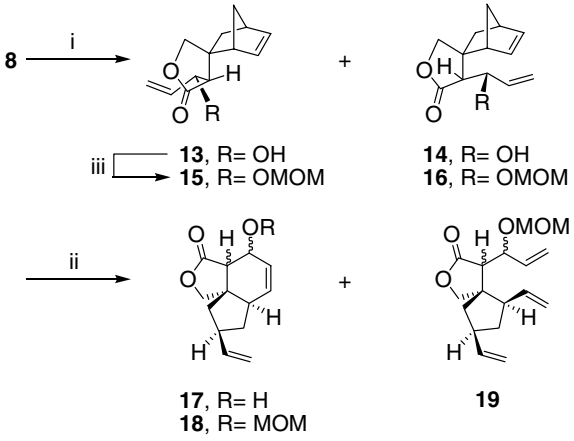
We were particularly interested in employing a process that would allow ring cleavage of norbornene with simultaneous ring closing so that a direct synthesis of the tricyclic core **2** could be achieved from norbornene **4**. Olefin metathesis[2] has no parallel in triggering such a domino process that involves ring opening followed by ring closing in an appropriately constructed norbornene system. Domino metathesis of norbornene derivatives and their oxa- and aza analogues has recently emerged as a powerful tool for the construction of fused bicyclic rings.[3] Domino metathesis of norbornene derivatives has also been very successful in the synthesis of natural products.[4] Very recently, we demonstrated[5] that a sequence of ROM-RCM of norbornenes with multiple alkene bearing chains leads to densely functionalized bridged and linearly arrayed tricycles. We envisaged that domino metathesis of norbornene **4** would provide the angularly fused tricycle of umbellactal. Herein we describe the results of the first synthetic attempt towards the synthesis of umbellactal using a domino metathesis approach.

To test the efficacy of the concept delineated in Scheme 1 we initially chose the norbornene derivative **9** (Scheme 2). Reaction of cyclopentadiene with itaconic anhydride followed by reduction of adduct **7**[6] afforded the known lactone **8**[7] in overall excellent yield. Alkylation of the lithium enolate of lactone **8** with allyl bromide produced a chromatographically inseparable mixture (ca. 4:1) of the allylated products **9** and **10** in 85% yield. Construction of a Drieding model of lactone **8** revealed that allylation would proceed preferentially from the face away from the ethylene bridge, as the other face is blocked to some extent by the ethylene bridge, to produce lactone **9** as the major product. This structural assignment of **9** and **10** was confirmed by their transformation to the tricyclic lactones **11** and **12**, respectively. Treatment of the mixture of **9** and **10** with Grubbs' catalyst I [$(PCy_3)_2Cl_2Ru$:CHPh] under an ethylene atmosphere[8] afforded a mixture (ca. 4:1) of lactones **11** and **12**[9] in 70% yield. The major product **11** having a *trans*-lactone, on treatment of the mixture of **11** and **12** with DBU in benzene under mild reflux, was transformed completely to *cis*-lactone **12** as evidenced by the disappearance of all the ^{13}C signals of the major component of the mixture with the appearance of only ^{13}C signals which were present as the minor component in the mixture. A quantum mechanical calculation[10] revealed that *cis*-lactone **12** is energetically more stable by 3.69 Kcal/mol, which led to facile isomerization of *trans*-lactone **11** to *cis*-lactone **12**. The stereocentres C-6a and C-8 remain unaltered as they are derived from C-1 and C-4 of norbornene **9**. With the establishment of the structures of lactones **11** and **12**, the structures of the allylated products from which these were derived were assigned as **9** and **10**, respectively. The tricyclic lactone **12** thus obtained represents the core structure of umbellactal.

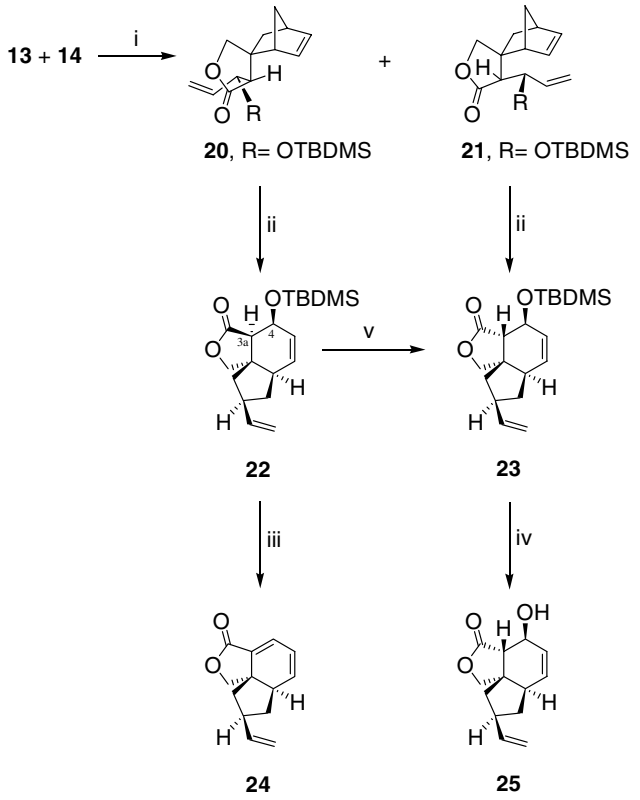
We next focused on the synthesis of a tricyclic lactone functionalized at the six-membered ring, which would allow introduction of the alkyl chain. Reaction of the enolate of **8** with acrolein afforded a mixture of adducts **13** and **14** along with the corresponding hydroxyl epimers in 83% yield (Scheme 3), the ratio of the four isomers being about 5:2:2:1. The assignment of stereochemistry at the newly generated carbon centres in **13** and **14** was based on analogy to the formation of **9** and **10** from **8**. The stereochemistry at the centres bearing the hydroxyl groups in **13** and **14** was based on their transformation to **22** and **23**, respectively (Scheme 4). Metathesis of this mixture of adducts



Scheme 2. Reagents and conditions: (i) $AlCl_3$, THF, 0 °C, 80%; (ii) $NaBH_4$, DMF, 0 °C, 70%; (iii) LDA, allyl bromide, THF, −78 °C, 85%; (iv) Grubbs I (5 mol %), DCM, C_2H_4, rt, 17 h, 70%; (v) DBU, C_6H_6, reflux, 2 h, 82%.



Scheme 3. Reagents and conditions: (i) LDA, acrolein, THF, −78 °C, 83%; (ii) Grubbs I (5 mol %), DCM, C_2H_4, rt, 23 h, 20% (for **17**), 50% (for **18**); (iii) $CH_2(OMe)_2$, $BF_3{\cdot}OEt_2$, DCM, 0 °C, 75%.



Scheme 4. Reagents and conditions: (i) TBDMSCl, DMAP, Im, Et_3N, DCM, rt, 50% (for **20**), 19% (for **21**); (ii) Grubbs I (5 mol %), DCM, C_2H_4, rt, 12 h, 72% (for **22**), 70% (for **23**); (iii) TBAF, THF, rt, 12 h, 85%; (iv) TBAF, THF, rt, 6 h, 75%, (v) DBU, C_6H_6, Δ, 1 h, 43% (**23**) and 35% (**24**).

with Grubbs' catalyst I produced a mixture of the tricycles **17**[11] in poor yield (20%) along with 50% of the unreacted norbornene derivatives.

RCM of dienes bearing free hydroxyl groups with Grubbs' I catalyst have occasionally been reported[12] to proceed with low yields possibly due to the decomposition of the active ruthenium-methylene catalyst generated after the first catalytic cycle. To investigate whether protecting groups have any influence on the efficiency of metathesis in the present case, the hydroxyl group in the above mixture of adducts **13** and **14** was protected with $CH_2(OMe)_2$ to afford the corresponding MOM protected ethers **15** and **16** along with the other two epimers at the MOM bearing stereocentres. Metathesis of the MOM protected derivatives gave tricycles **18**[11] in significantly improved yield (50%). However, a substantial amount of the ring-opened product **19** (25%) remained uncyclized under the above reaction conditions.

To enhance further the efficiency of the metathesis, the hydroxy group in the above mixture of aldol adducts was protected as the corresponding silyl ether. Column chromatography of the silylated mixture afforded the pure silyl ethers **20** and **21** in 50% and 19% yields, respectively. Metathesis of silyl ether **20** under the above conditions afforded, after chromatography, the tricyclic compound **22** in 72% yield.[9] Similarly metathesis of silyl ether **21** provided tricycle **23** in 70% yield. The stereochemical assignment of *trans*-lactone **22** (except the C4 centre) is based on analogy to the formation of **11** from **9**. To determine the stereochemistry of the C-4 substituent, lactone **22** was subjected to desilylation. The product isolated in 85% yield was found to be exclusively diene **24** presumably arising from facile dehydration of the in situ generated corresponding hydroxyl group. This indicated that C-3a H and the C-4 silyloxy group in **22** were *anti* to each other. In contrast, desilylation of **23** produced exclusively the hydroxy compound **25** (75%), which failed to undergo dehydration under a variety of conditions, indicating that C-3a H and C-4 OH in **25** were *syn* to each other. This also confirmed the stereochemical assignment of lactone **23**. The stereochemical assignment of **22** was further confirmed when the latter was found to isomerize to *cis*-lactone **23** (43%) on treatment with DBU in benzene under reflux. During isomerization of **22**, diene **24** was also isolated in ca. 35% yield. The IR absorption of the lactone carbonyl at an unusually higher frequency (ν_{max} 1787 cm^{-1}) in **22** than that (ν_{max} 1762 cm^{-1}) *m*/*z* for **23** also indicated the presence of a highly strained *trans*-lactone ring in **22**. Silyl ether **23** represents the highly functionalized tricyclic skeleton present in umbellactal.

In conclusion we have developed a concise stereoselective route for the synthesis of the functionalized tricycle present in umbellactal based on domino metathesis of an appropriately constructed norbornene derivative. Further investigation on the total synthesis of umbellactal based on this concept is underway.

Acknowledgements

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8. Representative experimental procedure for metathesis: Grubbs' 1st generation catalyst (18 mg, 5 mol %) was dissolved in CH_2Cl_2 (4 ml) and was added via syringe to a solution of a mixture of lactones **9** and **10** (90 mg, 0.44 mmol) in degassed CH_2Cl_2 (50 ml). This solution was then purged with ethylene and stirred at room temperature for 17 h under an ethylene atmosphere. The solvent was then removed by rotary evaporation and the residue was purified by flash chromatography on SiO_2 with petroleum ether/diethyl ether (9:1) to give an inseparable mixture of **11** and **12** as a colourless oil (63 mg, 70%).
9. All new compounds were characterized on the basis of IR, ^1H, ^{13}C NMR and HRMS data. Spectral data for selected compounds: Compound **11**: ^{13}C NMR (75 MHz, $CDCl_3$): δ (from the mixture of **11** and **12**) 20.5 (CH_2), 33.5 (CH_2), 40.5 (CH), 41.8 (CH_2), 42.1 (CH), 43.2 (CH), 50.8 (C), 77.3 (OCH_2), 113.4 (=CH_2), 123.1 (=CH), 133.5 (=CH), 142.5 (=CH), 176.4 (CO); HRMS *m/z* 227.1045 [$(M+Na)^+$; calcd for $C_{13}H_{16}O_2Na$: 227.1048]. Compound **12**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.08–1.22 (2H, m, CH_2), 1.55–1.63 (1H, m, CH_2), 1.83 (1H, dd, $J = 5.8$, 6.0 Hz, CH), 2.25–2.29 (1H, m, CH_2), 2.25–2.29 (1H, m, CH), 2.38 (1H, br s, CH), 2.43–2.51 (2H, m, CH_2), 3.97 (1H, d, $J = 8.5$ Hz, OCH_2), 4.10 (1H, d, $J = 8.5$ Hz, OCH_2), 4.90 (1H, d, $J = 10.2$ Hz, =CH_2), 4.98 (1H, d, $J = 17.1$ Hz, =CH_2), 5.58–5.62 (1H, m, =CH), 5.62–5.67 (1H, m, =CH), 5.69–5.75 (1H, m, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): 20.9 (CH_2), 40.2 (CH_2), 40.6 (CH), 41.7 (CH_2), 42.1 (CH), 42.2 (CH), 47.9 (C), 79.1 (OCH_2), 114.0 (=CH_2), 121.9 (=CH), 131.4 (=CH), 140.9 (=CH), 178.5 (CO); HRMS *m/z* 227.1047 [$(M+Na)^+$; calcd for $C_{13}H_{16}O_2Na$: 227.1048]. Compound **20**: IR (neat) 1778, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ −0.03 (3H, s, CH_3), 0.00 (3H, s, CH_3), 0.86 (9H, s, $3 \times CH_3$), 1.27 (1H, d, $J = 9.0$ Hz, CH_2), 1.34 (1H, dd, $J = 3.4$, 13.0 Hz, CH_2), 1.49 (1H, d, $J = 8.4$ Hz, CH_2), 2.17 (1H, dd, $J = 2.7$, 11.5 Hz, CH_2) 2.20 (1H, s, CHCO), 2.64 (1H, s, CH), 2.76 (1H, s, CH), 4.05 (1H, d, $J = 8.4$ Hz, OCH_2), 4.33 (1H, d, $J = 8.4$ Hz, OCH_2), 4.69 (1H, d, $J = 2.1$ Hz, CHOSi), 5.07 (1H, d, $J = 10.5$ Hz, =CH_2), 5.14 (1H, d, $J = 17.4$ Hz, =CH_2), 5.64–5.75 (1H, m, =CH), 5.96–5.99 (1H, m, =CH),6.24–6.27 (1H, m, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.0 (CH_3), −4.8 (CH_3), 17.9 (C), 25.86 (CH_3), 25.90 (CH_3), 25.93 (CH_3), 34.6 (CH_2), 41.9 (CH), 47.5 (CH_2), 49.3 (C), 50.9 (CH), 54.3 (CH), 74.8 (CHOSi), 79.5 (OCH_2), 115.4 (=CH_2), 133.7 (=CH), 139.9 (=CH), 140.0 (=CH), 180.0 (CO); HRMS *m/z* 357.1863 [$(M+Na)^+$; calcd for $C_{19}H_{30}O_3SiNa$: 357.1862]. Compound **21**: IR (neat) 1776, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.03 (3H, s, CH_3), 0.05 (3H, s, CH_3), 0.91 (9H, s, $3 \times CH_3$), 1.13 (1H, d, $J = 12.1$ Hz, CH_2), 1.42 (1H, d, $J = 8.8$ Hz, CH_2), 1.50 (1H, d, $J = 8.34$ Hz, CH_2), 1.90 (1H, dd, $J = 3.8$, 11.7 Hz, CH_2), 2.13 (1H, d, $J = 2.3$ Hz, CHCO), 2.85 (1H, s, CH), 2.95 (1H, s, CH), 4.01 (1H, d, $J = 7.7$ Hz, OCH_2), 4.45 (1H, d, $J = 7.7$ Hz, OCH_2), 4.57 (1H, d, $J = 4.7$ Hz, CHOSi), 5.22 (1H, d, $J = 10.2$ Hz, =CH_2), 5.34 (1H, d, $J = 17.3$ Hz, =CH_2), 5.86–5.97 (1H, m, =CH), 6.15–6.18 (1H, m, =CH), 6.26–6.29 (1H, m, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9 (CH_3), −4.4 (CH_3), 18.2 (C), 26.0 ($3 \times CH_3$), 41.6 (CH), 46.2 (CH_2), 47.8 ($2 \times CH_2$), 48.9 (C), 57.7 (CH), 74.8 (CHOSi), 80.2 (OCH_2), 116.4 (=CH_2), 135.4 (=CH), 139.3 (=CH), 139.9 (=CH), 178.3 (CO); HRMS *m/z* 357.1860 [$(M+Na)^+$; calcd for $C_{19}H_{30}O_3SiNa$: 357.1862]. Compound **22**: IR (neat) 1787, 1641, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.11 (3H, s, CH_3), 0.16 (3H, s, CH_3), 0.85 (9H, s, $3 \times CH_3$), 1.35–1.40 (1H, m, CH_2), 1.65 (1H, dd, $J = 6.6$, 13.1 Hz, CH_2), 2.21–2.26 (1H, m, CH_2), 2.45 (1H, t, $J = 12.3$ Hz, CH_2), 2.53–2.55 (1H, m, CH), 2.54 (1H, d, $J = 3.6$ Hz CH), 2.55–2.59 (1H, m, CH), 3.89 (1H, dd, $J = 1.9$, 8.2 Hz, OCH_2), 4.21 (1H, d, $J = 8.2$ Hz, OCH_2), 4.53 (1H, br s, CHOSi), 4.87 (1H, d, $J = 10.0$ Hz, =CH_2), 4.95 (1H, d, $J = 16.8$ Hz, =CH_2), 5.59 (1H, dd, $J = 1.9$, 9.8 Hz, =CH), 5.66–5.80 (2H, m, 2× =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.1 (CH_3), −4.4 (CH_3), 18.0 (C), 25.7 ($3 \times CH_3$), 35.9 (CH_2), 37.0 (CH_2), 42.0 (CH), 44.1 (CH), 47.2 (CHOSi), 49.7 (C), 61.4 (CH), 77.4 (OCH_2), 113.1 (=CH_2), 126.5 (=CH), 135.5 (=CH), 142.5 (=CH), 173.5 (CO); HRMS *m/z* 357.1857 [$(M+Na)^+$; calcd for $C_{19}H_{30}O_3SiNa$: 357.1862]. Compound **23**: IR (neat) 1762, 1645, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.02 (3H, s, CH_3), 0.06 (3H, s, CH_3), 0.83 (9H, s, $3 \times CH_3$), 1.15–1.24 (2H, m, CH_2), 2.09 (1H, dd, $J = 1.2$, 5.0 Hz, CH_2), 2.20–2.26 (1H, m, CH_2), 2.22 (1H, d, $J = 4.6$ Hz, CH), 2.36–2.42 (1H, m, CH), 2.45–2.49 (1H, m, CH), 4.09 (1H, d, $J = 7.7$ Hz, OCH_2), 4.17 (1H, d, $J = 7.1$ Hz, OCH_2), 4.52 (1H, t, $J = 5.0$ Hz, CHOSi), 4.96 (1H, d, $J = 10.3$ Hz, =CH_2), 5.04 (1H, d, $J = 17.1$ Hz, =CH_2), 5.70–5.75 (1H, m, =CH), 5.86 (1H, dd, $J = 1.7$, 9.9 Hz, =CH), 5.91–5.96 (1H, m, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2 (CH_3), −3.9 (CH_3), 17.9 (C), 25.7 ($3 \times CH_3$), 40.0 (CH), 40.2 (CH_2), 41.8 (CH), 46.7 (C), 48.4 (CH_2), 51.9 (CH), 63.4 (CHOSi), 80.3 (OCH_2), 144.5 (=CH_2), 126.0 (=CH), 134.3 (=CH), 140.0 (=CH), 177.7 (CO); HRMS *m/z* 357.1854 [$(M+Na)^+$; calcd for $C_{19}H_{30}O_3SiNa$: 357.1862].
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