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Synthesis and Stereochemical Confirmation of the Secoiridoid Glucosides Nudiflosides D and A

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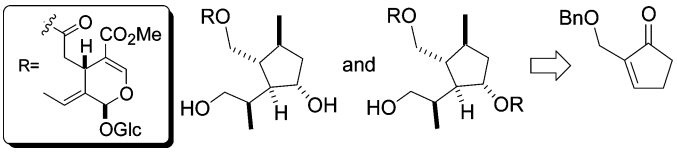
ABSTRACT



We describe herein an efficient access to the highly substituted cyclopentane unit present in the Nudifloside secoiridoid family via crotyl phosphonamide anion mediated conjugate addition to cyclopentenone.

The leaves and stems of *Jasminium nudiflorum* LINDL belonging to the Oleaceae genus are a rich source of oleoside-type secoiridoid glucosides containing tetrasubstituted cyclopentanoid monoterpene units. Leaf extracts from this plant have been used as remedies for inflammation and traumatic bleeding in China for years.

Extensive studies by Tanahashi and co-workers[1] have resulted in the isolation of several isomeric new iridoid glucosides containing essentially the same branched cyclopentane triols. Two representative examples named Nudiflosides D and A (**1** and **2**, respectively, Figure 1), were recently reported and their structures proposed, based on chemical correlation and NMR spectroscopic methods.

In this Letter, we describe the first stereocontrolled total synthesis of the common tetrasubstituted cyclopentane aglycon, and its conversion to the natural nudiflosides D and A (**1** and **2**), thereby confirming their structural identities and stereochemical assignment.

The main challenge in the elaboration of the substituted cyclopentane unit was the stereochemical control of four contiguous core stereogenic centers and an additional one

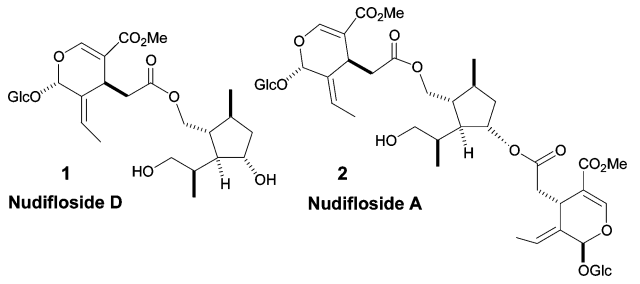


Figure 1. Proposed structures for Nudiflosides D and A[1].

in the branched hydroxyethyl side chain. Extensive studies of conjugate addition with C_2-symmetrical chiral nonracemic alkylphosphonamides in our laboratory have shown that allyl and crotyl reagents add to cyclic enones, lactones, and lactams, as well as to acyclic enoates with high diastereoselectivity.[2] Sequential alkylation of the resulting enolates in situ leads to the respective carbonyl compounds harboring two or three contiguous stereogenic carbons with excellent diastereoselectivities. The strategic sequence of three bond-

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forming reactions in the case of the cyclopentane subunit of **1** and **2** is shown in Figure 2.

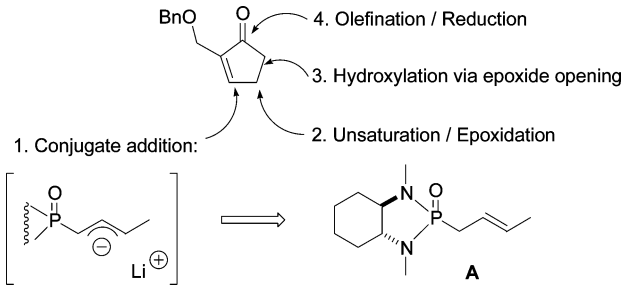
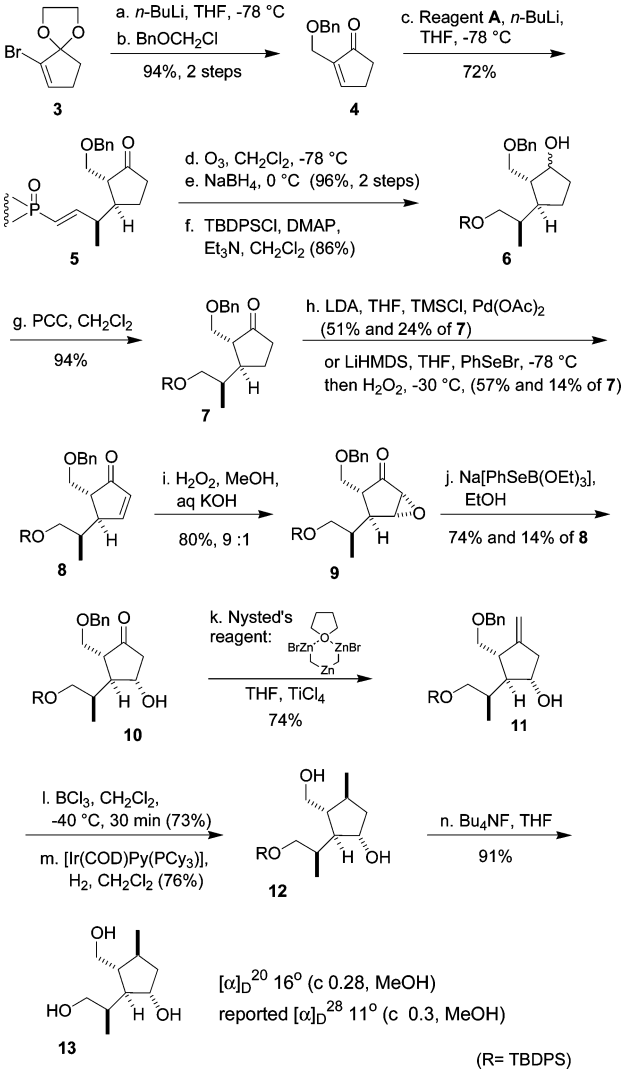


Figure 2. Strategic bond-forming sequence.

Starting with the *O*-protected 2-(hydroxymethyl)cyclopentenone, conjugate addition would be done with the crotyl phosphonamide reagent A, to introduce the side chain and concomitant stereocenters, followed by a stereocontrolled introduction of an epoxide, regiocontrolled reductive opening, and an olefination−reduction of the corresponding exo-methylene product. The success of this strategy would depend in large measure on the stereochemical outcome on the initial conjugate addition whereby three contiguous stereogenic centers could be secured in one step.

The ketal **3** readily available from cyclopentenone in two steps[3] was metalated with *n*-BuLi and the resulting lithio intermediate was treated with benzyloxymethyl chloride (BOMCl) in THF containing 2 equiv of HMPA at −78 °C to give the benzyl ether **4** in 94% yield. Addition of **4** to the lithium anion of the crotyl phosphonamide reagent A easily prepared from *N*,*N*′-dimethyl-1,2-diaminocyclohexane at −78 °C in THF[2] gave a single adduct **5** in 72% yield on a 1 g scale. Yields were slightly lower on a 5 g scale. Ozonolysis of the double bond, reduction of the resulting aldehyde with $NaBH_4$, and protection of the alcohol as the TBDPS ether gave **6** in high overall yield. Since it was not possible to chemoselectively reduce the aldehyde in the presence of the ketone, the mixture of alcohols was oxidized with PCC and the regenerated ketone **7** was converted to the enone **8** by using two methods.Thus, treatment of **7** with LDA/TMSCl followed by addition of $Pd(OAc)_2$ as described elsewhere[4] gave **8** in 51% yield with recovery of starting ketone **7** (24%). Alternatively, formation of α-phenylseleno ketone and oxidative elimination in the presence of hydrogen peroxide furnished **8** in 57% yield with recovery of starting ketone **7** (14%). Epoxidation of **8** in the presence of basic hydrogen peroxide afforded the desired epoxide **9** as the major isomer in addition to the diastereoisomeric epoxide (9:1) in a combined 80% yield. Evidently the spatial disposition of the

Scheme 1



vicinal substituents favored the desired **9**, albeit not with complete selectivity. Treatment of **9** with $Na[PhSeB(OEt)_3]$[5] in ethanol led to a regioselective reductive opening to afford **10** in 74% yield with recovery of **8** (14%). Treatment with samarium iodide was much less effective, affording a poor yield of **10** and recovery of **9**. The next step involved transformation of the hydroxy ketone **10** to the corresponding exo-methylene analogue, which was performed with Nysted's reagent[6] affording **11** in 74% yield. The last stereochemical hurdle en route to the intended cyclopentane subunit was to secure a stereocontrolled reduction of the exo-methylene group. Preliminary studies with a variety of catalysts (Pd/C or $Pd(OH)_2$/C in the presence of hydrogen, nickel chloride in the presence of $NaBH_4$, *p*-tosylhydrazine in xylene) afforded mixtures of isomers. We anticipated that a free hydroxymethyl group would provide a beneficial directing effect by prior coordination to a catalyst. Treatment of **11**

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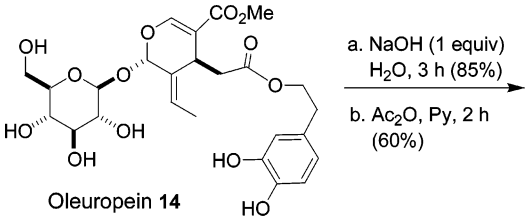
(6) (a) Matsubara, S.; Sugishara, M.; Utimoto, K. *Synlett* **1998**, 313. (b) Nysted, L. N. U.S. Patent 3865848, 1975; *Chem. Abstr.* **1975**, *83*, 10406q.

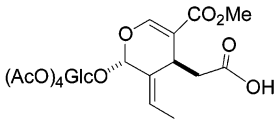
with BCl_3 in CH_2Cl_2 at −40 °C effected smooth debenzylation without affecting the robust TBDPS ether. Reduction in the presence of *p*-tosylhydrazine or hydrazine in the presence of hydrogen peroxide and copper sulfate gave a 1:1 mixture of epimeric *C*-methyl products. However, in the presence of the Crabtree catalyst[3] reduction took place to afford **12** as a single isomer in 74% yield. Removal of the TBDPS group with BuN_4F in THF proceeded uneventfully to give the cyclopentane triol **13**. Comparison of ^1H and ^{13}C NMR data indicated the structural identity of synthetic material and a sample obtained by hydrolysis of Nudifloside A.[1b] Stereochemical confirmation was also secured from optical rotation data, $[\alpha]^{28}_D$ +16 (*c* 0.28, MeOH), reported $[\alpha]^{20}_D$ +11 (*c* 0.3, MeOH).[1b]

Oleuropein **14**, readily available from commercial extracts of olive oil, proved to be an excellent source of the oleoside subunit[8] (Scheme 2). Treatment of **14** with 1 equiv of NaOH, followed by acetylation afforded the oleoside monomethyl ester peracetate **15** in good overall yield. Depending on the number of equivalents used, **15** was activated as the mixed anhydride according to Yamaguchi,[9] followed by treatment with **12,** to give the protected precursors to the intended targets. Sequential removal of the TBDPS group with Bu_4NF and the acetates with Et_2NH gave Nudiflosides D and A, respectively (Scheme 3).

Scheme 2



Oleuropein **14**



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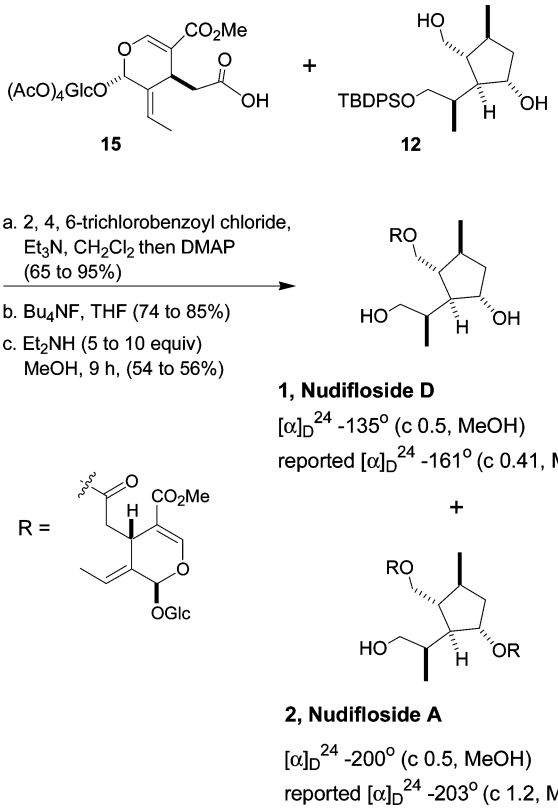
Scheme 3



In conclusion, we have developed a practical and stereocontrolled synthesis of the highly substituted cyclopentane ring present in the iridoids nudiflosides D and A, and confirmed their absolute stereochemical identities. A noteworthy feature of the synthesis is the utilization of a crotyl phosphonamide anion mediated conjugate addition to a cyclopentenone, thus creating three contiguous stereogenic centers in one step of which one resides on the side chain.

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Supporting Information Available: Full experimental procedures, compound characterizations, and selected ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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