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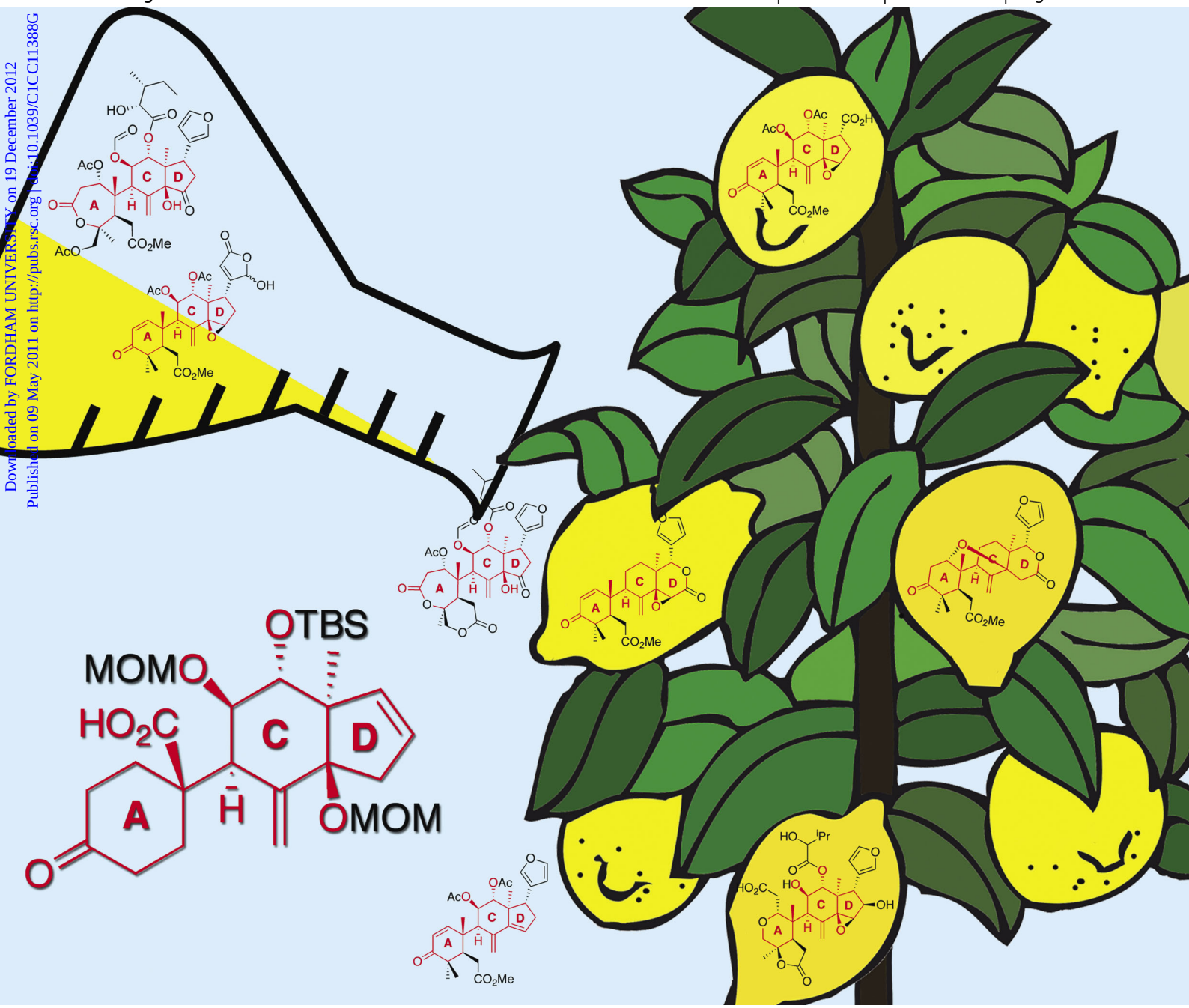

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COMMUNICATION

Synthesis of the B-*seco* limonoid scaffold†

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The underlying stereochemically complex and densely functionalized scaffold of the B-*seco* limonoids was synthesized employing an Ireland–Claisen rearrangement as key transformation.

Members of the highly oxygenated B-*seco* limonoids (Fig. 1)[1] like 21-hydroxytoonacilide **1**[2] and prieurianin **2**[3] display diverse and potent bioactivities. Remarkably, prieurianin **2** induces "appetite loss" in insects at the application level close to the leading compound azadirachtin.[4]

In the light of the biology oriented synthesis (BIOS) concept,[5] we sought a strategy to access the B-*seco* limonoid scaffold.

The richly decorated and stereochemically complex B-*seco* limonoids are exceptionally challenging synthesis targets. For instance, in 21-hydroxytoonacilide **1** and prieurianin **2**, an A-ring and a bicyclic *trans*-fused C–D ring system equipped with an *exo*-methylene group and six to seven stereogenic centers including two contiguous asymmetric quaternary centers at the ring-junction are linked by a C9–C10 bond surrounded by dense functionality including a quaternary carbon atom in the A ring.

Inspired by the decisive role of a Claisen rearrangement in the synthesis of azadirachtin by Ley *et al.*,[6] we envisioned that

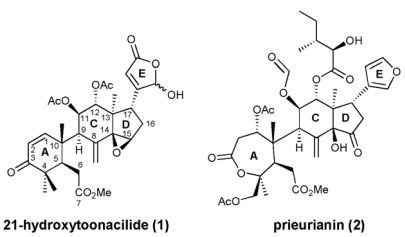

Fig. 1 Structures of representative B-*seco* limonoids 21-hydroxytoonacilide (**1**) and prieurianin (**2**).

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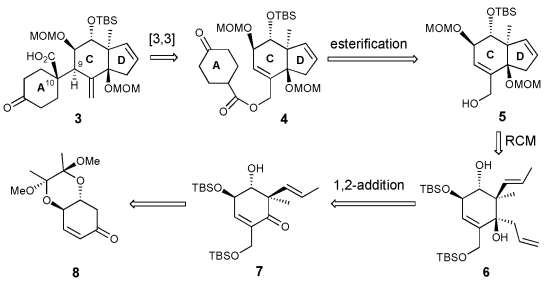
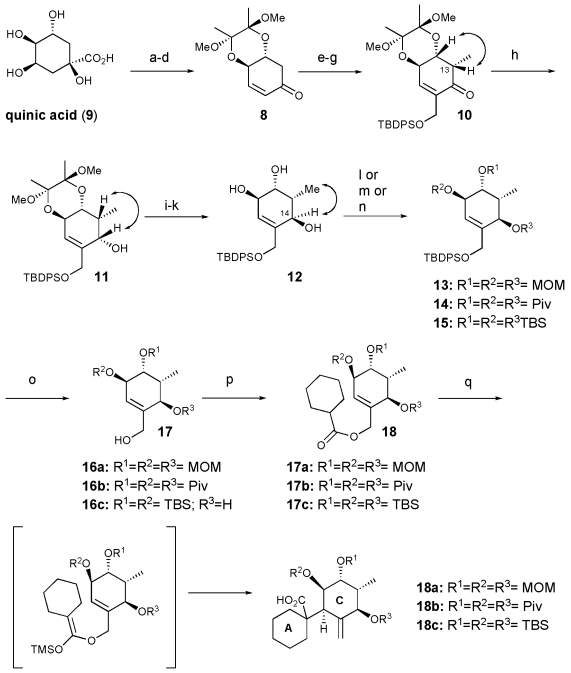
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc11388g



Scheme 1 Retrosynthetic analysis of the B-*seco* limonoid scaffold.

the C9–C10 linkage could be constructed by means of an Ireland–Claisen rearrangement (Scheme 1). It was planned to construct the all-carbon quaternary center at C13 from known enone **8**[7] by substrate controlled α-functionalization and to establish the second quaternary center at C14 by 1,2-addition to the keto group. Finally, ring closing metathesis (RCM) would give rise to bicyclic system **5**. Very recently, an acetal Claisen rearrangement was successfully employed in the synthesis of (±)-cipadonoid B.[8]

For feasibility and stereochemical model studies rearrangement precursors **17** (Scheme 2) were synthesized as suitable model systems. To this end enone **8**[7] was prepared from (−)quinic acid **9**.[9] The Baylis–Hillman reaction gave the desired hydroxymethylated product, which was subsequently protected as TBDPS–ether **10**. Substrate controlled α-methylation of the lithium enolate proceeded with full stereocontrol,[10] presumably due to the conformational rigidity of the butane-2,3-diacetal (BDA) protected *trans*-diequatorial diol[11] and the stereoelectronic preference for axial attack on the intermediary enolate. Luche reduction with unhindered axial attack of the hydride yielded alcohol **11** whose configuration was determined by ^{1}H NMR, nOe and Mosher ester analysis (see the arrows in Scheme 2). Subsequent Mitsunobu inversion of configuration established the required stereochemistry at C14. Selective cleavage of the BDA-protecting group with TFA in aqueous CH_2Cl_2 released triol **12** which was masked with protecting groups of different size and chemical nature to examine the face-selectivity of the Ireland–Claisen rearrangement. From **13–15** the silyl protecting groups were selectively removed, and the liberated primary alcohols were esterified with an undecorated model A-ring. Additional silylation of the secondary alcohol at C14 in **16c** then furnished the targeted rearrangement precursors **17a–c**.



Scheme 2 Synthesis and Ireland–Claisen rearrangement of model compounds **17a–c**. *Reagents and conditions*: (a) CSA, 2,3-butanedione, trimethylorthoformate, MeOH, reflux, 16 h, 93%; (b) $NaBH_4$, MeOH, rt, 24 h, quant.; (c) silica-gel supported $NaIO_4$, CH_2Cl_2/MeOH (20 : 1), rt, 30 min; quant.; (d) MsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 2 h, 85%; (e) paraformaldehyde, imidazole, THF/1 M $NaHCO_3$ (1 : 1), rt, 2.5 h, 74%; (f) TBDPSCl, DMAP, NEt_3, CH_2Cl_2, rt, 18 h, 93%; (g) LiHMDS, MeI, THF/DMPU (10 : 1), −78 °C to 0 °C, 1.5 h, 98%; (h) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 0 °C, 15 min, 86%; (i) Ph_3P, *para*-nitrobenzoic acid, DEAD, toluene, 15 h; (j) MeOH, Et_2O, aq. sat. K_2CO_3, rt, 2 h, 85% (2 steps); (k) CH_2Cl_2/TFA/H_2O (2 : 1 : 0.1), rt, 10 min, 85%; (l) DIPEA, MOMCl, NaI, THF, 65 °C, 4.5 h, 98% of **13**; (m) PivCl, DMAP, pyridine, rt, 4 days, 78% of **14**; (n) TBSCl, imidazole, DMF, rt, 18 h, 92% of **15**; (o) synthesis of **16a**: **13**, TBAF, THF, rt, 2 h, 95%; synthesis of **16b**: **14**, HF–pyridine, THF, rt, 24 h, 71%; synthesis of **16c**: **15**, 10% NaOH–MeOH, reflux, 6.5 h, 72%; (p) synthesis of **17a** and **17b**: EDC–HCl, DMAP, cyclohexane carboxylic acid, CH_2Cl_2, rt; for **17a**: 92% yield; for **17b**: 95% yield; synthesis of **17c**: (i) EDC–HCl, DMAP, cyclohexane carboxylic acid, CH_2Cl_2, rt, 20 h, 79%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 66%; (q) KHMDS, TMSCl, toluene, −78 °C to rt to 85 °C: for **18a**: 89% yield, de = 76%; for **18b**: 90% yield, de = 94%; for **18c**: 100% yield, de = 100%.

Treatment of **17a–c** with KHMDS and TMSCl in toluene yielded rearrangement products **18a–c** in 89% to quantitative yield and with de-values ranging from 76% to 100%. nOe experiments revealed that the configuration of the newly formed stereocenter matches the stereochemistry of the target natural product scaffold. The facial selectivity is strongly determined by the size of the protecting group (Scheme 2). With the small MOM group the lowest selectivity was observed, and the bulky TBS ether gave only one diastereomer.

Analysis of the ^{1}H-NMR spectrum of silyl-protected **17c** revealed that the coupling constant for H11 and H12 (toonacilide numbering, see Fig. 1) is 7.2 Hz whereas $J_{H12/H13}$ = 3.8 Hz. These values indicate that **17c** adopts a conformation with the two bulky OTBS groups in the *pseudo*-equatorial position (Fig. 2a). The OTBS group at C14 accordingly adopts a

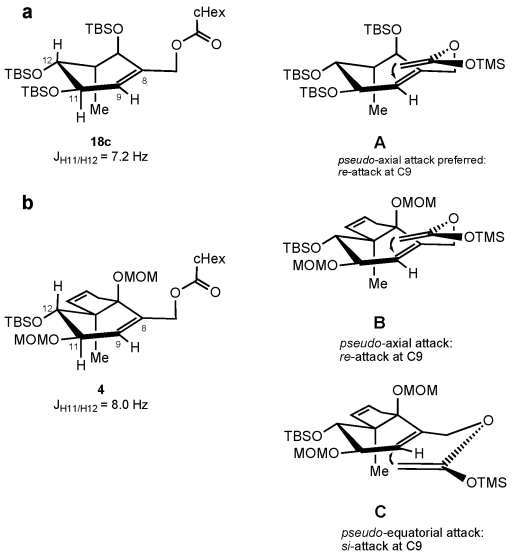
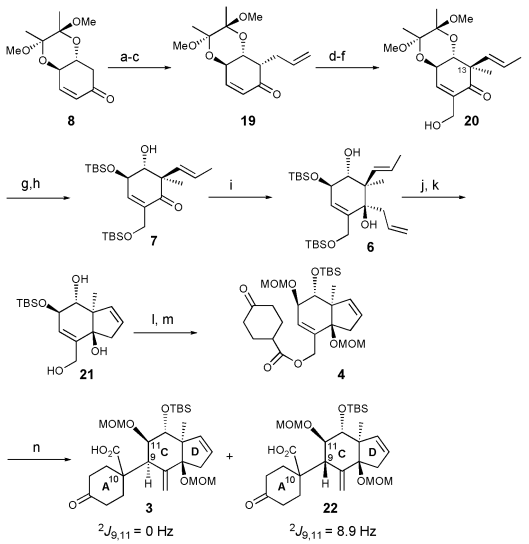


Fig. 2 Conformations of rearrangement precursors **17c** and **4** and possible transition states involved in the Ireland–Claisen rearrangements. In (a) and (b) the cyclohexyl rings are left out for clarity of presentation.

pseudo-axial orientation which minimizes allylic $A^{1,2}$-strain. Ireland and Varney previously demonstrated that in analogous rearrangements of cyclohexenyl acetates axial attack is strongly preferred over equatorial formation of the new C–C-bond.[12] By analogy in the rearrangement of model compounds **17** transition state **A** (Fig. 2) may be preferably passed in which the silyl ketene acetal (the cyclohexyl ring is omitted for clarity) attacks the double bond in the cyclohexene ring from the *pseudo*-axial direction. Most likely increasing steric demand of the protecting groups at C11, C12 and C14 increasingly locks the cyclohexene in the conformation shown in Fig. 2.

For synthesis of the analogous bicyclic rearrangement precursor **4** (Scheme 3) enone **8** was converted to the silyl enol ether, brominated with NBS, and subsequently converted to α-allylated product **19** using allyltributyltin and AIBN.[10a] For construction of the quaternary centre at C13 again substrate control was exploited, and the potassium enolate of **19** was trapped with MeI to furnish the desired product as a single diastereomer. Isomerization of the terminal double bond with cat. $PdCl_2(CH_3CN)_2$ and subsequent Baylis–Hillman reaction yielded compound **20**. For the stereoselective establishment of the second quaternary center we intended to employ an unprotected alcohol in the β-position, *i.e.* at C12 as a stereo-directing group. For selective masking the butane–2,3-diacetal was cleaved under acidic conditions and both the primary and the allylic hydroxy groups were selectively protected as TBS–ethers to give alcohol **7**.

For the stereoselective 1,2-allylation various reagents (*e.g.* allyl boronates, -stannanes and -silanes, allyl-indium, -magnesium, -cerium and -zinc reagents) and conditions were investigated. The best result was obtained with tetraallyltin and BuLi at −78 °C in THF. Under these conditions a 1 : 2 mixture of diastereomers was obtained. The stereochemistry was unambiguously confirmed by crystal structure analysis of a derivative of the major diastereomer (see the ESI†). In this



Scheme 3 Synthesis and Ireland–Claisen rearrangement of bicyclic allyl ester precursor **4**. *Reagents and conditions*: (a) LiHMDS, TMSCl, THF, −78 °C to 0 °C, 45 min; (b) NBS, THF, 0 °C, 30 min, 68% (2 steps); (c) allyltributyltin, AIBN, toluene, 80 °C, 18 h, 81%, de = 80%; (d) KHMDS, THF, 30 min −78 °C, then MeI, 30 min rt, 74%, de = 100%; (e) $PdCl_2(CH_3CN)_2$, toluene, 65 °C, 2 days, 70% (81% brsm); (f) paraformaldehyde, imidazole, THF/1 M $NaHCO_3$ (2 : 1), rt, 19 h, 74%; (g) TFA/H_2O (3 : 1), rt, 30 min, 84%; (h) TBSCl, imidazole, DMF, rt, 18 h, 94%; (i) tetraallyltin, BuLi, THF, −78 °C to rt, 30 min, 72%, dr = *ca.* 2 : 1; (j) Grubbs I, CH_2Cl_2, rt, 18 h; (k) HF–pyridine, THF, 0 °C to rt, 20 h, 99%; (l) EDC–HCl, 4-oxocyclohexyl carboxylic acid, DMAP, CH_2Cl_2, rt, 16 h, 80%; (m) DIPEA, MOMCl, NaI, THF, 50 °C, 16 h, 62%; (n) LiHMDS, supernatant of a centrifuged mixture of TMSCl/NEt_3 (v/v = 1/1) and toluene, toluene, −78 °C to 65 °C in 6 h, 60 h at 65 °C, 88% yield, dr = 1 : 2 (**3** : **22**).

case the preference for axial attack predominates over the stereo-directing influence of the β-hydroxy group.

Ring closing metathesis and subsequent selective deprotection of the primary silyl ether successfully delivered bicyclic triol **21**. Esterification and protection of the remaining hydroxy groups as MOM–ethers, which was accompanied by silyl migration, gave rise to rearrangement precursor **4**.

For rearrangement of allyl ester **4** variation of the reaction conditions was necessary. The Ireland–Claisen rearrangement proceeds successfully upon gradual warming of the reaction mixture from −78 °C to 65 °C over a period of 6 h. Also it was crucial to employ the supernatant of a centrifuged mixture of TMSCl, NEt_3 and toluene instead of the unactivated TMSCl for formation of both the required intermediate silyl ketene acetal and the silyl enol ether of the cyclohexanone. Under these conditions the Ireland–Claisen rearrangement proceeded smoothly to give a 1 : 2 mixture of isomers **3** and **22** in 88% combined yield. The configuration of the diastereomers was assigned based on the coupling constants recorded for the protons at C9 and C11 and nOe signal enhancements (Scheme 3).

In contrast to the high face-selectivity in the synthesis of model systems **18a–c**, the rearrangement to bicyclic products **3** and **22** proceeds with low diastereoselectivity and with preference for the undesired stereoisomer at C9 which must be formed by means of *pseudo*-equatorial attack (Fig. 2b).

We assume that bicyclic intermediate **4** is conformationally more rigid than cyclization precursors **17**, such that transition states **B** and **C** can compete without preference for a conformation that clearly favours axial attack.[13] The synthetic strategy described here should facilitate the total synthesis of natural products with B-*seco* limonoid scaffold and analogues thereof and fuel investigations aimed at unraveling the molecular basis for their manifold biological activity.

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