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Benzannulation of podocarpic acid derivatives via directed *ortho* metallation and lithium-copper(I) transmetallation

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Abstract

Three podocarpic acid (**1**) derivatives have been converted into benzannulated derivatives via directed *ortho* metallation followed by lithium-copper(I) transmetallation, alkylation and cyclization.

Key words: Podocarpic acid; Lithium; Copper; Benzannulation

1. Introduction

We have reported the formation of cyclopentaannulated derivatives from podocarpic acid (**1**) via a chromium carbene complex [1], via tetracarbonylmanganese complexes [2–4], and via (η^6-arene)tricarbonylchromium(0) complexes [5,6]. Recently, we reported the ring expansion of two cyclopentaannulated derivatives into benzannulated derivatives in moderate yield by cleavage of the new ring D with ozone/oxygen followed by aldol cyclization [7]. More recently we have reported the synthesis of a highly substituted octahydrochrysene via a phthalide derivative of podocarpic acid [8]. In the present work we report the formation of such benzannulated derivatives through lithiation directed [9,10] *ortho* to an aryl tertiary amide [11] followed by Li–Cu^{I} transmetallation. The tetracyclic products have potential for synthesis of aromatic D-homo steroidal analogues, and also as precursors in the synthesis of oxygenated hydrochrysene-derived antifeedants such as Nic-*1* (**16**) [12–17]. A number of naturally occurring alkylated (5,6,6a,7,8,9,10,10a)-octahydrochrysenes (rings C and D aromatic) have been reported by Tan and Heit [18].

2. Results and discussion

Earlier we reported *ortho* metallation-quenching studies pertinent to the goal of benzannulation across C13 and C14 of the tertiary amides **2** and **3** [19]. In order to enhance the kinetic basicity of the deprotonating reagent, a LICKOR base [20] was used in conjunction with hexamethylphosphoric triamide (HMPA) to promote aryllithium formation prior to quenching with chlorotrimethylsilane. Although the improved yield (46%) in trapping the bulky TMS group was encouraging, it was thought that iodomethane, being a small alkylating agent, might give an even greater yield. In the event, treatment of the tertiary amide **3** with t-BuLi/t-BuOK (both 2.2 molar equivalents) at −100°C, followed by iodomethane/HMPA gave the 14-methyl diterpenoid **4** (77%), together with the ketone **5** (15%). In the absence of HMPA, **4** was formed in 71% yield, together with **5** (15%). When the reaction was carried out at −78°C, and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) used instead of HMPA, **4** was formed in 66% yield, along with **5** (11%). When this procedure was carried out at −100°C, but with only 1.5 molar equivalents of t-BuLi/t-BuOK, the yield of **4** decreased to 25%. Transmetallation from lithium to copper(I) prior to quenching with iodomethane returned only starting material, while BuLi/t-BuOK at −100°C gave **4** (21%), and the pentanone **6** (46%).

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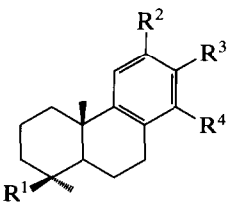
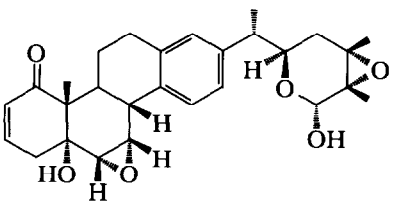
Sibi *et al.* [21] found that treatment of *N,N*-diethylbenzamide with s-BuLi/ TMEDA/ tetrahydrofuran (THF)/ − 78°C (inverse addition technique) [22], followed by the addition of excess allyl bromide, returned only starting material, or afforded polymeric products. However, [illegible] at −78°C, and the resulting mixture warmed to room temperature before being cooled to −78°C, and quenched with allyl bromide, the desired *o*-allyl benzamide was obtained. Several substituted benzamides (including several 2-methoxybenzamides) were converted similarly into the corresponding *o*-allyl products in good yield. Although annulation of benzene derivatives often requires a multi-step sequence, Sibi *et al.* [23] have reported a one-step anion-induced benzannulation which allows access to substituted 1-naphthols; several methoxy-substituted *o*-allyl benzamides were thus converted into 1-naphthols in good yields by treatment with methyllithium. It was envisaged that this methodology could be applied to suitable podocarpic acid (**1**) derivatives, resulting in the formation of octahydrochrysen-1-ols.

[illegible] via directed *ortho* metallation (DoM) [25] (s-BuLi/ TMEDA/ THF/ − 78°C), lithium–magnesium exchange ($MgBr_2 \cdot OEt_2$/ − 78°C to room temperature) and quenching with allyl bromide (−78°C to room temperature) were unsuccessful, returning mostly starting material and some of the corresponding 2-methylbutanones **18** and **7**. The failure of the s-BuLi/ TMEDA/E^+ system to generate *o*-functionalized products points towards a lack of acceptable conversion of the amide into the required *o*-lithio intermediate. t-Butyllithium has been used successfully for de-



(**1**: $R^1 = CO_2H$, $R^2 = OH$, $R^3 = H$, $R^4 = H$
2: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = CONEt_2$, $R^4 = H$
3: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CONEt_2$, $R^4 = H$
4: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CONEt_2$, $R^4 = Me$
5: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = COCMe_3$, $R^4 = H$
6: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CO(CH_2)_3Me$, $R^4 = H$
7: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = COCH(Me)Et$, $R^4 = H$
8: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CONEt_2$, $R^4 = CH_2CHCH_2$
9: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = CONEt_2$, $R^4 = CH_2CHCH_2$
10: $R^1 = CO_2Me$, $R^2 = OMe$, $R^3 = COCMe_3$, $R^4 = H$
11: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CONMe_2$, $R^4 = H$
12: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = Br$, $R^4 = H$
13: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CONMe_2$, $R^4 = CH_2CHCH_2$
14: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CON(Me)(CH_2)_2CHCH_2$, $R^4 = H$
15: $R^1 = CH_2OMe$, $R^2 = OMe$, $R^3 = CONHMe$, $R^4 = H$)



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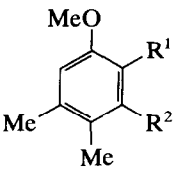
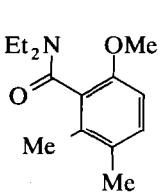


(**17**: $R^1 = CONEt_2$, $R^2 = H$
18: $R^1 = COCH(Me)Et$, $R^2 = H$
19: $R^1 = CONEt_2$, $R^2 = CH_2CHCH_2$
20: $R^1 = COCMe_3$, $R^2 = H$
21: $R^1 = CONMe_2$, $R^2 = H$
22: $R^1 = CONMe_2$, $R^2 = CH_2CHCH_2$
23: $R^1 = CON(Me)(CH_2)_2CHCH_2$, $R^2 = H$
24: $R^1 = CONHMe$, $R^2 = H$
25: $R^1 = CO(CH_2)_3Me$, $R^2 = H$)



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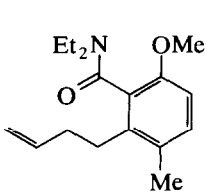

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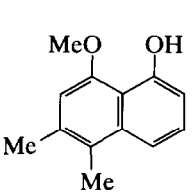

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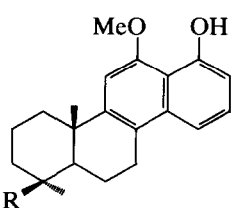
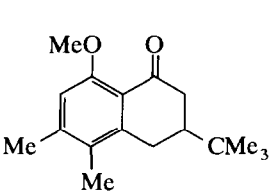


(**29**: R = CH_2OMe
30: R = CO_2Me)



(31)

protonation of a related system although extensive experimentation was necessary to define the specific conditions required for each substrate. The resulting *ortho*-lithiated derivative was then trapped with iodomethane [26].

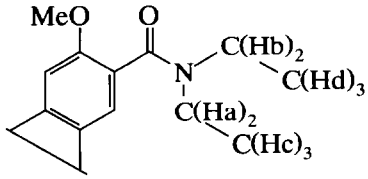
Allylic electrophiles can be coupled with α-lithio enol carbamates in the presence of copper(I) salts to give S_N2' products [27]. This successful sequence suggested that Li–Cu^I transmetallation [28,29] might allow allylation in DoM reactions of *N,N*-diethylamides. After exhaustive experimentation, it was found that lithiation of **3** (t-BuLi/TMEDA (both 2.2 molar equivalents)/THF/ −78°C/30 min), and then transmetallation with Cu^I ($CuBr.SMe_2$ (2.2 molar equivalents)/ −78°C/40 min), followed by the addition of excess allyl bromide gave the desired 14-allyl diterpenoid **8** (87%). Under identical conditions, the 19-methoxycarbonyl analogue **2** gave the 14-allyl diterpenoid **9** (92%). The appearance of two signals (ratio 1:0.9) for some protons and carbons in the ^1H and the ^{13}C NMR spectra indicated the existence of two distinct conformers. The steric bulk of the allyl substituent possibly restricts rotation about the C13–CO bond causing the conformers to have the amide C=O group above and below the plane of the arene ring respectively. Further, separate signals due to $(H_c)_3$, $(H_d)_3$, $(H_a)_2$, $(H_b)_2$, $C(H_d)_3$, $C(H_c)_3$, $C(H_b)_2$, and $C(H_a)_2$ (Scheme 1) were observed in both the ^1H and ^{13}C NMR spectra because of the existence of two amide rotamers [19].

The 2,2-dimethylpropanones **5** (9%) and **10** (5%) were each produced from the appropriate reaction.

o-Allylation of the monocycle **17**, used as a model compound for the diterpenoids **2** and **3**, via the Li–Cu^I transmetallation methodology gave the *N,N*-diethylbenzamide **19** (95%). A small amount of the ketone **20** (3%) was also formed. The benzamide **17** was sometimes contaminated with various amounts of the inseparable regioisomeric benzamide **26**. Consequently, the butenyl derivative **27** was also formed via *ortho* benzylic deprotonation.

Benzannulation of the monocyclic *o*-allyl benzamide **19** which was considered a suitable model for the 14-allyl diterpenoids **8** and **9**, was achieved in high yield using methyllithium in ether or THF, giving the naphthol **28** (97% and 96%).

Experimentation revealed that for benzannulation



Scheme 1.

of the diterpenoid **8**, the best results were achieved when a solution of the substrate in ether was treated with methyllithium (2.2 molar equivalents) at 0°C and the cooling bath was removed after 5 min; the chrysenol **29** was then obtained in 98% yield. When the cooling bath (−78°C or 0°C) was not removed after 5 min, either a low yield resulted, or there was no cyclization at all. When the above procedure was carried out using t-BuLi (1.2 molar equivalents), the yield of **29** decreased to 55%.

Unfortunately, benzannulation of the 19-methoxycarbonyl analogue **9** could not be achieved in high yield. The best yield of the chrysen-1-ol derivative **30** (29%) was obtained by treating a solution of **9** in ether with t-BuLi (1.1 molar equivalents) at room temperature for 12 h. When this reaction was carried out in THF (−78°C, 5 min; then room temperature, 2 h), the yield of **30** was only 11%; increasing the reaction time at room temperature to 12 h gave **30** in 19% yield. The use of methyllithium with ether as solvent (−78°C or room temperature) afforded a complicated mixture. Addition of trimethylsilyl trifluoromethanesulfonate to an attempted methyllithium-mediated benzannulation (with the aim of trapping a cyclized alkoxide and promoting the overall conversion) returned mostly starting material.

In contrast to diethyl amides, simple *ortho*-lithiated dimethylbenzamides cannot usually be generated by deprotonation. For example, it has been shown that *N,N*-dimethylbenzamides undergo nucleophilic attack by BuLi to give aryl ketones. They are, however, accessible at lower temperatures by metal-halogen exchange [30], or with the assistance of cooperative (*meta*-OR directed metallation groups (DMG's)) or steric hindrance (*ortho*-OR DMG's) effects. However, a report describes a modification of the general transmetallation procedure utilized for tertiary amides where an *o*-allyl *N,N*-dimethylbenzamide was obtained in 77% yield [21].

As a model substrate for the diterpenoid **11**, the *N,N*-dimethylbenzamide **21** (85%) was prepared. Treatment of **21** with t-BuLi at −100°C (5 min), followed by transmetallation (Li–Cu^I) and quenching with allyl bromide gave four products, *viz.* the desired *o*-allyl derivative **22** (30%), the *N*-butenyl derivative **23** (17%), the secondary amide **24** (15%), and the ketone **20** (18%). When the reaction was carried out at −78°C, the amides **22** (28%) and **23** (16%) were recovered, together with a relatively higher yield of the ketone **20** (31%). Attempted allylation of the amide **21** via deprotonation using a LICKOR-reagent (BuLi/t-BuOK) at −78°C, followed by transmetallation (Li–Cu^I) and quenching with allyl bromide gave a complicated mixture, from which only the ketone **25** (29%) was recov-

ered. Methyllithium-mediated benzannulation of **22** gave the 1-naphthol **28** in 63% yield. The use of t-BuLi afforded **28** in the same yield, as well as the 1-dihydronaphthalenone **31** (23%). Computational analysis was used to model the stereochemistry of the non-aromatic ring in **31**; the t-butyl group was seen to be equatorial, as expected. The ^{1}H NMR signals corresponding to H2eq (δ 3.00, ddd, J 16.4, 4.0, 2.4 Hz) and H4eq (2.67, ddd, J 15.3, 3.3, 2.5 Hz) exhibited W-type ^4J coupling between them (torsional angle 3°).

The diterpenoid *N,N*-dimethylamide **11** was formed (89%) by treating the 13-bromo precursor **12** [19] with t-BuLi followed by *N,N*-dimethylcarbamoyl chloride. The justification for attempting a D*o*M sequence using the *N,N*-dimethylamide **11** was a report [23] which claimed a significant increase in the yield of the benzannulated product from an *N,N*-dimethylbenzamide relative to that obtained from the diethyl homologue. However, treatment of **11** with t-BuLi (2.2 molar equivalents) at −78°C (5 min), followed by transmetallation (Li–Cu^I) and quenching with allyl bromide gave four products: the desired 14-allyl derivative **13** (23%), existing not only as two amide rotamers but also as a mixture (1 : 1) of two conformers as shown by the pairs of signals due to some protons and carbons in the ^{1}H and ^{13}C NMR spectra; the *N*-butenyl derivative **14** (10%); the secondary amide **15** (9%); and the propanone **5** (17%). Methyllithium-mediated benzannulation of **13** gave the chrysen-1-ol **29** in 68% yield.

The establishment of experimental conditions for the benzannulation of podocarpic acid derivatives via the C13 tertiary amides opens the way for further elaboration of the ring C/D aromatic hydrochrysene products.

3. Experimental section

For general experimental details see ref. 1. High field ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ on a Bruker AM400 or Bruker AC200 instrument. All air-sensitive reactions were carried out in a flame-dried nitrogen-flushed multi-necked flask under a nitrogen atmosphere. Air sensitive reagents were added by means of a syringe or a side-arm solids addition tube.

3.1. Allylation of N,N-diethyl-(2-methoxy-4,5-dimethyl) benzamide (17)

A solution of the benzamide **17** (0.93 g, 3.95 mmol) in THF (6 ml) was cooled to −78°C. TMEDA (1.31 ml, 8.68 mmol) was added and then t-butyllithium (6.89 ml, 1.26 mol l^{-1} in pentane, 8.68 mmol). The deep red solution was stirred for 15 min at −78°C and $CuBr.SMe_2$ (0.18 g, 8.68 mmol) then added. The mixture was stirred for a further 15 min and allyl bromide (1.37 ml, 15.8 mmol) was added producing again a deep red colour. The mixture was allowed to warm to room temperature overnight, during which the colour changed from red to brown to green. A few drops of EtOH were added and all solvents were removed, leaving a green residue. This was extracted with ether and the extracts were washed with saturated aq. NH_4Cl, water and brine, and dried ($MgSO_4$); solvents were removed to leave an oil, which was subjected to flash chromatography (hexanes/ethyl acetate, 1:1 as eluant) to give (i) 1′-(2′-methoxy-4′,5′-dimethylphenyl)-2,2-dimethylpropanone (**20**) (29 mg, 3%) as a white solid, m.p. 112–113°C (hexanes) (Found: C, 76.3; H, 9.2. $C_{14}H_{20}O_2$ calcd.: C, 76.4; H, 9.2%). ν_{max} (KBr disc) 1688 (CO), 1613, 1503, 1466, (C=C), 1302, 1213 cm^{-1}, δ_H 1.21, s, C(CH$_3$)$_3$; 2.18, s, 5′-CH$_3$; 2.26, s, 4′-CH$_3$; 3.76, s, ArOCH$_3$; 6.69, s, H3′; 6.78, s, H6′. δ_C 18.7, 5′-CH$_3$; 20.1, 4′-CH$_3$; 26.8, C(*C*H$_3$)$_3$; 44.8, *C*(CH$_3$)$_3$; 112.5, C3′; 127.4, C6′; 128.0, C5′; 128.6, C1′; 138.2, C4′; 153.3, C2′; 214.1, CO. m/z 220 (4, M$^+$), 205 (1, M − Me), 163 (100, M − C(CH$_3$)$_3$), 120 (4), 105 (5); and (ii) *N,N*-diethyl-(2-methoxy-4,5-dimethyl-6-prop-2′-enyl)benzamide (**19**) (1.04 g, 95%) as a pale yellow oil, b.p. 132°C/0.2 mmHg (Kugelrohr) (Found: M$^{+\bullet}$, 275.1883. $C_{17}H_{25}NO_2$ calcd.: M, 275.1885). ν_{max} 1663 (CO), 1598, 1464, 1276, 1137, 1088 cm^{-1}. δ_H 1.02, t, J 7.1 Hz, (H$_c$)$_3$; 1.23, t, J 7.1 Hz, (H$_d$)$_3$; 2.12, s, 5-CH$_3$; 2.28, s, 4-CH$_3$; 3.04, 3.14, 2 sextets, J 7.1 Hz, (H$_a$)$_2$; 3.33, m, (H$_b$)$_1$, (H1′)$_2$; 3.75, s, ArOCH$_3$; 3.81, sextet, J 7.1 Hz, (H$_b$)$_1$; 4.93, dd, J 17.1, 1.7 Hz, H3′ *trans*; 4.99, dd, J 10.2, 1.5 Hz, H3′ *cis*; 5.85, ddt, J 17.1, 10.2, 5.2 Hz, H2′; 6.61, s, H3. δ_C 12.8, C(H$_d$)$_3$; 13.5, C(H$_c$)$_3$; 14.6, 5-CH$_3$; 21.2, 4-CH$_3$; 35.0, C1′; 38.0, C(H$_b$)$_2$; 42.7, C(H$_a$)$_2$; 55.3, ArOCH$_3$; 110.7, C3; 115.3, C3′; 124.6, C1; 127.9, C5; 135.0, C6; 135.7, C2′; 137.8, C4; 152.9, C2; 168.7, CO. m/z 275 (25, M$^+$), 260 (3, M − Me), 246 (3), 203 (100, M − NEt$_2$), 187 (8), 175 (25, M − OCNEt$_2$).

When **17** was contaminated with *N,N*-diethyl-(2-methoxy-5,6-dimethyl)benzamide (**26**), *N,N*-diethyl-(2-methoxy-5-methyl-6-but-3′-enyl)benzamide (**27**) was obtained as a minor product, b.p. 126°C/0.2 mmHg (Kugelrohr) (Found: M$^{+\bullet}$, 275.1890. $C_{17}H_{25}NO_2$ calcd.: M, 275.1885). ν_{max} 1633 (CO), 1588, 1479, 1433 (C=C), 1279, 1262, 1078 cm^{-1}. δ_H 1.04, t, J 7.1 Hz, (H$_c$)$_3$; 1.24, t, J 7.1 Hz, (H$_d$)$_3$; 2.15, 2.38, 2m, H2′; 2.26, s, 5-CH$_3$; 2.48, td, J 12.0, 5.1 Hz, (H1′)$_1$; 2.67, td, J 12.0, 5.0 Hz, (H1′)$_1$; 3.07, 3.14, 2 sextets, J 7.1 Hz, (H$_a$)$_2$; 3.30, 3.91, 2 sextets, J 7.1 Hz, (H$_b$)$_2$; 3.76, s, ArOCH$_3$; 4.97, ddd, J 10.2, 2.0, 1.1 Hz, (H4′)$_1$; 5.05, ddd, J 17.1, 3.3, 1.6 Hz, (H4′)$_1$; 5.88, ddt, J 17.1, 10.2, 6.5, Hz, H3′; 6.65, d, J 8.4 Hz, H3′; 6.65, d, J 8.4 Hz, H3; 7.08, d, J 8.4 Hz, H4. δ_C 12.6, C(H$_d$)$_3$; 13.5, C(H$_c$)$_3$; 18.6, 5-CH$_3$;

30.2, C1'; 33.7, C2'; 38.2 ($C(H_b)_2$; 42.7, $C(H_a)_2$; 55.3, $ArOCH_3$; 108.4, C3; 114.4 C4'; 126.5, C1; 128.7, C5; 130.8, C4; 137.6, C6; 138.3, C3'; 153.6, C2; 168.4, CO. *m/z* 275 (25, M^+), 260 (2, M − Me), 244 (7), 220 (16), 203 (100, M − NEt_2), 187 (15), 175 (72, M − $OCNEt_2$).

3.2. Benzannulation of N,N-diethyl-(2-methoxy-4,5-dimethyl-6-prop-2'-enyl)benzamide (19)

3.2.1. In diethyl ether

A solution of **19** (15 mg, 0.06 mmol) in diethyl ether (2 ml) was cooled to −78°C and methyllithium (0.14 ml, 0.84 mol l^{-1} in ether, 0.12 mmol) was added dropwise. After 5 min the cooling bath was removed, and at room temperature the system turned orange-red. Stirring at room temperature was continued overnight, resulting in formation of white suspension. Solvents were removed and the residue was extracted with ether. Water was added and the system acidified with aqueous HCl (2 mol l^{-1}). The organic layer was washed with water and brine and dried ($MgSO_4$) and subjected to chromatography on silica gel (Pasteur pipette; hexanes/ethyl acetate, 9:1) to give 8-methoxy-5;6-dimethyl-1-naphthol (**28**) (11 mg, 97%) as white crystals, m.p. 70–72°C (hexanes) (Found: C, 77.1; H, 7.0. $C_{13}H_{14}O_2$ calcd.: C, 77.2; H, 7.0%). ν_{max} 3324 (OH), 1614, 1508, 1422 (C=C), 1393, 1121, 744 cm^{-1}. δ_H 2.45, s, 5-CH_3; 2.47, s, 6-CH_3; 4.03, s, $ArOCH_3$; 6.62, s, H7; 6.85, dd, *J* 7.6, 1.0 Hz, H2; 7.38, t, *J* 7.6 Hz, H3; 7.44, dd, *J* 7.6, 1.0 Hz, H4; 9.49, s, OH. δ_C 14.7, 5-CH_3; 21.1, 6-CH_3; 56.0, $ArOCH_3$; 107.3, C7; 109.4, C2; 113.7, C5; 114.9, C3; 124.5, C8a; 127.5, C4; 132.9, C4a; 136.0, C6; 153.9, C1; 154.9, C8. *m/z* 202 (100, M^+), 187 (43, M − Me), 159 (24), 144 (8), 115 (8).

3.2.2. In tetrahydrofuran

Methyllithium (0.16 ml, 0.84 mol l^{-1} in ether, 0.14 mmol) was added dropwise to a stirred solution of **19** (17 mg, 0.06 mmol) in THF (2 ml) at room temperature. The resulting deep red mixture was warmed gently on a waterbath for 30 min during which the colour changed to golden-brown. The mixture was stirred at room temperature for 12 h; a few drops of methanol were then added. The solvents were removed and the residue extracted with ether. Workup and chromatography on silica gel (Pasteur pipette, hexanes/ethyl acetate, 9:1) gave **28** (12 mg, 96%).

3.3. Preparation of N,N-dimethyl-2-methoxy-4,5-dimethylbenzamide (21)

t-Butyllithium (7.44 ml, 0.75 mol l^{-1} in pentane, 5.58 mmol) was added slowly to a solution of 1-bromo-2-methoxy-4,5-dimethylbenzene (0.60 g, 2.79 mmol) in THF (5 ml) cooled to −100°C, and the solution was stirred for 3 min. Dimethylcarbamoyl chloride (0.34 ml, 3.68 mmol) was added and the mixture was allowed to warm to room temperature overnight. Methanol (3 drops) was added and all solvents were then removed. The residue was extracted with dichloromethane and workup followed by flash chromatography (hexanes/ethyl acetate, 1:1) afforded *N,N*-dimethyl-2-methoxy-4,5-dimethylbenzamide (**21**) (0.51 g, 85%) as a pale yellow gum, b.p. 50°C/0.03 mmHg (Kugelrohr) (Found: $M^{+\bullet}$, 207.1255. $C_{12}H_{17}NO_2$ calcd.: M, 207.1259). ν_{max} (KBr disc) 1640 (CO), 1614 (C=C), 1490, 1452, 1407, 1064 cm^{-1}. δ_H 2.02, s, 5-CH_3; 2.10, s, 4-CH_3; 2.70, s, $(H_a)_3$; 2.93, s, $(H_b)_3$; 3.63, s, $ArOCH_3$; 6.55, s, H3; 6.84, s, H6. δ_C 18.0, 5-CH_3; 19.5, 4-CH_3; 34.0, $C(H_b)_3$; 37.6, $C(H_a)_3$; 55.0, $ArOCH_3$; 112.0, C3; 123.0, C1; 128.0, C5; 128.3, C6; 138.1, C4; 152.8, C2; 169.0, CO. *m/z* 207 (17, M^+), 192 (1, M − Me), 176 (2), 163 (100, M − NMe_2), 148 (3, 163 − Me).

3.4. Allylation of N,N-dimethyl-2-methoxy-4,5-dimethylbenzamide (21)

3.4.1. Preparation A

A solution of **21** (80 mg, 0.39 mmol) in THF (4 ml) was cooled to −100°C. TMEDA (0.13 ml, 0.85 mmol) and t-butyllithium (0.68 ml, 1.26 mol l^{-1} in pentane, 0.85 mmol) were added and the solution was stirred for 5 min. CuBr.SMe_2 (0.18 g, 0.85 mmol) was then added. The solution was stirred for 10 min then allyl bromide (0.13 ml, 1.54 mmol) was added; the deep red mixture gradually turned brown during 1 h at −100°C. The mixture was allowed to warm to room temperature overnight and the solution was cooled to 0°C and acidified with aqueous HCl (2 mol l^{-1}). Workup followed by PLC (benzene/ethyl acetate, 7:3) gave (i) *N*-methyl-(2-methoxy-4,5-dimethyl)benzamide (**24**) (11 mg, 15%) as a white solid (Found: $M^{+\bullet}$, 193.1126. $C_{12}H_{17}NO_2$ calcd.: M, 193.1103). ν_{max} (KBr disc) 3405 (NH), 1652 (CO), 1613, 1538, 1497 (C=C), 1260 cm^{-1}. δ_H 2.23, s, 5-CH_3; 2.28, s, 4-CH_3; 2.98, s, $(H_a)_3$ *cis*; 2.99, s, $(H_b)_3$ *trans*; 3.92, s, $ArOCH_3$; 6.73, s, H3; 7.81, bs, NH; 7.96, s, H6. δ_C 18.5, 5-CH_3; 20.1, 4-CH_3; 26.4, $C(H_a)_3$, $C(H_b)_3$; 55.9, $ArOCH_3$; 112.7, C3; 118.6, C1; 129.2, C5; 132.9, C6; 141.6, C4; 155.4, C2; 166.1, CO. *m/z* 193 (20, M^+), 163 (100, M − HNMe), 148 (4, 163 − Me), 133 (10, 148 − Me), 105 (12); (ii) *N,N*-dimethyl-(2-methoxy-4,5-dimethyl-6-prop-2'-enyl)benzamide (**22**) (28 mg, 30%) as a pale yellow oil (Found: $M^{+\bullet}$, 247.1582. $C_{15}H_{21}NO_2$ calcd.: M, 247.1572). ν_{max} 1634 (CO), 1599, 1502, 1468 (C=C), 1409, 1136 cm^{-1}. δ_H 2.11, s, 5-CH_3; 2.26, s, 4-CH_3; 2.74, s, $(H_a)_3$; 3.08, s, $(H_b)_3$; 3.28, dd, *J* 15.7, 4.9 Hz, $(H1')_1$; 3.39, dd, *J* 13.9,

7.0 Hz, (H1'); 3.75, s, $ArOCH_3$; 4.90, bd, *J* 17.1 Hz, (H3'); 4.97, bd, *J* 10.0 Hz, (H3'); 5.82, ddt, *J* 17.1, 10.0, 5.2 Hz, H2'; 6.59, s, H3. δ_C 14.5, 5-CH_3; 21.2, 4-CH_3; 34.3, $C(H_b)_3$; 34.9, C1'; 38.0, $C(H_a)_3$; 55.5, $ArOCH_3$; 110.7, C3; 115.1, C3'; 124.3, C1; 127.9, C5; 135.1, C6; 135.7, C2'; 128.1, C4; 152.8, C2; 169.6, CO. *m/z* 247 (20, M^+), 232 (3, M − Me), 219 (4), 203 (100, M − NMe_2), 188 (7, 203 − Me), 175 (27), 163 (19); (iii) *N*-but-3'-enyl-*N*-methyl-(2-methoxy-5,6-dimethyl)benzamide (**23**) (16 mg, 17%) as a pale yellow oil. ν_{max} 1634 (CO), 1615, 1505, 1484, 1466 (C=C), 1268 cm^{-1}. δ_H 2.16, s, 5-CH_3; 2.22, s, 4-CH_3; 2.22, q, *J* 6.9 Hz, $(H2')_1$; 2.40, q, *J* 6.9 Hz, $(H2')_1$; 2.81, s, $(H_a)_3$; 3.06, s, $(H_b)_3$; 3.19, t, *J* 7.2 Hz, $(H1')_1$; 3.59, t, *J* 7.2 Hz, $(H1')_1$; 3.77, s, $ArOCH_3$; 4.95, bd, *J* 9.9 Hz, $(H4')_1$ *cis*; 4.96, bd, *J* 17.1 Hz, $(H4')_1$ *trans*; 5.04, dd, *J* 10.2, 0.8 Hz, $(H4')_1$ *cis*; 5.12, bd, *J* 17.1, $(H4')_1$ *trans*; 5.57, ddt, *J* 17.1, 9.8, 6.9 Hz, $(H3')_1$; 5.86, ddt, *J* 17.1, 10.2, 6.9 Hz, $(H3')_1$; 6.66, s, H3; 6.94, 6.95, 2s, H6. δ_C 18.6, $C(H_b)_3$; 20.1, $C(H_a)_3$; 31.6, 32.6, C1'; 32.4, 5-CH_3; 36.3, 4-CH_3; 46.5, 50.2, C2'; 55.5, 55.6, $ArOCH_3$; 112.4, 112.5, C3; 116.4, 116.8, C4'; 123.5, 124.0, C1; 128.5, 128.7, C5; 128.8, 128.9, C6; 134.7, 135.6, C3'; 138.4, 138.5, C4; 153.1, 153.2, C2; 169.5, 169.7, CO. *m/z* 247 (6, M^+), 232 (3, M − Me), 206 (2), 203 (7), 163 (100, M − $N(CH_3)(C_4H_7)$), 91 (6); and (iv) **20** (15 mg, 18%).

3.4.2. Preparation B

A solution of **21** (0.14 g, 0.65 mmol) in THF (6 ml) was cooled to −78°C. TMEDA (0.22 ml, 1.44 mmol) and t-butyllithium (1.14 ml, 1.26 mol l^{-1} in pentane, 1.44 mmol) were added and the mixture was stirred for 15 min. $CuBr.SMe_2$ (0.30 g, 1.44 mmol) was added in portions and the solution was stirred for a further 15 min. Allyl bromide (0.23 ml, 2.41 mmol) was then added, and the deep red solution gradually turned brown during 1 h at −78°C. The system was allowed to warm to room temperature overnight. Workup as above gave (i) **22** (45 mg, 28%); (ii) **23** (21 mg, 16%); and (iii) **20** (45 mg, 31%).

3.5. Attempted allylation of N,N-dimethyl-2-methoxy-4,5-dimethylbenzamide (22) with a LICKOR reagent

Sublimed potassium t-butoxide (96 mg, 0.86 mmol) in THF (5 ml) was cooled to −78°C. TMEDA (0.13 ml, 0.86 mmol), butyllithium (0.95 ml, 0.90 mol l^{-1} in hexanes, 0.86 mmol), and then a solution of **22** (81 mg, 0.39 mmol) in THF (1 ml) were added, and the solution was stirred for 15 min. $CuBr.SMe_2$ (0.18 g, 0.86 mmol) was then added and the mixture stirred for a further 15 min. Allyl bromide (0.19 g, 1.56 mmol) was then added and the mixture was allowed to warm to room temperature overnight. A few drops of methanol were added and solvents removed. The residue was extracted with ether and worked up to give an oil which was shown (TLC) to contain a number of components. Flash chromatography (hexane/ethyl acetate, 4:1, 1:1) gave only 1'-(2'-methoxy-4',5'-dimethylphenyl)-1-pentanone (**25**) (25 mg, 29%) as a white solid. ν_{max} 1678 (CO), 1608, 1498, 1460 (C=C), 1267 cm^{-1}. δ_H 0.81, t, *J* 7.3 Hz, $(H5)_3$; 1.15, sextet, *J* 7.3 Hz, $(H4)_2$; 1.35, p, *J* 7.3 Hz, $(H3)_2$; 2.17, s, 5'-CH_3; 2.21, t, *J* 7.3 Hz, $(H2)_2$; 2.27, s, 4'-CH_3; 3.61, s, $ArOCH_3$; 6.66, s, H3'; 7.31, s, H6'. δ_C 14.3, C5; 18.6, 5'-CH_3; 20.2, 4'-CH_3; 20.3, C4; 28.8, C3; 50.7, C2; 55.3, $ArOCH_3$; 112.9, C3'; 126.5, C1'; 128.3, C5'; 131.2, C6'; 141.5, C4'; 156.0, C2'; 204.7, CO. *m/z* 220 (8, M^+), 191 (5, M − C_2H_5), 163 (100, M − C_4H_9), 105 (9).

3.6. Benzannulation of N,N-dimethyl-(2-methoxy-4,5-dimethyl-6-prop-2'-enyl)benzamide (22)

A solution of dimethylbenzamide **22** (41 mg, 0.17 mmol) in THF (3 ml) was cooled to −78°C and methyllithium (0.44 ml, 0.84 mol l^{-1} in ether, 0.37 mmol) was added dropwise. The orange solution was stirred at −78°C for 1 h and then warmed to room temperature during 1 h. Methanol (2 drops) was added to the resulting crimson solution, and workup followed by flash chromatography (hexanes/ethyl acetate, 9:1) gave **28** (21 mg, 63%).

3.7. Cyclization of N,N-dimethyl-(2-methoxy-4,5-dimethyl-6-prop-2'-enyl)benzamide (22) with t-butyllithium

A solution of the dimethylbenzamide **22** (45 mg, 0.18 mmol) in THF (4 ml) was cooled to −78°C and t-butyllithium (0.32 ml, 1.26 mol l^{-1} in pentane, 0.40 mmol) was added dropwise. The crimson mixture was stirred at −78°C for 1 h and then warmed to room temperature during 3 h. The colour faded on the addition of 2 drops of methanol. Solvents were removed and the residue extracted with ether. Workup followed by flash chromatography (hexanes/ethyl acetate, 4:1) gave (i) **28** (23 mg, 62%), and (ii) 3-t-butyl-3,4-dihydro-8-methoxy-5,6-dimethyl-1(2*H*)-naphthalenone (**31**) (11 mg, 23%) as a clear oil (Found: $M^{+\bullet}$, 260.1768. $C_{17}H_{24}O_2$ calcd.: M, 260.1776). ν_{max} (KBr disc) 1676 (CO), 1593, 1560, 1470 (C=C), 1311, 1273 cm^{-1}. δ_H 0.97, s, $C(CH_3)_3$; 1.18, ddt, *J* 14.2, 12.2, 3.6 Hz, H3; 2.15, s, 5-CH_3; 2.29, dd, *J* 15.3, 14.2 Hz, H4ax; 2.33, s, 4-CH_3; 2.40, dd, *J* 16.4, 12.2 Hz, H2ax; 2.67, ddd, *J* 15.3, 3.3, 2.5 Hz, H4eq; 3.00, ddd, *J* 16.4, 4.0, 2.4 Hz, H2eq; 3.87, s, $ArOCH_3$; 6.67, s, H7. δ_C 14.7, 5-CH_3; 21.8, 6-CH_3; 27.0, $C(CH_3)_3$, C4; 32.5, $C(CH_3)_3$; 42.4, C2; 44.2, C3; 55.9, $ArOCH_3$; 111.5, C7; 111.8, C4a; 126.3, C8a; 143.4, C5; 144.5, C6; 157.9, C8; 199.2, CO. *m/z* 260 (100, M^+), 245 (13, M − Me), 231 (67), 217 (14), 203 (50), 189 (22), 175 (33).

3.8. Methylation of N,N-diethyl-12,19-dimethoxypodocarpa-8,11,13-triene-13-carboxamide (3)

3.8.1. Preparation A

Resublimed potassium t-butoxide (32 mg, 0.28 mmol) in THF (2 ml) was cooled to −100°C. A solution of **3** (50 mg, 0.13 mmol) in THF (0.5 ml) was added, followed by t-butyllithium (0.23 ml, 1.26 mmol l^{-1} in pentane, 0.28 mmol), and the yellow solution was stirred for 20 min. Iodomethane (41 μl, 0.65 mmol) and then HMPA (0.5 ml) in THF (0.5 ml) were added, causing the colour to fade, and the mixture was allowed to warm to room temperature overnight. Solvents were removed and the residue was extracted with ether. Flash chromatography (hexanes/ethyl acetate, 3:2) gave (i) 1-(12′,19′-dimethoxypodocarpa-8′,11′,13′-trien-13′-yl)-2,2-dimethylpropanone (**5**) (7 mg, 15%); and (ii) 13-*N*,*N*-diethyl-12,19-dimethoxy-14-methylpodocarpa-8,11,13-triene-13-carboxamide (**4**) (40 mg, 77%) as a yellow oil, b.p. 180°C/0.05 mmHg (Kugelrohr) (Found: $M^{+\bullet}$; 401.2911. $C_{25}H_{39}NO_3$ calcd.: M, 401.2930). ν_{max} 1638 (CO), 1597, 1459 (C=C), 1283, 1110 cm^{-1}. δ_H 1.02, m, H3ax; 1.03, t, *J* 7.1 Hz, $(H_c)_3$; 1.04, s, $(H18)_3$; 1.17, s, $(H20)_3$; 1.24, t, *J* 7.9 Hz, $(H_d)_3$; 1.40, dd, *J* 12.7, 1.5 Hz, H5; 1.42, m, H1ax; 1.65, m, H2ax, H2eq, H6ax; 1.87, bd, *J* 13.7 Hz, H3eq; 2.03, m, H6eq; 2.04, s, 14-CH_3; 2.26, bd, *J* 12.0 Hz, H1eq; 2.51, ddd, *J* 17.1, 11.0, 6.7 Hz, H7ax; 2.70, dd, *J* 17.1, 5.8 Hz, H7eq; 3.11, septet, *J* 7.1 Hz, $(H_a)_2$; 3.25, 3.52, 2d, *J* 9.1 Hz, $(H19)_2$; 3.335, 3.337, 2s, CH_2OCH_3; 3.44, q, *J* 7.9 Hz, $(H_b)_1$; 3.74, s, $ArOCH_3$; 3.74, m, $(H_b)_1$; 6.67, s, H11. δ_C 12.7, 12.8, $C(H_d)_3$; 13.65, 13.69, $C(H_c)_3$; 15.9, 16.0, 14-CH_3; 19.1, C2, C6; 25.45, 25.50, C20; 27.5, C18; 28.14, 28.35, C7; 35.8, C3; 37.9, C4, C10; 38.3, $C(H_b)_2$; 39.2, 39.4, C1; 42.36, 42.40, $C(H_a)_2$; 50.6, 50.7, C5; 55.3, 55.4, $ArOCH_3$; 59.3, CH_2OCH_3; 75.7, 75.9, C19; 104.6, 104.8, C11; 124.3, C8; 126.3, C14; 133.00, 133.05, C13; 150.7, 150.8, C9; 153.05, 153.10, C12; 169.11, 169.14, CO. *m/z* 401 (22, M^+), 386 (42, M − Me), 329 (100, M − NEt_2), 117 (45), 57 (52).

3.8.2. Preparation B

When the above procedure was carried out in the absence of HMPA, the products isolated were (i) **5** (7 mg, 15%), and (ii) **4** (37 mg, 71%).

3.8.3. Preparation C

When the above procedure was carried out with butyllithium in the absence of HMPA, the products isolated were (i) 1-(12′,19′-dimethoxypodocarpa-8′,11′,13′-trien-13′-yl)pentan-1-one (**6**) (22 mg, 46%); and (ii) **4** (11 mg, 21%).

3.8.4. Preparation D

When procedure A was carried out at −78°C and TMEDA (2.2 molar equivalents) was used (instead of HMPA), the products isolated were (i) **5** (11%), and (ii) **4** (66%).

3.8.5. Preparation E

When procedure D was carried out at −100°C and only 1.5 molar equivalents of t-butyllithium were used, the yield of **4** decreased to 25%.

3.8.6. Preparation F

When procedure D was carried out but with the addition of $CuBr.SMe_2$ (2.2 molar equivalents) 15 min before iodomethane was added, mainly starting material was recovered.

3.9. Allylation of N,N-diethyl-12,19-dimethoxypodocarpa-8,11,13-triene-13-carboxamide (3)

A solution of the diethylbenzamide **3** (1.40 g, 3.63 mmol) in THF (15 ml) was cooled to −78°C. TMEDA (1.20 ml, 7.98 mmol) and t-butyllithium (6.33 ml, 1.26 mol l^{-1} in pentane, 7.98 mmol) were added and the reddish-brown solution was stirred at −78°C for 30 min. $CuBr.SMe_2$ (1.64 g, 7.98 mmol) was added and the mixture was stirred for a further 40 min at −78°C. Allyl bromide (1.23 ml, 14.5 mmol) was added and the deep red mixture was allowed to warm to room temperature overnight. A few drops of methanol were added and then all solvents were removed. The residue was extracted with ether. Workup and then flash chromatography (hexanes/ethyl acetate, 3:2) gave (i) **5** (0.13 g, 9%), and (ii) *N*,*N*-diethyl (12,19-dimethoxy-14-prop-2′-enylpodocarpa-8,11,13-triene)-13-carboxamide (**8**) (1.38 g, 89%), as white crystals, m.p. 121–122°C (hexanes) (Found: C, 76.0; H, 9.8; N, 3.2. $C_{27}H_{41}NO_3$ calcd.: C, 75.8; H, 9.7; N, 3.3%) (Found: $M^{+\cdot}$, 427.3090. $C_{27}H_{41}NO_3$ calcd.: M, 427.3087). ν_{max} 1628 (CO), 1590 (C=C), 1454, 1378, 1275, 1108 cm^{-1}. δ_H 1.01, s, $(H18)_3$; 1.01, t, *J* 7.2 Hz, $(H_c)_3$; 1.07, m, H3ax; 1.14, s, $(H20)_3$; 1.19, t, *J* 7.2 Hz, $(H_d)_3$; 1.30, 1.40, 2d, *J* 12.7 Hz, H5; 1.42, td, *J* 13.1, 3.9 Hz, H1ax; 1.65, m, H2eq, H2ax, H6ax; 1.82, 1.87, 2d, H3eq; 1.97, dd, *J* 13.2, 7.4 Hz, H6eq; 2.22, 2.27, 2d, *J* 13.1 Hz, H1eq; 2.59, ddd, *J* 17.0, 11.4, 7.4 Hz, H7ax; 2.81, dd, *J* 17.0, 5.8 Hz, H7eq; 2.92–3.39, m, $(H_a)_2$, $(H_b)_1$, $(H1')_2$, $(H19)_1$; 3.30, 3.31, 2s, CH_2OCH_3; 3.49, 3.50, 2d, *J* 9.1 Hz, $(H19)_1$; 3.72, s, $ArOCH_3$; 3.78, sextet, *J* 7.2 Hz, $(H_b)_1$; 4.89, 4.97, 2dd, *J* 10.6, 1.6 Hz, H3′ *cis*; 4.92, 4.97, 2dd, *J* 17.1, 1.6 Hz, H3′ *trans*; 5.79, ddt, *J* 17.1, 10.6, 5.0 Hz, H2′; 6.68, s, H11. δ_C 12.5, $C(H_d)_3$, 13.4, $C(H_c)_3$; 19.1, C2, C6; 25.5, 25.7, C20; 27.2, C7; 27.4, 27.5, C18; 34.3, 34.4, C1′; 35.7, C3; 37.9, C1, C10; 38.3, C4; 39.2, 39.4, $C(H_b)_2$; 42.6, 42.7, $C(H_a)_2$; 50.6, 50.7, C5; 55.1, 55.2, $ArOCH_3$; 59.3, CH_2OCH_3; 75.7, 75.9,

C19; 105,3, 105,4, C11; 115.2, 115.4, C3′; 124.6, C8; 126.55, 126.62, C13; 134.5, C14; 135.6, C2′; 151.20, 151.23, C9; 153.16, 153.22, C12; 168.62, 168.68, CO. *m/z* 427 (45, M^+), 412 (19, M − Me), 396 (7), 355 (100, M − NEt_2), 315 (8), 100 (15, $^+OCNEt_2$), 72 (18, $^+NEt_2$).

3.10 Benzannulation of N,N-diethyl (12,19-dimethoxy-14-prop-2′-enylpodocarpa-8,11,13-triene)-13-carboxamide (8)

3.10.1. Preparation A

A solution of the diethylamide **8** (84 mg, 0.20 mmol) in diethyl ether (2.5 ml) was cooled to 0°C and methyllithium (0.53 ml, 0.81 mol l^{-1} in ether, 0.43 mmol) was added dropwise. The deep red solution was stirred for 5 min at 0°C before the cooling bath was removed. The colour gradually faded, and after 3 h at room temperature 2 drops of methanol were added and the solvents were removed. Workup followed by flash chromatography (hexanes/ethyl acetate, 9:1) gave [6aR-(6aα, 7β,10aβ)]-5,6,6a,7,8,9,10,10a-octahydro-12-methoxy-7-methoxymethyl-7,10a-dimethylchrysen-1-ol (**29**) (68 mg, 98%) as white crystals, m.p. 149–151°C (hexanes) (Found: C, 78.0; H, 8.6. $C_{23}H_{30}O_3$ calcd.: C, 77.9; H, 8.5%) (Found: $M^{+\bullet}$, 354.2195. $C_{23}H_{30}O_3$ calcd.: M, 354.2195) ν_{max} (KBr disc) 3364 (OH), 1614, 1578, 1516, 1435 cm^{-1} (C=C). δ_H 1.04, td, *J* 13.7, 4.1 Hz, H8ax; 1.10, s, 7-CH_3; 1.30, s, 10a-CH_3; 1.43, td, *J* 12.9, 3.7 Hz, H10ax; 1.50, dd, *J* 12.8, 1.3 Hz, H6a; 1.64, dp, *J* 14.1, 3.4 Hz, H9eq; 1.77, m, H6ax, H9ax; 1.91, bd, *J* 13.5, H8eq; 2.17, dd, *J* 13.3, 7.4 Hz, H6eq; 2.34, bd, *J* 12.5 Hz, H10eq; 2.93, ddd, *J* 17.1, 11.8, 7.5 Hz, H5ax; 3.12, dd, *J* 17.0, 6.0 Hz, H5eq; 3.30, 3.38, 2d, *J* 9.1 Hz (H7β)$_2$; 3.37, s, CH_2OCH_3; 4.04, s, $ArOCH_3$; 6.77, s, H11; 6.86, dd, *J* 6.5, 2.1 Hz, H2; 7.36, t, *J* 6.6 Hz, H4; 7.37, bd, *J* 6.6 Hz, H3; 9.48, s, OH. δ_C 19.2, C9; 19.3, C6; 24.6, 10a-CH_3; 27.6, 7-CH_3; 28.3, C5; 35.9, C8; 37.9, C7; 38.3, C10a; 39.1, C10; 51.3, C6a; 55.9, $ArOCH_3$; 59.4, CH_2OCH_3; 75.9, CH_2OCH_3; 101.5, C11; 109.9, C2; 113.2, C4b; 114.3, C3; 123.1, C12a; 127.6, C4; 135.4, C4a; 146.5, C10b; 154.6, C1; 154.8, C12. *m/z* 354 (100, M^+), 307 (20, M − Me − MeOH), 239 (12), 227 (12), 213 (15), 187 (10).

3.10.2. Preparation B

The above procedure was followed using **8** (78 mg, 0.18 mmol), diethyl ether (3 ml), and t-butyllithium (0.18 ml, 1.26 mol l^{-1} in pentane, 0.22 mmol) to give **29** (36 mg, 55%).

3.11. Allylation of methyl 13-(N,N-diethylcarbamoyl)-12-methoxypodocarpa-8,11,13-trien-19-oate (2)

A solution of the diethylbenzamide **2** (0.41 g, 1.03 mmol) in THF (6 ml) was cooled to −78°C. TMEDA (0.34 ml, 2.26 mmol) and t-butyllithium (1.79 ml, 1.26 mol l^{-1} in pentane, 2.26 mmol) were added and the solution was stirred for 30 min. $CuBr.SMe_2$ (0.47 g, 2.26 mmol) was added and the mixture was stirred at −78°C for a further 40 min. Allyl bromide (0.36 ml, 4.12 mmol) was added and the deep red solution was allowed to warm to room temperature overnight. A few drops of ethanol were added and then solvents were removed. Workup and flash chromatography (hexanes/ethyl acetate, 3:2) gave (i) 1-[13′-(methyl-12′-methoxypodocarpa-8′,11′,13′-trien-19′-oate)]-2,2-dimethylpropanone (**10**) (20 mg, 5%) as a yellow oil (Found: $M^{+\bullet}$, 386.2462. $C_{24}H_{34}O_4$ calcd.: M, 386.2457). ν_{max} 1726 (CO ester), 1694 (CO ketone), 1610, 1497, 1463 (C=C), 1141 cm^{-1}. δ_H 1.03, s, (H20′)$_3$; 1.09, td, *J* 14.1, 4.5 Hz, H3′ax; 1.20, s, $C(CH_3)_3$; 1.27, s, (H18′)$_3$; 1.41, td, *J* 13.4, 4.4 Hz, H1′ax; 1.52, d, *J* 11.3 Hz, H5′; 1.61, bd, *J* 14.0 Hz, H2′eq; 1.92, qd, *J* 13.1, 5.7 Hz, H6′ax; 1.97, qt, *J* 14.0, 3.5 Hz, H2′ax; 2.16, bd, 14.1 Hz, H3′eq; 2.17, dd, *J* 13.1, 5.9 Hz, H6′eq; 2.24, d, *J* 13.4 Hz, H1′eq; 2.70, ddd, *J* 16.5, 12.5, 5.9 Hz, H7′ax; 2.18, dd, *J* 16.5, 4.3 Hz, H7′eq; 3.66, s, CO_2CH_3; 3.74, s, $ArOCH_3$; 6.68, s, H11′; 6.75, s, H14′. δ_C 19.9, C2′; 21.0, C6′; 28.2, C20′; 26.8, $C(CH_3)_3$; 28.5, C18′; 31.2, C7′; 37.6, C3′; 38.8, C10′; 39.4, C1′; 44.0, C4′; 44.8, C2; 51.3, C5′; 52.7, $ArOCH_3$; 55.4, CO_2CH_3; 107.9, C11′; 126.7, C14′; 127.2, C8′;129.0, C13′; 149.6, C9′; 153.5, C12′; 177.8, CO (ester); 214.2, CO (ketone). *m/z* 386 (3, M^+), 369 (1), 329 (100, M − CMe_3), 149 (12), 57 (22, $^+CMe_3$); and (ii) methyl [13-(*N*,*N*-diethylcarbamoyl)-12-methoxy-14-prop-2′-enyl]podocarpa-8,11,13-trien-19-oate (**9**) (0.42 g, 92%) as a yellow oil, b.p. 250°C/0.2 mmHg (Kugelrohr) (Found: $M^{+\bullet}$, 441.2880. $C_{27}H_{39}NO_4$ calcd.: M, 441.2879). ν_{max} 1726 (CO ester), 1634 (CO amide), 1596, 1464 (C=C), 1272, 1219 cm^{-1}. δ_H 1.02, 1.06, 2s, (H20)$_3$; 1.04, t, *J* 7.1 Hz, $(H_c)_3$; 1.12, m, H3ax; 1.22, t, *J* 7.1 Hz, $(H_d)_3$; 1.25, 1.27, 2s, (H18)$_2$; 1.44, 1.52, 2td, *J* 13.3, 3.9 Hz, H1ax; 1.44, 1.52, 2dd, *J* 12.3, 1.3 Hz, H5; 1.64, m, H2eq; 1.86, qd, *J* 12.4, 5.2 Hz, H6ax; 2.02, qt, *J* 13.8, 3.6 Hz, H2ax; 2.23, m, H1eq, H2eq, H6eq; 2.54, ddd, *J* 16.8, 12.7, 6.3 Hz, H7ax; 2.87, dd, *J* 16.8, 4.8 Hz, H7eq; 2.98–3.43, m, $(H_a)_2$, $(H_b)_1$, (H1′)$_2$; 3.64, 3.65, 2s, CO_2CH_3; 3.76, s, $ArOCH_3$; 3.84, sextet, *J* 7.1 Hz, $(H_b)_1$; 4.96, dd, *J* 10.3, 1.7 Hz, H3′ *cis*; 4.98, dd, *J* 17.1, 1.7 Hz, H3′ *trans*; 5.82, ddt, *J* 17.1, 10.3, 4.9 Hz, H2′; 6.71, 6.72, 2s, H11. δ_C 12.6, 12.7, $C(H_d)_3$; 13.6, $C(H_c)_3$; 20.0, C2; 20.9, C9; 22.8, 22.9, C20; 28.2, C7; 28.4, C18; 34.4, 34.7, C1′; 37.4, 37.5, C3; 39.94, 38.01, $C(H_b)_2$; 39.09, 39.11, C10; 39.8, 39.9, C1; 42.7, 42.8, $C(H_a)_2$; 43.9, C4; 51.2, 51.3, CO_2CH_3; 52.25, 52.33, C5; 55.3, $ArOCH_3$; 106.28, 106.33, C11; 115.4, 115.5, C3′; 124.8, C8; 127.15, 127.24, C13; 134.63, 134.68, C14; 135.7, C2′; 149.52, 149.54, C9; 153.29,

153.37, C12; 168.71, 168.74, CO (amide); 177.86, 177.95, CO (ester). *m/z* 441 (49, M^+), 426 (21, M − Me), 409 (10), 369 (100, M − NEt_2), 341 (14), 293 (10), 187 (20).

3.12. Benzannulation of methyl [13-(N,N-diethylcarbamoyl)-12-methoxy-14-prop-2'-enyl]-podocarpa-8,11,13-trien-19-oate (9)

3.12.1. Preparation A

t-Butyllithium (48 μl, 1.26 mol l^{-1} in pentane, 0.06 mmol) was added to a solution of the diethylbenzamide **9** (24 mg, 0.06 mmol) in diethyl ether (2 ml), and the orange solution was stirred overnight. A few drops of ethanol were added and solvents removed. Workup gave a solid that contained several components (TLC). Flash chromatography (hexanes/ethyl acetate, 9:1, 3:2) gave methyl [6aR-(6aα,7α,10aβ)]-5,6,6a,7,8,9,10,10a-octahydro-1-hydroxy-12-methoxy-7,10a-dimethylchrysene-7-carboxylate (**30**) (6 mg, 29%), m.p. 157–159°C (hexanes), as white crystals (Found: C, 75.0; H, 7.8. $C_{23}H_{28}O_4$ calcd.: C, 75.0; H, 7.7%) (Found: $M^{+\bullet}$, 368.1983. $C_{23}H_{28}O_4$ calcd.: M, 368.1988). ν_{max} (KBr disc) 3402 (OH), 1713 (CO), 1614, 1578, 1427 cm^{-1} (C=C). δ_H 1.12, td, *J* 13.5, 4.2 Hz, H3ax; 1.13, s, 10a-CH_3; 1.32, s, 7-CH_3; 1.37, td, *J* 13.2, 4.3 Hz, H10ax; 1.59, bd, *J* 11.3, H6a; 1.66, dp, *J* 14.2, 2.9 Hz, H9eq; 2.02, qd, *J* 12.7, 5.6 Hz, H6ax; 2.04, qt, *J* 13.8, 3.7 Hz, H9ax; 2.28, bd, *J* 13.3 Hz, H8eq; 2.31, bd, *J* 13.6 Hz, H10eq; 2.37, dd, *J* 13.8, 6.5 Hz, H6eq; 2.87, ddd, *J* 16.8, 12.4, 6.5 Hz, H5ax; 3.19, dd, *J* 16.7, 4.7 Hz, H5eq; 3.69, s, CO_2CH_3; 4.03, s, $ArOCH_3$; 6.72, s, H11; 6.85, dd, *J* 7.1, 1.3 Hz, H2; 7.39, t, *J* 7.2 Hz, H3; 7.39, dd, *J* 7.1, 1.3 Hz, H4; 9.45, s, OH. δ_C 20.0, C9; 20.8, C6; 21.7, 10a-CH_3; 28.4, 7-CH_3; 28.9, C5; C8; 39.0, C10a; 39.6, C10; 43.9, C7; 51.3, CO_2CH_3; 52.6, C6a; 55.9, $ArOCH_3$; 102.1, C11; 110.1, C2; 113.3, C4b; 114.4, C3; 123.8, C12a; 127.7, C4; 135.5, C4a; 144.8; C1; 155.6, C10b; 154.8, C12; 177.9, CO. *m/z* 368 (100, M^+), 353 (4, M − Me), 293 (35, 353 − CH_3CO_2H), 237 (10), 213 (9), 187 (12).

3.12.2. Preparation B

When the above reaction was carried out in THF at −78°C for 5 min and then warmed to room temperature over 2 h, **30** was obtained in 11% yield.

3.12.3. Preparation C

Methyllithium (0.49 ml, 0.84 mol l^{-1} in ether, 0.41 mmol) was added to **9** (83 mg, 0.19 mmol) in THF (3 ml) at −78°C. The solution was stirred for 10 min at −78°C and warmed to room temperature overnight. Workup as above and flash chromatography (hexanes/ethyl acetate, 9:1, 1:1) gave **30** (13 mg, 19%).

3.12.4. Preparation D

When the benzannulation was attempted using methyllithium in ether as the solvent at either −78°C or room temperature, a complicated mixture resulted, although NMR analysis of the crude material indicated the presence of some benzannulated product.

3.12.5. Preparation E

Trimethylsilyl trifluoromethanesulfonate (27 μl, 0.15 mmol) was added to a solution of **9** (59 mg, 0.13 mmol) in THF (3 ml) at 0°C. The mixture was stirred for 10 min at 0°C and then cooled to −78°C. Methyllithium (0.35 ml, 0.84 mol l^{-1} in ether, 0.3 mmol) was added, and after 10 min at −78°C the cooling bath was removed and the mixture warmed to room temperature. Workup as above gave a complicated mixture (TLC), which included a large amount of starting material.

3.13. N,N-Dimethyl-12,19-dimethoxypodocarpa-8,11,13-triene-13-carboxamide (11)

A solution of the bromoarene **12** (0.60 g, 1.63 mmol) in THF (5 ml) was cooled to −100°C. t-Butyllithium (4.36 ml, 0.75 mol l^{-1} in pentane, 3.27 mmol) was added dropwise and the solution was stirred at −100°C for 3 min before dimethylcarbamoyl chloride (0.20 ml, 2.15 mmol) was added. The mixture was allowed to warm to room temperature overnight, the solvents were removed, and the residue was extracted with dichloromethane. Workup followed by flash chromatography (hexanes/ethyl acetate, 1:1, 7:13) of the product gave *N,N*-dimethyl-12,19-dimethoxypodocarpa-8,11,13-triene-13-carboxamide (**11**) (0.52 g, 89%) as a pale yellow solid, b.p. 140°C/0.03 mmHg (Kugelrohr) (Found: $M^{+\bullet}$, 359.2454. $C_{22}H_{33}NO_3$ calcd.: M, 359.2460). ν_{max} 1635 (CO), 1568, 1494, 1465 (C=C), 1254, 1106 cm^{-1}. δ_H 1.00, td, *J* 12.9, 4.2 Hz, H3ax; 1.02, s, $(H18)_3$; 1.17, s, $(H20)_3$; 1.39, d, *J* 12.8 Hz, H5; 1.41, td, *J* 12.5, 4.0 Hz, H1ax; 1.61, m, H2ax, H6ax; 1.72, dp, *J* 13.7, 3.2 Hz, H2eq; 1.86, bd, *J* 12.9, H3eq; 1.95, dd, *J* 13.1, 6.9 Hz, H6eq; 2.25, bd, *J* 12.5, H1eq; 2.73, ddd, *J* 18.4, 11.6, 7.3 Hz, H7ax; 2.81, dd, *J* 18.4, 6.4 Hz, H7eq; 2.84, s, $C(H_a)_3$; 3.08, s, $C(H_b)_3$; 3.22, 3.50, 2d, *J* 9.1 Hz, $(H19)_2$; 3.31, s, CH_2OCH_3; 3.31, s, $ArOCH_3$; 6.74, s, H11; 6.87, s, H14. δ_C 18.4, C2; 18.6, C6; 24.8, C20; 27.0, C18; 29.3, C7; 33.9, $C(H_b)_3$; 35.3, C3; 37.3, $C(H_a)_3$; 37.4, C10; 37.5, C4; 38.3, C1; 50.5, C5; 54.8, CH_2OCH_3; 58.6, $ArOCH_3$; 75.2, CH_2OCH_3; 106.3, C11; 123.2, C8; 126.6, C13; 127.5, C14; 151.1, C9; 152.7, C12; 168.8, CO. *m/z* 359 (27, M^+), 344 (5, M − Me), 329 (7, 344 − Me), 315 (100, M − NMe_2), 232 (7), 163 (7), 72 (20, $^+OCNMe_2$), 44 (14, $^+NMe_2$).

3.14. Allylation of N,N-dimethyl-12,19-dimethoxypodocarpa-8,11,13-triene-13-carboxamide (11)

A solution of the dimethylbenzamide **11** (0.11 g, 0.31 mmol) in THF (5 ml) was cooled to −78°C. TMEDA (0.10 ml, 0.67 mmol) and t-butyllithium (0.53 ml, 1.26 mol l^{-1} in pentane, 0.67 mmol) were added and the orange solution was stirred for 5 min before $CuBr.SMe_2$ (0.14 g, 0.67 mmol) was added. After 30 min allyl bromide (0.11 ml, 1.23 mmol) was added and the deep red mixture was kept at −78°C for 1 h and then allowed to warm to room temperature overnight. Workup and PLC (benzene/ethyl acetate, 9:1, 6 sweeps) gave (i) *N*-methyl-12,19-dimethoxypodocarpa-8,11,13-triene-13-carboxamide (**15**) (10 mg, 9%) as a yellow oil, (Found: $M^{+\bullet}$, 345.2303. $C_{21}H_{31}NO_3$ calcd.: M, 345.2304). ν_{max} 3414 (NH), 1645 (CO), 1537, 1492, 1459 (C=C), 1256, 1108 cm^{-1}. δ_H 1.03, td, *J* 13.6, 4.1 Hz, H3ax; 1.04, s, $(H18)_3$; 1.20, s, $(H20)_3$; 1.40, d, *J* 12.8 Hz, H5; 1.45, td, *J* 13.2, 4.0 Hz, H1ax; 1.65, m, H2ax, H2eq, H6ax; 1.89, bd, *J* 13.6, H3eq; 1.99, dd, *J* 13.3, 7.4 Hz, H6eq; 2.27, bd, *J* 13.1 Hz, H1eq; 2.80, ddd, *J* 17.1, 11.5, 7.3 Hz, H7ax; 2.91, dd, *J* 17.1, 5.5 Hz, H7eq; 2.98, s, $C(H_a)_3$; 2.99, s, $C(H_b)_3$; 3.30, 3.52, 2d, *J* 9.1 Hz, $(H19)_2$; 3.33, s, CH_2OCH_3; 3.91, s, $ArOCH_3$; 6.82, s, H11; 7.80, bs, NH; 7.87, s, H14. *m/z* 345 (100, M^+), 330 (28, M − Me), 315 (50, M − HNMe), 298 (16), 255 (24), 218 (68); (ii) *N,N*-dimethyl-(12,19-dimethoxy-14-prop-2′-enylpodocarpa-8,11,13-triene)-13-carboxamide (**13**) (28 mg, 23%) as a yellow oil, (Found: $M^{+\bullet}$, 399.2788. $C_{25}H_{37}NO_3$ calcd.: M, 399.2773). ν_{max} 1635 cm^{-1} (CO). δ_H 1.01, td, *J* 13.6, 4.2 Hz, H3ax; 1.03, 1.05, 2s, $(H18)_3$; 1.17, 1.24, 2s, $(H20)_3$; 1.20, td, *J* 13.2, 4.0 Hz, H1ax; 1.32, 1.41, 2bd, *J* 12.7 Hz, H5; 1.41, m, H2eq; 1.68, m, H2ax, H6ax; 1.82, 1.88, 2d, *J* 13.6 Hz, H3eq; 2.00, dd, *J* 13.2, 7.4 Hz, H6eq; 2.25, 2.29, 2d, *J* 13.1 Hz, H1eq; 2.61, ddd, *J* 17.1, 11.5, 7.4 Hz, H7ax; 2.76, 2.78, 2s, $C(H_a)_3$; 2.88, dd, *J* 17.1, 5.6 Hz, H7eq; 3.09, 3.10, 2s, $C(H_b)_3$; 3.23, 3.50, 2d, *J* 9.1 Hz, $(H19)_2$; 3.25, m, H1′; 3.33, s, CH_2OCH_3; 3.76, s, $ArOCH_3$; 4.91, 4.98, 2dd, *J* 17.1, 1.7 Hz, H3′ *trans*; 4.92, 4.98, 2dd, *J* 10.1, 1.7 Hz, H3′ *cis*; 5.81, ddt, *J* 17.1, 10.1, 5.3 Hz, H2′; 6.72, s, H11. δ_C 19.18, 19.23, 19.28, C2, C6; 25.60, 25.66, C20; 27.33, 27.70, C7; 27.54, C18; 34.29, $C(H_b)_3$; 34.33, 34.49, C1′; 35.8, C3; 37.95, C4; 37.98, C10; 38.08, 38.15, $C(H_a)_3$; 39.31, 39.48, C1; 50.69, 50.79, C5; 55.53, 55.58, $ArOCH_3$; 59.4, CH_2OCH_3; 75.79, 76.00, C19; 105.37, 105.55, C11; 115.10, 115.25, C3′; 124.38, C8; 126.64, 126.70, C13; 134.85, C14; 135.64, 135.67, C2′; 151.61, C9; 153.29, 153.34, C12; 169.67, 169.77, CO. *m/z* 399 (29, M^+), 384 (15, M − Me), 355 (100, M − NMe_2), 227 (12), 149 (13), 72 (28, $^+OCNMe_2$), 44 (30, $^+NMe_2$); (iii) N-but-3′-enyl-N-methyl-12,19-dimethoxypodocarpa-8,11,13-trien-13-carboxamide (**14**) (12 mg, 10%) as a yellow oil, (Found: $M^{+\bullet}$, 399.2776. $C_{25}H_{37}NO_3$ calcd.: M, 399.2773). ν_{max} 1637 (CO), 1462, 1408, 1108 cm^{-1}. δ_H 0.99, m, H3ax; 1.04, s, $(H18)_3$; 1.18, s, $(H20)_3$; 1.20, m, H1ax, H5; 1.40, m, H2eq; 1.65, m, H2ax, H6ax; 1.89, bd, *J* 13.6 Hz, H3eq; 1.98, dd, *J* 13.2, 7.4 Hz, H6eq; 2.26, m, $(H2')_1$, H1eq; 2.41, q, *J* 7.0 Hz, $(H2')_1$; 2.60–2.90, m, H7ax, H7eq; 2.83, s, $C(H_a)_3$; 3.07, s, $C(H_b)_3$; 3.22, m, $(H1')_1$, $(H19)_1$; 3.33, s, CH_2OCH_3; 3.51, d, *J* 9.1 Hz, $(H19)_1$; 3.62, t, *J* 7.1 Hz, $(H1')_1$; 3.76, 3.77, 2s, $ArOCH_3$; 4.98, 5.08, 2dd, *J* 10.2, 0.8 Hz, H4′ *cis*; 4.98, 5.14, 2dd, *J* 17.2, 1.2 Hz, H4′ *trans*; 5.62, 5.87, 2ddt, *J* 17.2, 10.2, 7.0 Hz, H3′; 6.75, s, H11; 6.85, 6.87, 2s, H14. *m/z* 399 (17, M^+), 384 (4, M − Me), 368 (9), 315 (100, M − $MeNC_4H_7$), 187 (8), 149 (14); and (iv) **5** (19 mg, 17%).

3.15. Benzannulation of N,N-dimethyl-(12,19-dimethoxy-14-prop-2′-enylpodocarpa-8,11,13-triene)-13-carboxamide (13)

A solution of the dimethylbenzamide **13** (20 mg, 0.05 mmol) in THF (3 ml) was cooled to −78°C. Methyllithium (0.13 ml, 0.84 mol l^{-1} in ether, 0.11 mmol) was added dropwise and the cooling bath was removed immediately, producing a deep red solution. After 1 h at room temperature a few drops of ethanol were added and solvents removed. The residue was extracted with ether, and workup followed by flash chromatography (hexanes/ethyl acetate, 4:1) gave **29** (12 mg, 68%).

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