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A New and Extremely Efficient, General Strategy for the Synthesis of Enantiomerically Pure Iridoid Aglycones

José Marco-Contelles* and Juliana Ruiz

Instituto de Química Orgánica General (CSIC), Juan de la Cierva, 3. 28006-Madrid (Spain)

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Abstract.- A new and efficient approach for the synthesis of chiral iridoid aglycones is described.
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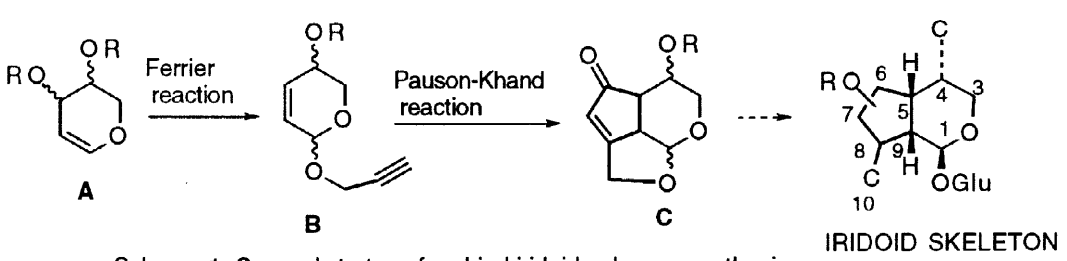
The iridoids are a large family of natural products which are characterized by a highly oxygenated, fused cyclopenta[c]pyran ring skeleton (*cis*-2-oxabicyclo[4.3.0]nonane).[1] Most naturally occurring iridoids have a β-non-reducing link to a sugar (D-glucose) at C-1 and a double bond at C-3/C-4. Certain iridoids are key intermediates in the biosynthesis of many of the important families of plant derived alkaloids,[2] possess interesting biological activities ranging from sedative to antimicrobial to antileukemic effects[1] or, as specionin, have shown potent antifeedant activity for some common insect pests.[3]

Most past synthesis have relied on the oxidative cleavage of bicyclooctenes,[4] enol [2+2] cycloaddition/retroaldol cleavage[5] or the Norrish I cleavage of norbornanones.[6] More recently, Curran has shown that a combination of the Claisen rearrangement plus nitrile oxide cycloaddition sequence has allowed a rapid annulation of a cyclopentane ring into a simple glycal derived from D-xylose.[7] Finally, Miwa and coworkers have described the synthesis of loganin derivatives by a very efficient free radical approach for cyclopentane annulation on sugar derivatives.[8] Such methods have proved to be very general, although not without limitations, and a true general strategy is still lacking.

In this communication we report a new and extremely efficient, general strategy for the synthesis of chiral iridoid aglycones. The present approach takes adavantage of our recently discovered Pauson-Khand[9] reaction on sugar pyranoside templates. We[10] and others[11] have shown that the Pauson-Khand reaction of conveniently functionalized 1,6-enynes in carbohydrate templates is an excellent method for the rapid and highly stereoselective synthesis of annulated sugars. Based on these grounds, the key elements of our new synthetic strategy for the synthesis of iridoid aglycones are shown in Scheme 1. Chiral intermediates **B**, as the α or β anomers, are readily available from D-xylal or L-arabinal[12] starting materials (**A**). Ferrier reaction[13] on L-arabinal derivatives gives major β-anomers.[14] Subsequent Pauson-Khand reaction should proceed from the same face where the *O*-glycosyl branch is linked at C-1, affording the cyclopentannulated intermediate **C**. This is a highly functionalized material with the suitable stereochemistry and functionality for further developments directed towards the synthesis of natural iridoid aglycones.



Scheme 1. General strategy for chiral iridoid aglycone synthesis

This simple route has been implemented as shown in Scheme 2. Starting form 3,4-di-*O*-acetyl-L-arabinal (**1**),[12b] and according to Koreeda's version[15] of the Ferrier reaction, with propargyl alcohol, we obtained a mixture of α and β anomers **2**[16] in 1:2.2 ratio, in 70% yield, that we could easily separate by flash chromatography. The β anomer was identified as the major isomer following previous reports on this reaction

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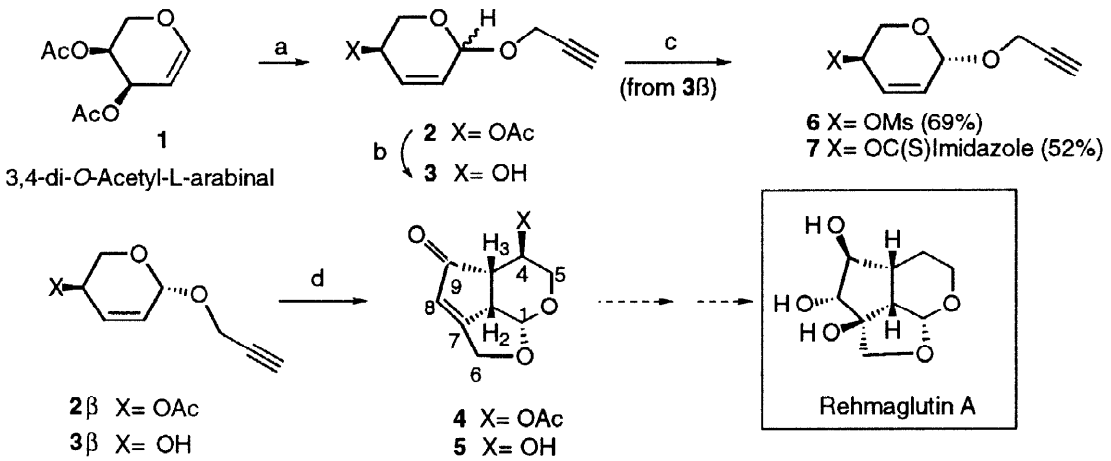
with this substrate.[14] Very gratifyingly, the "one-pot-two-steps" Pauson-Khand reaction of **2β**, under chemical activation,[17] afforded product **4**[16] in 40% yield. Reaction of **2β** with octacarbonyldicobalt afforded the corresponding cobalt-complex in 89% yield. Thermal reaction of this complex resulted in decomposition and product **4** could not be isolated. Similar trends were observed for precursor **3β**,[16] obtained from acetate **2** after deacetylation and separation. In this case, the adduct **5**[16] was obtained from major isomer **3β** in 35% yield, after chemical activation of the intermediate, not-isolated cobalt-complex. Very interestingly, mesylate **6**[16] or thiocarbonylimidazole **7**,[16] in the same conditions, only gave decomposition products.

Note that compounds **4** and **5** are *nor*-iridoid aglycones with the correct absolute configuration at C-5 and C-9, as shown in the iridoid skeleton (Scheme 1); more exactly, the absolute configuration at C-1 is also the same as in rehmaglutin A (Scheme 2), a natural iridoid.[18] In addition, these intermediates have suitable and appropriate functionality for further transformation into this and related molecules.



Scheme 2. Reagents: a) Propargyl alcohol, I_2, THF; b) MeOH, Et_3N, H_2O; c) ClMs, Et_3N, CH_2Cl_2; d) 1.$Co_2(CO)_8$, CH_2Cl_2; 2. NMO, 0 °C.

In summary, a simple and efficient approach has been described for the synthesis of iridoid aglycones. This work is now in progress and will be reported in due course.

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16. All new compounds showed excellent analytical and spectroscopic data. Selected spectroscopic data. **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (br s, 1 H, H-8), 5.50 (d, *J*= 5.4 Hz, 1 H, H-1), 4.83 (m, 1 H, H-4), 4.78 and 4.73 (d, d, AB system, *J*= 15.3 Hz, 2 H-6), 3.67 (dd, *J*= 12.2 and 2.7 Hz, 1 H, H-5), 3.58 (dd, *J*= 12.2 and 5.4 Hz, 1 H, H-5'), 3.40 (m, 1 H, H-2), 3.02 (dd, *J*= 7.0 3.6 Hz, 1 H, H-3), 2.15 (s, 3 H, $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.4 (C-9), 181.0 (C-7), 169.8 ($OCOCH_3$), 125.1 (C-8), 96.5 (C-1), 66.7 (C-4), 65.8 (C-6), 62.1 (C-5), 49.6 (C-2), 46.9 (C-3), 21.0 ($OCOCH_3$) (sugar numbering).
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