Silicon-tethered Radical Cyclization and Intramolecular Diels–Alder Strategies are combined to provide a Ready Route to Highly Functionalized Decalins

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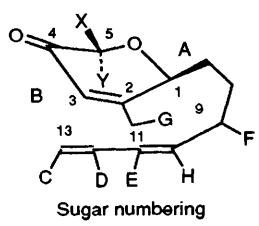
Stereoselective addition of carbon branches at C(1) and C(2) of L-rhamnal is achieved *via* silicon-mediated radical procedures, and the product is readily processed to give a hex-2-enopyranosid-4-ulose whose intramolecular Diels–Alder reaction has been examined.

Diels–Alder[1] and radical cyclization[2] processes have been used in our laboratory, and in others,[3] as key reactions in carbohydrate-to-carbocycle transformations.[4] Recently, we introduced structure **1** as a synthon for the A/B ring system of densely functionalized terpenoids, and illustrated its applicability by preparation of a key intermediate for forskolin.[5] In that study a β-D precursor (*e.g.* **1a**) was used and in view of the encouraging success, a shorter route for its preparation was desirable. In this manuscript, we report that such an alternative route can be readily realized, based upon the application of radical cyclization processes, and we further report on results of its intramolecular Diels–Alder (IMDA) reaction.

Comparison of synthon **1** with a normal hexose indicates the need for a substituent at C(2), which is destined to become the angular, frequently functionalized C(10)-methyl group of the terpenoid.[6] Synthon **1** has two chiral centres; however, that at C(5) is lost during processing of the product **2**.[5] On the other hand, that at C(1) controls transition-state selectivity in the IMDA, and it is preserved thereafter at C(1) of the terpenoid, which is frequently a stereogenic centre. From these considerations it is only the *S* chirality at C(1) of synthon **1** that is crucial, and this is found in *C*-glycosides of β-D (*e.g.* **1a**, as used previously)[5] or α-L (*e.g.* **1b**) configurations.



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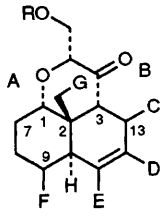
a; X = CH_2R, Y = H β-D
b; X = H, Y = CH_2R α-L



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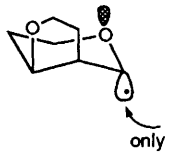
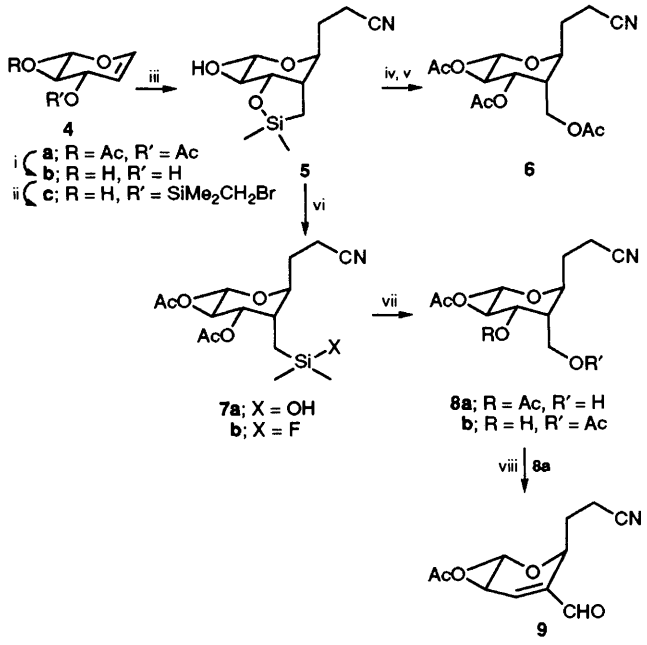


3

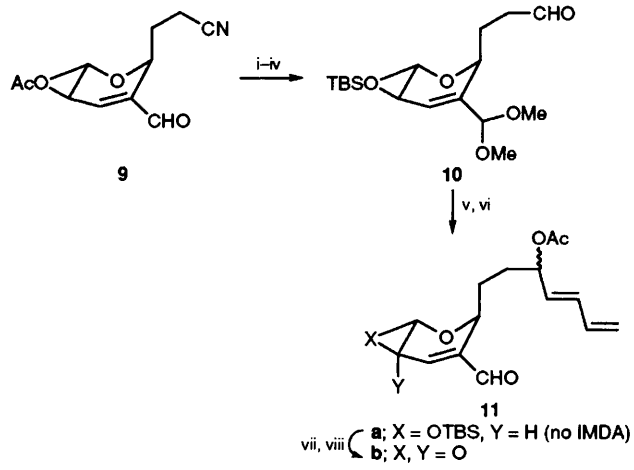
The need for carbon branches at C(1) and C(2) suggested that our recently developed strategy for serial radical reactions on glycals[7] could be the method of choice. Thus, the bicyclic serial intermediate, such as **3**, combines the well-documented anomeric effect[8,9] of a C(1) radical with a strong stereochemical bias, that makes the process of carbon–carbon bond formation at C(1) completely stereoselective. These considerations led to the choice of commercially available L-rhamnal diacetate **4a** as a starting material for the α-L synthon **1b**.

Horton and coworkers[10] have shown that silylation of rhamnal **4b**[11] occurs preferentially at O(3) and conditions developed by us afforded compound **4c** with complete regioselectivity. Radical cyclization of silylmethylene ether[12] **4c** under Stork's conditions[13] in the presence of an excess of acrylonitrile, followed by oxidative workup as described by Tamao,[14] and subsequent acetylation gave the triacetate **6**.

With this ready procedure for installing the C(1) and C(2) carbon branches, the next task was to introduce the C(2)–C(3) unsaturation. If the C(2) substituent had been a formyl group, β-elimination would be facilitated based on an excellent precedent developed by Perlin.[15] Such a possibility required differentiation of the hydroxy groups of **6** and a procedure for achieving this took advantage of intermediate **5**. Thus, it was found that reaction with potassium fluoride in the presence of acetic anhydride led to a 9:1 mixture of the silanol and corresponding fluoride, **7a** and **7b**, respectively.[16] The extensive work of Tamao *et al.* has shown that the presence of a single heteroatom is sufficient for C-silicon oxidative cleavage,[17] and indeed treatment of the mixture with *meta*-



Scheme 1 *Reagents and conditions*: i, $Ba(OH)_2 \cdot 8H_2O$, MeOH, 15 °C, 16 h, 89%; ii, 1.05 equiv. of $ClSiMe_2CH_2Br$, CH_2Cl_2–Et_3N (10:1), −20 °C, 1 h; iii, 0.1 equiv. of Bu_3SnCl, 2 equiv. of $NaBH_3CN$, 0.1 equiv. of AIBN, 5 equiv. of acrylonitrile, Bu^{t}OH, reflux, 18 h; iv, 10 equiv. of H_2O_2, 2 equiv. of $KHCO_3$, 4 equiv. of KF, THF–MeOH (1:1), reflux, 12 h; v, an excess of Ac_2O, pyridine, room temp., 8 h, 51% from **4b**; vi, an excess of Ac_2O, 3 equiv. of KF, pyridine, room temp., 16 h; vii, 3 equiv. of MCPBA, 3 equiv. of KF, DMF, room temp., 16 h; viii, 6 equiv. of SO_3/pyridine complex, DMSO–Et_3N (4:1), room temp., 1 h, 27% from **4b**. [AIBN = 2,2'-azobis(isobutyronitrile); MCPBA = *m*-chloroperbenzoic acid; DMF = *N*,*N*-dimethylformamide.]



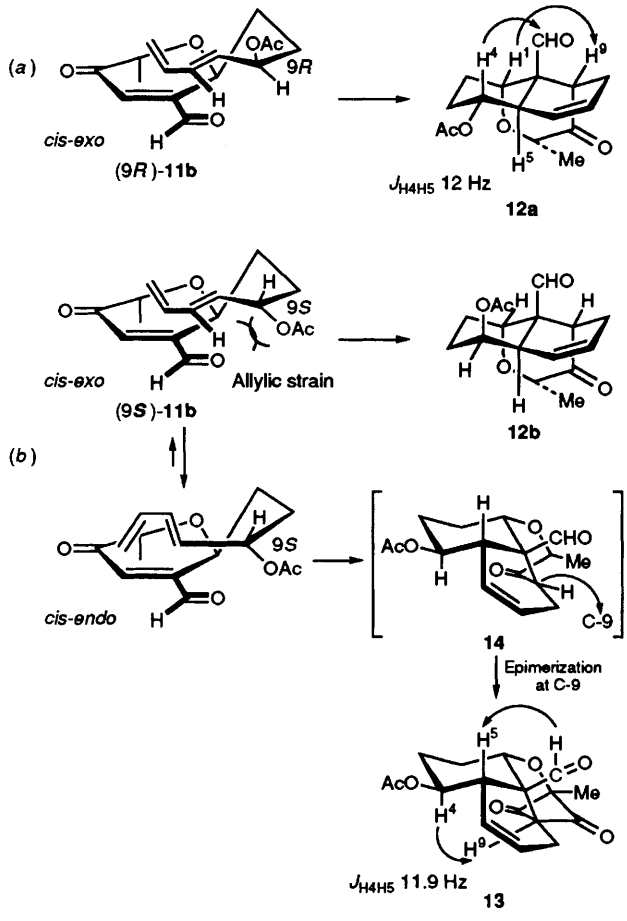
Scheme 2 *Reagents and conditions*: i, trimethyl orthoformate (10 equiv.), Amberlyst-15, room temp., 3 h, 92%; ii, an excess of Na_2CO_3, MeOH, room temp., 8 h, 94%; iii, Bu^{t}Me$_2$SiCl (1.3 equiv.), imidazole (1.5 equiv.), DMF, room temp., 8 h, 75%; iv, DIBAL-H (1.5 equiv.), CH_2Cl_2, −40 °C, 15 min. then, AcOH–H_2O (1:1), −40 to 0 °C, 10 min, 84%; v, butadienyllithium (3 equiv.), THF, −78 °C, 30 min then Ac_2O (10 equiv.), DMAP (2 equiv.), 0 °C, 1 h, 70%; vi, silica gel containing 10% H_2O, 0.2 equiv. of oxalic acid, CH_2Cl_2, room temp., 5 h, 83%; vii, HF/pyridine complex–THF–pyridine (1:4:2), 0 °C to room temp., 18 h, 89%; viii, 1.3 equiv. of oxalyl chloride, 1.5 equiv. of DMSO, CH_2Cl_2, −78 °C, 20 min, then NEt_3 (3 equiv.), −78 °C to room temp., 1 h, 92%. (DIBAL-H = diisobutylaluminium hydride, THF = tetrahydrofuran, DMAP = 4-*N*,*N*-dimethylaminopyridine).

chloroperbenzoic acid in the presence of potassium fluoride[18] led to the diacetate **8a** with only traces of the acetyl migration product **8b**.† Oxidation as prescribed by Perlin *et al.*[15] then afforded enal **9** in 75% yield.

It is to be noted that the sequence requires only one chromatographic fractionation, and that the procedure can be operated on a multi-gram scale giving **9** with a 27% overall yield.‡

In order to introduce the diene moiety, the formyl group was protected as a dimethyl acetal, the C(4) acetyl was replaced by silyl, and the nitrile was reduced to give aldehyde **10**. Treatment with 1-butadienyllithium[19] followed by acetylation led to a 1:1 mixture of epimers, and then the acetal was cleaved by treatment with oxalic acid in methylene chloride over wet silica gel[20] to give **11a**.

Attempts to carry out an IMDA on this enal, **11a**, were unsuccessful. Better luck was had with the doubly activated dienophile **11b** which, upon refluxing in xylene for four days, gave a 1.5:1:0.7 mixture of **12a**, **12b** and **13** (84% yield), the structures of which were readily assigned on the basis of the coupling constants and NOE (nuclear Overhauser effect) experiments shown in Scheme 3. These products all result from 'top side' (*i.e.* α-L) facial approach this being dictated by the geometric restrictions of the IMDA transition state.[21] *Exo* is the only mode of addition observed for the 9*R* (sugar



Scheme 3

† The acetyl migration product, **8b**, becomes the main reaction product when the oxidative cleavage is carried out with H_2O_2 in the presence of potassium fluoride.

‡ On a typical run **4b** (10 g), led after chromatography to **4a** (6.5 g, 39.5% recovered, TLC R_f 0.8 light petroleum : ethyl acetate 4:1) and a mixture of **7a**,**b** (R_f 0.3) that is then processed to **9** (3 g, 27% yield based on recovered starting material).

numbering) isomer of **11b** (Scheme 3a) and leads to **12a**. On the other hand, the 9*S* isomer of **11b** gives rise to **12b** and **13**. We suggest that compound **12b** arises from an expected *cis-exo* mode of addition, and that relief of allylic 1,3-strain[22] (as in Scheme 3b) favours the *cis-endo* adduct **14**,[23] that subsequently epimerizes at C(9)[24] (terpenoid numbering) to give **13**.

A concise method that combines serial radical cyclization on glycals with IMDA processes and which allows expeditious entry to decaline systems present in terpenoids has been developed. Oxygenated functions have been incorporated at key sites in the skeleton. The oxygenated substituent at C(4) (terpenoid numbering) provides a handle for further functionalization at this centre, as well as providing the means for equilibration to a *trans*-decalin *via* a 4-oxo derivative.

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