CH(TMS)), 0.42 (s, 9H; TMS-benzyl), 0.59 (s, 9H; TMS-fluorenyl), 0.95 (mb, 4H; THF), 1.93 and 1.96 (2 s, 6H; NMe_2), 2.59 (mb, 4H; THF), 6.12 (t, $^3J(H,H) = 7.5$ Hz, 1H; benzyl), 6.27 (d, $^3J(H,H) = 7.8$ Hz, 1H; benzyl), 6.31 (t, $^3J(H,H) = 7.5$ Hz, 1H; benzyl), 6.88 (d, $^3J(H,H) = 8.4$ Hz, 1H; benzyl), 7.04 (t, $^3J(H,H) = 7.5$ Hz, 1H; fluorenyl), 7.09 (t, $^3J(H,H) = 7.5$ Hz, 1H; fluorenyl), 7.24 (t, $^3J(H,H) = 7.2$ Hz, 1H; fluorenyl), 7.31 (t, $^3J(H,H) = 7.5$ Hz, 1H; fluorenyl), 7.93 (d, $^3J(H,H) = 7.8$ Hz, 1H; fluorenyl), 8.03 (d, $^3J(H,H) = 8.4$ Hz, 1H; fluorenyl), 8.14 (d, $^3J(H,H) = 8.4$ Hz, 1H; fluorenyl), 8.17 (d, $^3J(H,H) = 7.8$ Hz, 1H; fluorenyl); ^{13}C NMR (600 MHz, C_6D_6, 20 °C): $\delta = 2.43$ (TMS), 2.44 (TMS), 24.9 (THF), 41.8 (NMe), 44.5 (NMe), 44.9 (CH(TMS)), 68.5 (THF), aromatics: 87.0, 112.8, 116.5, 116.8, 119.4, 121.2, 121.4, 121.7, 121.9, 123.3, 124.2, 124.3, 124.4, 126.4, 128.3, 135.0, 140.7, 140.9, 147.0.

Crystal structure determination of **3**: Crystals grown from benzene solution contain up to three equivalents of benzene per Ca atom and crack upon cooling resulting in broad peak profiles and poor diffraction. Crystals grown from warm hexane also show solvent incorporation but remain stable upon cooling. Measurement on an Enraf Nonius CAD4 diffractometer at −90 °C, $Mo_{K\alpha}$, $2\theta_{max} = 50°$, 13501 independent reflections ($R_{int} = 0.011$), 10658 reflections observed with $I > 2\sigma(I)$. Crystal data: $C_{32}H_{45}CaNOSi_2$ triclinic, space group $P\bar{1}$, $a = 13.5981(13)$, $b = 16.8236(12)$, $c = 18.2031(15)$ Å, $\alpha = 70.779(6)$, $\beta = 77.084(7)$, $\gamma = 82.671(7)°$, $V = 3826.1(6)$ Å^3, $Z = 4$, $R = 0.0456$, $wR2 = 0.1466$, GOF = 1.08, $\rho_{max} = 0.57$ e Å^{-3}, $\rho_{min} = -0.44$ e Å^{-3}. The unit cell contains a hole with two severely disordered hexane molecules (confirmed by NMR analysis). Disorder was treated with the bypass method using the program SQUEEZE[17] incorporated in PLATON.[18] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-165023. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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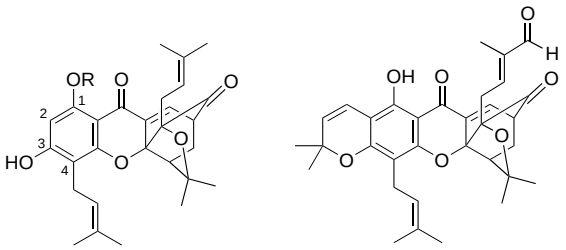
"Biomimetic" Cascade Reactions in Organic Synthesis: Construction of 4-Oxatricyclo-[4.3.1.0]decan-2-one Systems and Total Synthesis of 1-*O*-Methylforbesione via Tandem Claisen Rearrangement/Diels–Alder Reactions**

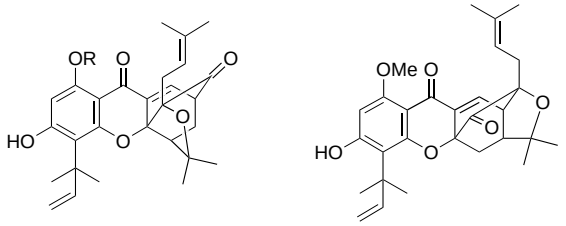
K. C. Nicolaou* and Jim Li

The intriguing 4-oxatricyclo[4.3.1.0]decan-2-one ring system is found in a growing class of biologically active natural products isolated from the genus *Garcinia* of the Guttiferae family of plants. Among the members of this class of compounds are forbesione (**2**, isolated from *Garcinia forbesii*),[1] morellin (**3**, from *G. morella*),[2] and the cytotoxic agents



1: R = Me: 1-*O*-methylforbesione
2: R = H: forbesione

3: morellin



4: R = H: bractatin
5: R = Me: 1-*O*-methylbractatin

6: 1-*O*-methylneobractatin

bractatin (**4**), 1-*O*-methylisobractatin (**5**), and 1-*O*-methylneobractatin (**6**), all of which were found in the species *G. bracteata*,[3] as well as lateriflorone (from *G. lateriflora*),[4]

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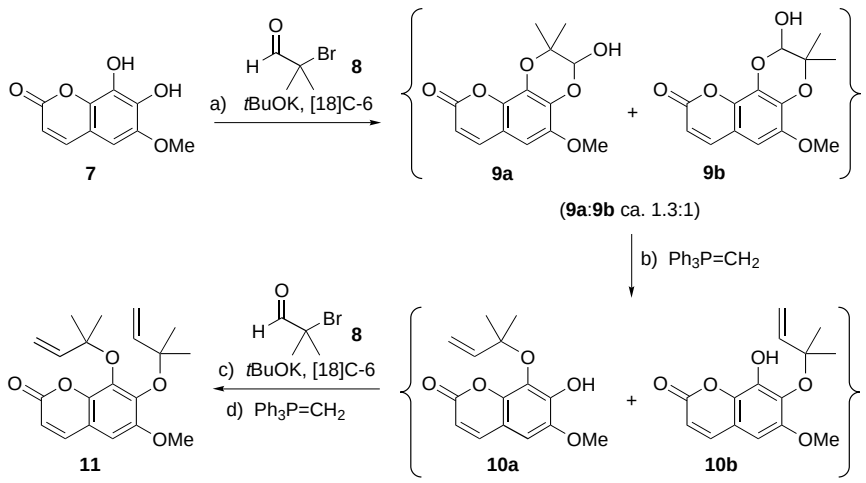
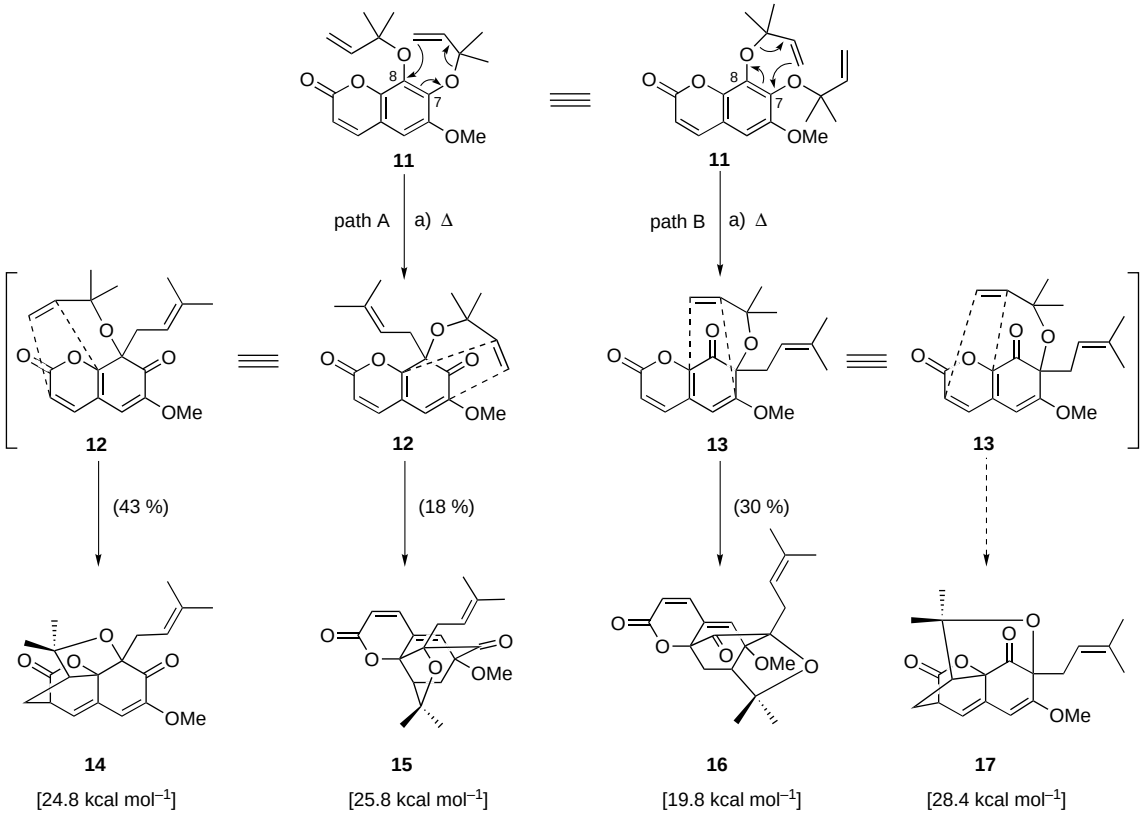
hanburin (from *G. hanburyi*),[5] and the gaudichaudiones and gaudichaudiic acids (from *G. gaudichaudii*).[6] An elegant proposal for the biosynthesis of morellins was put forward by Quillinan and Scheinmann over 30 years ago.[7] This biosynthetic hypothesis, in which a Claisen rearrangement followed by an intramolecular Diels–Alder reaction was postulated, was supported by the results of a model study involving unsubstituted allyl ethers which led to rearranged products upon prolonged heating in refluxing decalin in unspecified yields. Here we report the development of this Claisen rearrangement/intramolecular Diels–Alder cascade into a useful strategy for the construction of the fully substituted polycyclic systems found in the two types of natural products represented by the aforementioned compounds. In addition to providing credence to the proposed biogenetic origin of these natural products, the described new synthetic technology found application in the first total synthesis of 1-*O*-methylforbesione (**1**).

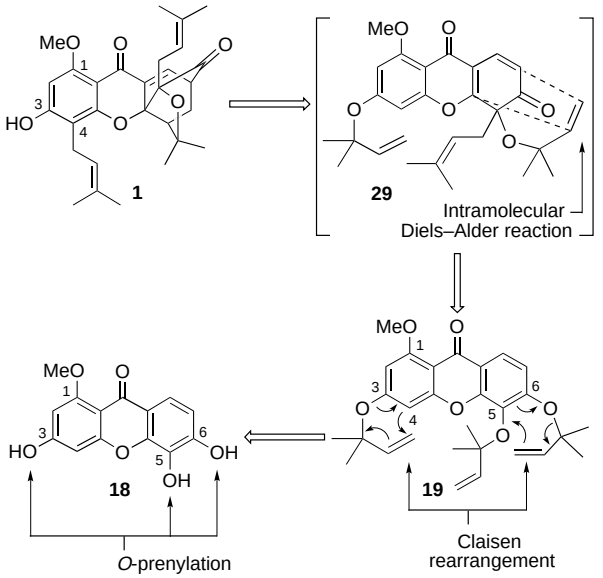


Scheme 1. Synthesis of cascade precursor **11**. a) *t*BuOK (2.1 equiv), THF, 0 °C, 30 min; then concentrated under reduced pressure and suspended in MeCN; [18]C-6 (1.5 equiv), 15 min, 0 °C; **8** (2.5 equiv), 0 →40 °C, 2 h, 92 %; b) $CH_3PPh_3^+Br^-$ (2.0 equiv), NaHMDS (2.0 equiv), THF, 0 →25 °C, 96 %; c) *t*BuOK (1.1 equiv), THF, 0 °C, 30 min, then concentrated under reduced pressure and suspended in MeCN; [18]C-6 (1.0 equiv), 15 min, 0 °C; **8** (1.5 equiv), 0 °C, 1 h; d) $CH_3PPh_3^+Br^-$ (2.0 equiv), NaHMDS (2.0 equiv), THF, 0 °C, 87 % for two steps. NaHMDS = sodium bis(trimethylsilyl)amide.

Coumarin **7** (Scheme 1) was chosen as the entry point to our explorations of the Claisen rearrangement/intramolecular Diels–Alder reaction cascade not only because of the commercial availability of this compound, but also due to the opportunities for molecular diversity it presented. Specifically, it was anticipated that a precursor such as compound **11**, synthesized from **7**, could engage in two possible Claisen rearrangement pathways (A and B, Scheme 2) to furnish the two intermediates **12** and **13**. These two intermediates could then undergo two different intramolecular Diels–Alder reactions as shown in Scheme 2 which would lead to a maximum of four possible final products (**14**–**17**). Molecular



Scheme 2. One-pot cascade Claisen rearrangement/intramolecular Diels–Alder reaction of precursor **11**. a) decalin, 125 °C, 15 min; **14**, 43 %; **15**, 18 %; **16**, 30 %. Energies given in square brackets are differences of strain energies relative to precursor **11**.

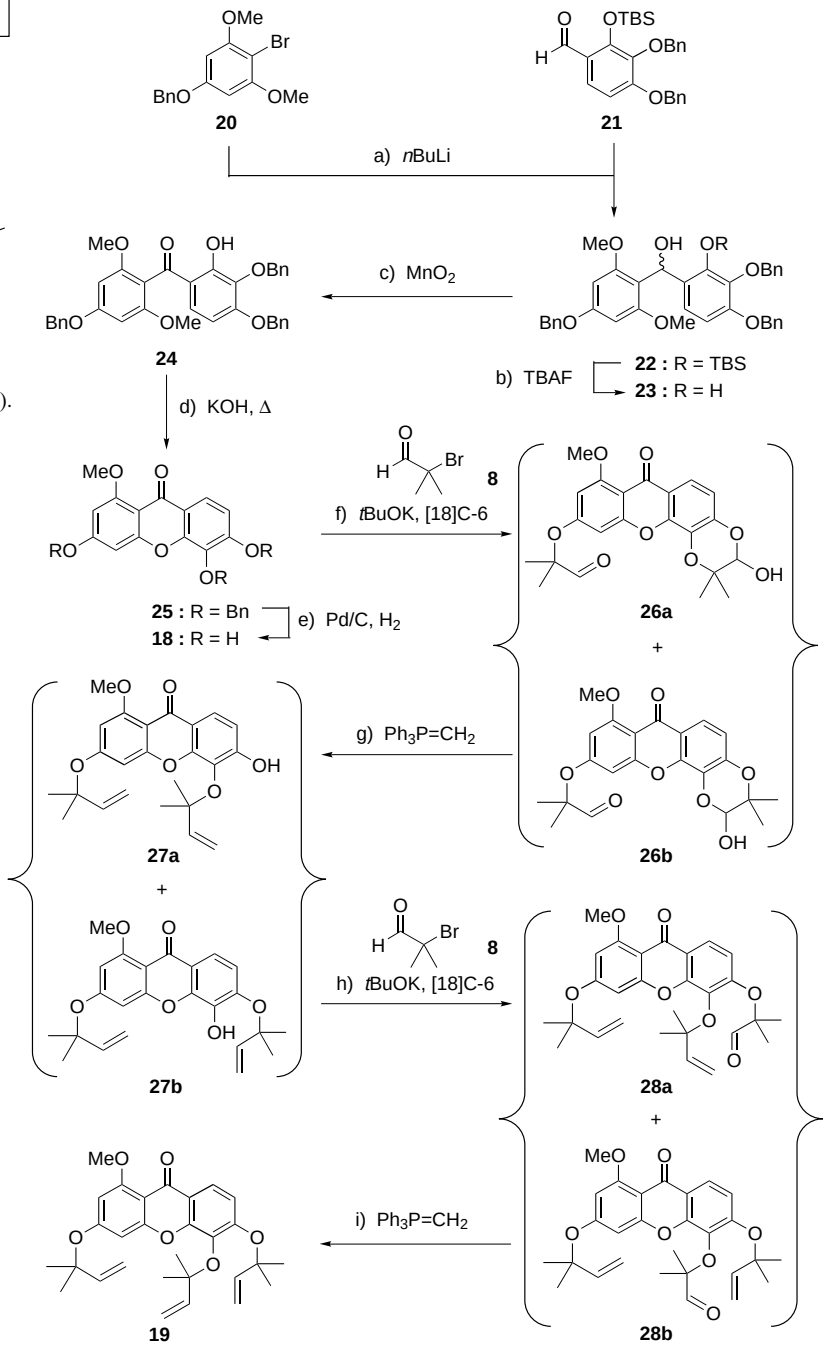


Scheme 3. Retrosynthetic analysis of 1-*O*-methylforbesione (**1**).

mechanics calculations on these cagelike compounds revealed the following relative (to precursor **11**) strain energies: 24.8, 25.8, 19.8, and 28.4 kcal mol^{-1} for compounds **14**, **15**, **16**, and **17**, respectively.[8]

The synthesis of the required precursor **11** from **7** was not trivial given the challenge associated with the construction of the crowded *ortho*-bis-(α,α-dimethylallyl) aryl ethers.[9] Indeed, early attempts to directly allylate or propargylate the catechol system of **7** failed,[10] which prompted us to develop a stepwise approach involving initial reaction of the phenoxide anions of **7** with α-bromoisobutyraldehyde (**8**) followed by Wittig olefination (Scheme 1). This sequence turned out to be both efficient and general as demonstrated by several examples.[11] For the case at hand, the di-potassium salt of **7** reacted with aldehyde **8** in acetronitrile and in the presence of [18]crown-6[12] to afford a mixture of the two regioisomeric lactols **9a**:**9b** (ca. 1.3:1 ratio) in 92% total yield. Treatment of this mixture with 2 equiv of $Ph_3P{=}CH_2$ gave a mixture of mono-olefins **10a** and **10b** (ca. 1.3:1 ratio) in 96% yield. Reiteration of this two-step *O*-alkylation procedure with this mixture resulted in the installation of the second allyl group (87% overall yield) to furnish the desired cascade precursor **11** (Scheme 1).

Heating compound **11** in decalin[13] at 125 °C for 15 min furnished cleanly three products, **14** (43%), **15** (18%), and **16** (30%), which were chromatographically separated and fully characterized by spectroscopic means and X-ray crystallographic analysis.[14] None of the fourth possible structure (**17**) was formed, undoubtedly as a consequence of its highly strained nature relative to the other three products (**14**–**16**, see Scheme 2). These results were both rewarding in terms of confirming the Quillinan–Scheinmann biosynthetic hypothesis[7] and encouraging in terms of possibly facilitating a "biomimetic" total synthesis of a number of natural products. We consequently selected 1-*O*-methylforbesione (**1**) as a



Scheme 4. Synthesis of cascade precursor **19**. a) *n*BuLi (1.05 equiv), THF, −78 °C, 15 min; then aldehyde **21** (1.0 equiv) in THF, −78 → 0 °C, 45 min; b) TBAF (1.2 equiv), THF, 0 °C, 15 min, 92% for two steps; c) MnO_2 (10.0 equiv), CH_2Cl_2, 25 °C, 4 h; d) KOH (10.0 equiv), MeOH, reflux, 6 h, 86% for two steps; e) 10% Pd/C (10% wt/wt), H_2 (1 atm), 25 °C, 45 min, 98%; f) *t*BuOK (3.2 equiv), THF, 0 °C; then concentrated and suspended in MeCN; [18]C-6 (3.0 equiv), 15 min, 0 °C; **8** (4.0 equiv), 0 → 40 °C, 2 h, **26a**:**26b** (ca. 1:2), 73%; g) $CH_3PPh_3^+Br^-$ (3.0 equiv), NaHMDS (3.0 equiv), THF, 0 °C, 1 h, 87%, **27a**:**27b** (ca. 1:2); h) *t*BuOK (1.2 equiv), THF, 0 °C; then concentrated and suspended in MeCN; [18]C-6 (1.0 equiv), 15 min, 0 °C; **8** (1.5 equiv), 0 °C, 2 h, **28a**:**28b** (ca. 1:2), 94%; i) $CH_3PPh_3^+Br^-$ (2.0 equiv), NaHMDS (2.0 equiv), THF, 0 °C, 1 h, 92%. TBS = *tert*-butyldimethylsilyl, Bn = benzyl, TBAF = tetrabutylammonium fluoride.

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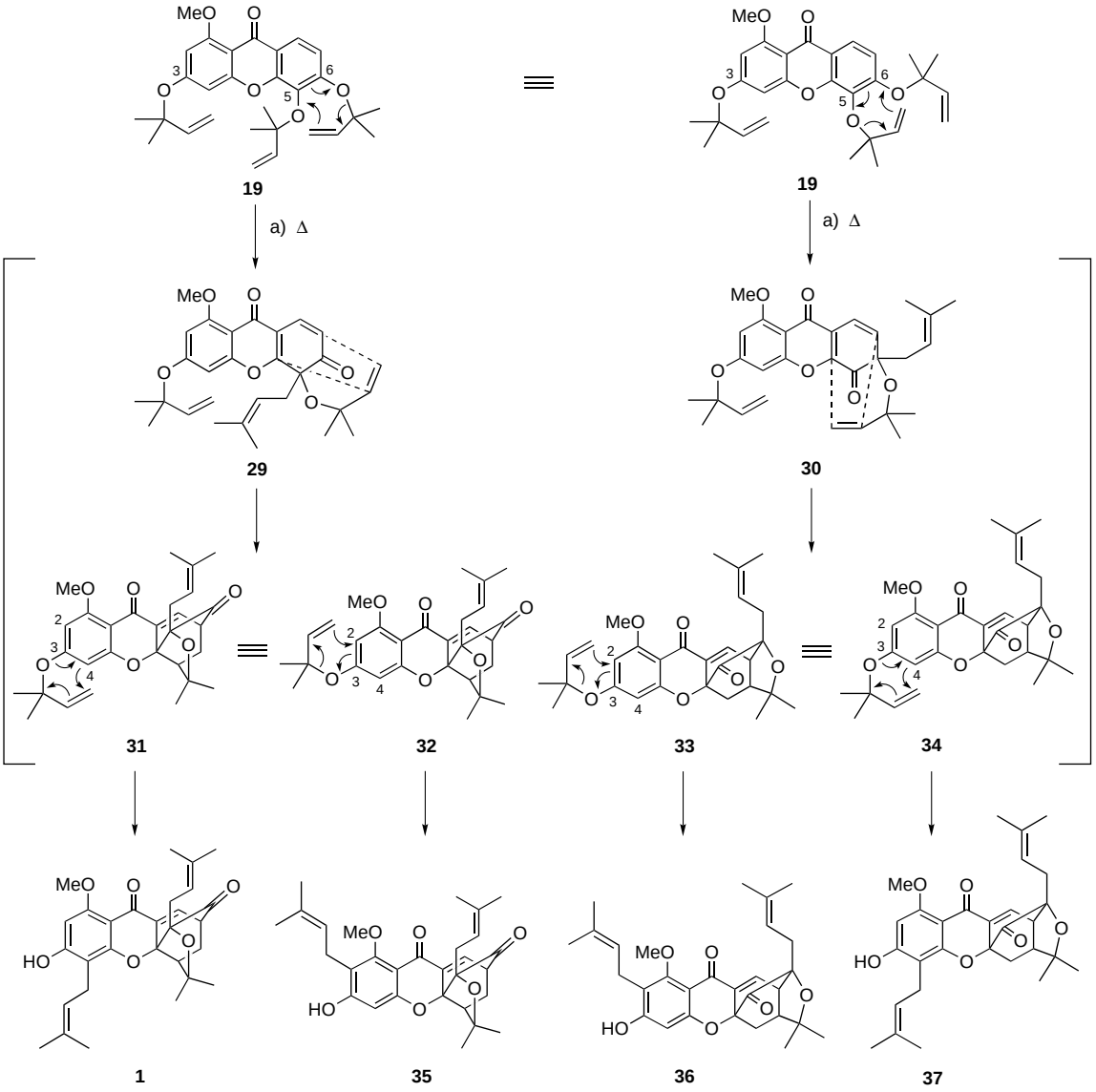
synthetic target to demonstrate the applicability of this cascade-based synthetic technology to natural product synthesis.

The structure of forbesione contains a xanthone skeleton, two apparent prenyl groups, and a tricyclo[4.3.1.0]decan-2-one system, a cagelike structure which hides a third prenyl moiety. Relying on the one-pot Claisen rearrangement/intramolecular Diels–Alder reaction cascade just described, the tris-(α,α-dimethylallyl) aryl ether **19** may be retrosynthetically defined as a possible precursor to the targeted methyl derivative of forbesione (**1**) (Scheme 3). Compound **19** may, in turn, be derived via the above described two-step allylation protocol from xanthone **18** whose origins can be traced back to benzenoid systems **20** and **21** (Scheme 4).

Coupling of the lithium derivative of **20**[15] with aldehyde **21**[16] followed by desilylation (92% overall yield) and MnO_2 oxidation furnished benzophenone **24** via intermediates **22** and **23** (Scheme 4). Exposure of **24** to KOH in refluxing MeOH led, after hydrogenolysis, to trihydroxy xanthone **18** (85% overall yield) which was subjected to α,α-dimethylallylation as shown in Scheme 1. Thus, treatment of **18** with 3.2 equiv *t*BuOK in THF at 0 °C followed by solvent exchange (THF → MeCN) and sequential addition of [18]crown-6 and α-bromoisobutyraldehyde (**8**) furnished a mixture of aldehyde–lactols (**26a**:**26b** ca. 1:2) in 73% yield. Wittig olefination ($Ph_3P{=}CH_2$) of this mixture then led to a mixture of hydroxy di-olefins (**27a**:**27b**, ca. 1:2, 87% yield) which was allylated further by reiteration of this two-step sequence to afford the targeted precursor **19** (86% over yield) via aldehyde mixture **28a**:**28b**.

Gratifyingly, upon heating prenylated xanthone **19** in DMF at 120 °C for 20 min, the expected compound, 1-*O*-methylforbesione (**1**), was indeed obtained as the major product (63% yield), presumably by the anticipated double Claisen rearrangement followed by an intramolecular Diels–Alder reaction, as outlined in Scheme 5. Accompanying **1** were its isomers **35** (2% yield), **36** (<1% yield, presumed structure[17]), and **37** (26% yield), presumably formed via the



Scheme 5. Synthesis of 1-*O*-methyl forbesione (**1**), and 4-oxatricyclo[4.3.1.0]decan-2-ones **35**, **36** and **37** via a "biomimetic" double Claisen rearrangement/intramolecular Diels–Alder cascade reaction. a) DMF, 120 °C, 20 min; **1**, 63%; **35**, 2%; **36**, <1%; **37**, 26%.

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pathways outlined in Scheme 5. The timing of the two Claisen rearrangements has not been determined and the sequences shown in Scheme 5 are simply for purposes of convenience.[18] The structure of 1-*O*-methylforbesione (**1**) was confirmed by both spectroscopic means (see Table 1) and X-ray crystallographic analysis[14] (see Figure 1), whereas those of **35**–**37** were based on spectroscopic evidence and comparisons of their NMR spectra to those of model systems **14**–**17** (Scheme 2) and those reported for the bractatins.[3]

Table 1. Selective analytical data for 1-*O*-methylforbesione (**1**).

Light yellow solid; mp = 192–196 °C (dec.) (ethyl acetate/hexanes, 2:1); R_f = 0.31 (silica gel, ethyl acetate/hexanes, 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.23 Hz, 1H), 6.26 (bs, 1H), 6.10 (s, 1H), 5.23 (m, 1H), 4.51 (m, 1H), 3.85 (s, 3H), 3.46 (m, 2H), 3.41 (m, 1H), 2.55 (m, 1H), 2.45 (m, 2H), 2.26 (dd, J = 16.05, 5.68 Hz, 1H), 1.81 (s, 3H), 1.76 (d, J = 1.19 Hz, 3H), 1.65 (s, 3H), 1.37 (s, 3H), 1.31 (dd, J = 15.31, 11.55 Hz, 1H), 1.25 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.1, 174.9, 162.0, 161.3, 160.1, 136.4, 135.8, 134.5, 132.3, 121.2, 117.6, 106.4, 104.6, 93.9, 90.6, 84.5, 83.0, 56.2, 49.0, 46.7, 30.2, 29.1, 28.8, 26.0, 25.8, 25.6, 22.6, 18.0, 17.0; HR-MS (MALDI-FT): calcd for $C_{29}H_{34}O_6$ [M+H$^+$]: 479.2428; found: 479.2417

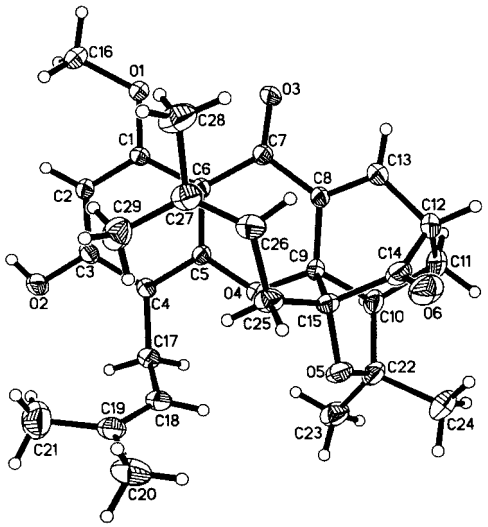

Figure 1. X-Ray crystallographic structure of 1-*O*-methylforbesione (**1**) in ORTEP representation.

The development of the Claisen rearrangement/intramolecular Diels–Alder cascade reaction as a powerful and practical method for the construction of complex molecules is a further demonstration of the value of "biomimetically" inspired synthetic strategies toward natural products. The described expedient total synthesis of racemic 1-*O*-methylforbesione (**1**) bodes well for further applications of this synthetic technology to other members of this constantly expanding class of natural products containing the 4-oxatricyclo[4.3.1.0]decan-2-one ring framework and related systems.

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[8] Computational studies on compounds **11** and **14**–**17** were performed using the program DISCOVER packaged in Insight II software on a SGI workstation. High temperature (1000 K) molecular dynamics (MD) was used to generate conformations of each compound. Molecular mechanics potentials (AMBER force field) were determined relative to **11**.

[9] To the best of our knowledge (SciFinder and Beilstein databases), this type of highly hindered *ortho*-bis-(α,α-dimethylallyl) aryl ether has not been previously reported.

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[11] Further details of this two-step sequence for the preparation of various aryl allyl ethers will be reported in due course.

[12] Applications of crown ethers in organic synthesis can be found in the following selected references: a) D. Dehm, A. Padwa, *J. Org. Chem*. **1975**, *40*, 3139; b) F. Terrier, G. Ah-Kow, M. Pouet, M. Simonnin, *Tetrahedron Lett*. **1976**, 227; c) C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, K. Smith, *Tetrahedron Lett*. **1974**, 2417.

[13] Among several solvents evaluated for this one-pot cascade reaction, decalin was found to be the most suitable in terms of yields and convenience.

[14] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-168029 (**14**), -168031 (**15**), -168028 (**16**), and -168030 (**1**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[15] Aryl bromide **20** was prepared from 3,5-dimethoxyphenol by bromination with NBS in CH_2Cl_2 followed by benzylation with BnBr and K_2CO_3 in refluxing acetone.

[16] Compound **21** was prepared from 2,3,4-trihydroxybenzaldehyde by benzylation with BnBr and K_2CO_3 in refluxing acetone, followed by selective debenzylation at C2 with $MgBr_2 \cdot OEt_2$, and silylation of the resulting phenolic group with TBSCl.

[17] Owing to the low yield in which this presumed product was formed, its full characterization is still pending.

[18] A small amount of intermediate **31** isolated in some experiments suggested the indicated order of events in the conversion of **19** to **1** as illustrated in Scheme 5.

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