Carbohydrate based IMDA/aldol strategy towards the densely functionalized *trans*-decalin subunit of azadirachtin

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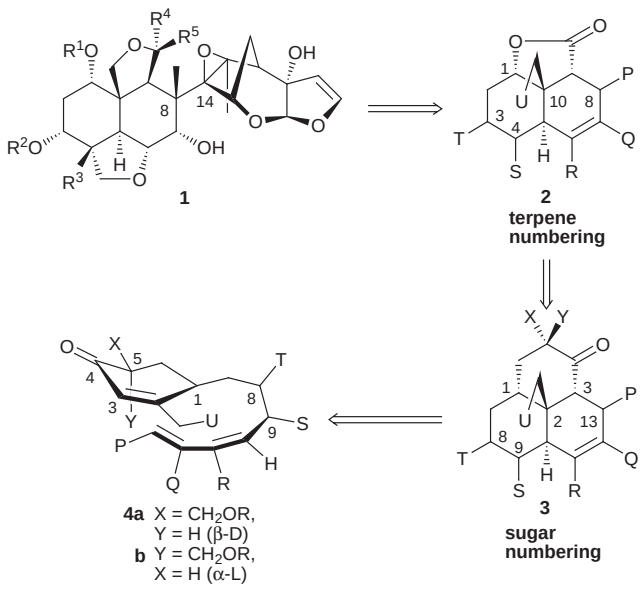
L-Rhamnal is converted into an hex-2-en-4-ulo *C*-glycopyranoside in which properly configured diastereomeric centers, asymmetric as well as geometric, are developed in the pendant anomeric substitutent *via* a Claisen aldol addition, and the resulting product proceeds *via* an IMDA reaction to provide a highly functionalised terpene AB ring system.

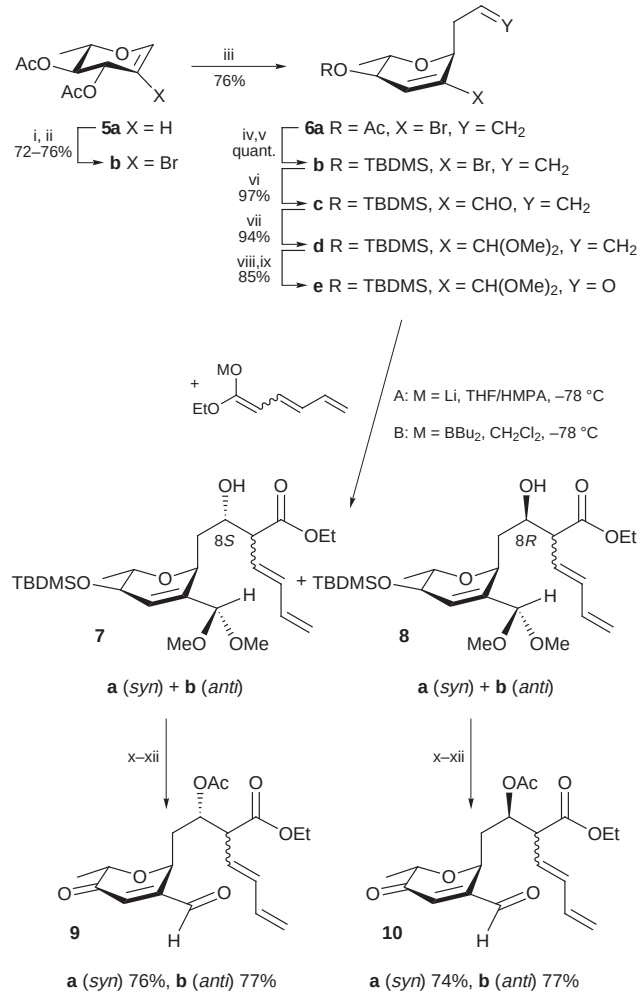
The development of synthetic routes from carbohydrates to densely functionalized carbocycles has been a sustained area of interest in our research group.[1,2] The intramolecular Diels–Alder (IMDA) strategy depicted in Scheme 1[3,4] takes advantage of the preferred β-D-face approach in reactions of pyranosidic 2-ene-4-ones. The desired (*S*)-configuration exists in β-D- and α-L-derivatives, but either may be used since the sugar's C5 stereocenter, whereby D or L is designated, does not survive in the advanced retron **2**. Thus a regioselective Baeyer–Villiger oxidation of **3** permits its ready removal. This simplifying retroanalysis also makes provisions for an array of functional groups such as is found in the clerodane family of terpenes,[5] exemplified by the 'western half' of the azadirachtins **1**.[6] An IMDA approach, based on **4** with appropriate synthons at P, Q, R, S, T and U, for this family of potent pharmacologically active compounds,[7] is therefore desirable.[8]

Dibromination of diacetyl L-rhamnal **5a**, followed by dehydrobromination, gave the 2-bromo glycal **5b** in 72–76% yield (Scheme 2). Danishefsky's version[9] of the Ferrier rearrangement[10] gave a 76% yield of α-L-*C*-glycoside **6a** (along with 19% of the corresponding β-anomer). The acetyl group was replaced by TBDMS and a THF solution of the latter was mixed with 5 equiv. of DMF, and then 6 equiv. of Bu^{t}Li were added slowly (*ca*. 2 h) at −78 °C to furnish, after aqueous work-up, enal **6c** in almost quantitative yield.



Scheme 1

The *trans*-decalin subunit of azadirachtin **1**, as well as of related terpenoids, invariably possesses hydroxy and carbon substituents at C3 and C4 respectively,[6] positions that correlate with C8 and C9 of the sugar IMDA precursor. These functionalities could conceivably be furnished by an aldol reaction. Accordingly, the aldehyde group of **6c** was first protected by acetalization. Cleavage of the terminal double bond *via* OsO_4 induced dihydroxylation followed by periodate cleavage in two discrete steps, but not in the one-pot Lemieux–Johnson protocol,[11] gave aldehyde **6e** in 85% yield.



Scheme 2 *Reagents and conditions*: i, Br_2, CH_2Cl_2; ii, A: one-pot, DBU, 76% + 14% of **5a**, or B: work-up, then DBN, toluene–DMSO, 72% + 4% of **5a**; iii, allyltrimethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to room temp.; iv, NaOMe, MeOH; v, NaH, TBDMSCl, THF; vi, THF, DMF (5.0 equiv.), −78 °C, then Bu^{t}Li (6.0 equiv.); vii, CSA, $Me_2C(OMe)_2$, reflux; viii, NMO, 1% OsO_4, THF–H_2O; ix, $NaIO_4$, THF–H_2O; x, Ac_2O, Py, cat. DMAP, CH_2Cl_2, 0 °C to room temp.; xi, HF·Py, THF, room temp.; xii, PCC, SiO_2, CH_2Cl_2, room temp.

Our next task was to elaborate the anomeric *C*-substituent into the required dienic tether. A Claisen-type aldol addition with ethyl sorbate seemed an ideal approach. Indeed that an 8-hydroxy-9-ethoxycarbonyl addition product had formed was apparent from NMR examination of the crude material. Separation of the four diastereomeric aldol adducts was achieved by (repeated) flash chromatography, and *syn*- and *anti*-configuration were easily distinguished on basis of the coupling constant between the protons attached to C8 and C9 (*syn*: ^3J ~ 5.0 Hz, *anti*: ^3J ~ 9.0 Hz). However, the absolute configuration at C8 and C9 was assigned in retrospect upon isolation of IMDA products **11**–**14** (Table1).

For proof-of-concept, the major component (assigned in retrospect as **7a**, *vide infra*) was acetylated and treatment of the crude material with HF–pyridine in THF for one day at ambient temperature effected desilylation as well as cleavage of the rather acid-sensitive dimethyl acetal. Final activation was accomplished by oxidation with PCC on silica gel to furnish the corresponding aldehyde enone **9a** in 76% yield for the whole four-step sequence. Heating of **5a** in toluene at reflux for 30 h afforded a 23% yield of **11**, the structure being confirmed independently by NMR (Table 1) and X-ray analyses.

Conceivably, the efficiency of the IMDA step, as well as the correct C3 configuration in the resultant product, could both be ensured by fine-tuning the preparative procedures. Thus under conditions A (Scheme 2) variations in the equivalents of enolate, and the duration of the reaction revealed that rapid equilibration was occuring at −78 °C (Table 2). Our studies also showed (*a*) that compounds **7a**+**b**, having the undesired (8*S*)-configuration, were kinetically favored, and (*b*) that the *syn*:*anti* ratios were generally poor. We therefore examined the *syn*-selective protocol of Evans[12] (conditions B) on **6e**, and were rewarded with a 61% yield of **8a**+**b** in an 11:1 ratio.

Steric factors on the tether can substantially affect the course of IMDA reactions.[4,13] We were therefore pleased to see, from the formation of **13** and **14** (Table 1), that the required (*R*)-configuration at C8 of precursors **10a**+**b** presents no obstacle to the success of the IMDA reaction. Conceptually, either configuration at C9 is acceptable in view of the future quaternization at C4 of compounds **13** and **14**. Furthermore, the results in Table 1 suggest that selective formation of the IMDA products may be possible by judicious choice of temperature and duration of the reaction. The bulk of the C8-hydroxy protecting group might also have a salutary effect.

These and other refinements for this IMDA/aldol approach to compounds such as **1** are underway.

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Table 1 Influence of the configuration of C8 and C9 in the dienic tether on the course of the IMDA reaction (E = CO_2Et)

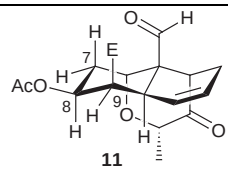
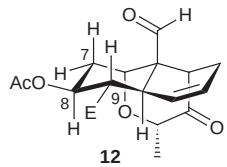
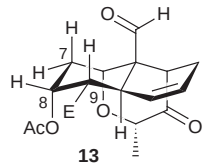
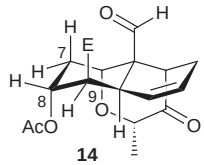
IMDA precursor	Conditions	Yield	Product	^3J/Hz
9a	toluene reflux, 30 h	23%	 **11**	7,8: 12.4 7',8: 5.0 8,9: 6.0 9,10: 5.6
9b	benzene reflux, 5 h	85%	 **12**	7,8: 11.5 7',8: 4.7 8,9: 10.6 9,10: 12.6
10a	toluene reflux, 18 h	70%	 **13**	7,8: 2.9 7',8: 3.8 8,9: 3.6 9,10: 12.6
10b	xylenes reflux, 24 h	44%	 **14**	7,8: 3.2 7',8: 3.8 8,9: 3.1 9,10: 2.6

Table 2 Diastereomeric product distribution in the aldol addition of **9b**

Method	Enolate/ equiv.	*t*/min	Yield (%) **7a**	**7b**	**8a**	**8b**	**7**:**8**	Yield of **6e** (%)
A	2.0	2	29	26	12	12	2.3:1	15
A	2.0	20	24	27	17	11	1.8:1	15
A	2.0	60	24	27	18	11	1.8:1	13
A	4.0	2	35	28	14	13	2.3:1	6
B	2.5	300	29	6	58	5	1:1.8	—

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