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Direct and Indirect Radical Denitrations of Intermediates in the Synthesis of Sorgolactone and Its Nuclear Analogs+

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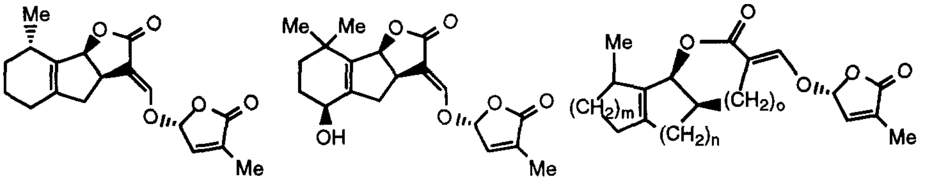
Abstract: Denitration of various important intermediates in the synthesis of sorgolactone and its analogs using radical chemistry on nitroketones or on the derived isocyanides is described. The nitro group is needed for the first step of the annellation process, the Michael addition of substituted nitroalkanes to cyclopentenones. Then it can be removed directly or after reduction to the amine or *via* the ketone obtained by the Nef-reaction.

Sorgolactone[1,2] **1**, a compound closely related in structure and activity to strigol[3,4] **2** was discovered recently. In bioactivity tests[1,2] this terpenoid dilactone shows a powerful germination stimulating activity in subhormonal concentrations on various African parasitic plants. These plants cause serious damage in various crop cultures. As part of our ongoing program related to the synthesis of natural products we decided to synthesize **1** and certain nuclear analogs **3** (**Scheme 1**).



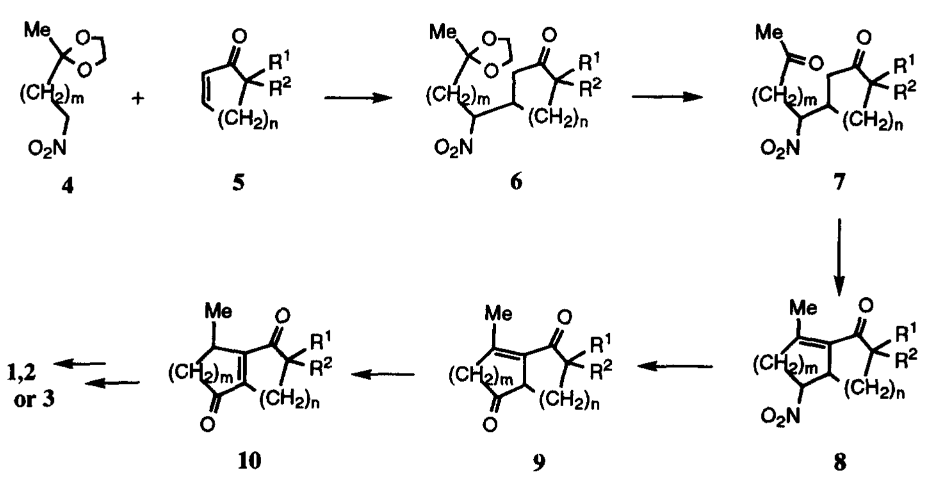
1 **2** **3**

Scheme 1

The plan for the synthesis of sorgolactone and similar compounds was related to our synthetic schemes developed for the total synthesis of strigol and its nuclear analogs.[5,6] There are only a limited number of attempts[7] known from the literature for developing syntheses with the aim of sorgolactone.

The key step in our synthesis for strigol and various analogs is the annellation of suitably protected nitroketones **4** to substituted cycloalkenones **5** (**Scheme 2**). The substituted cycloalkanones **6** thus obtained could be denitrated at this stage or transformed further to remove the ketal functionality that furnishes diketone **7**. This compound again could be denitrated or cyclized to the bicyclic ketone **8**. This is the point in our synthetic scheme where it can be carried toward either the sorgolactone (denitration, **8** to **11**) or strigol (Nef-reaction, **8** to **9**) series. At final stages the two series can be joined by the Barton-McCombie radical deoxygenation reaction.[8]

------- +Dedicated with respect, sincere appreciation and gratitude to Sir Derek H. R. Barton, FRS, Dow Distinguished Professor of Chemical Invention.



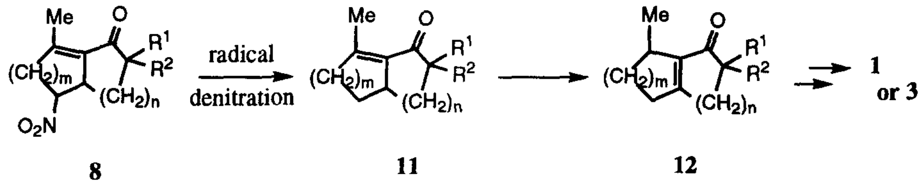
$R^1 = R^2 = H, CO_2R, (CH_2)_yCH_2CO_2R$ R = Me, Et; m,n = 1,2; y = 0, 1

In: **a**: m = 2, n = 1, $R^1 = R^2 = H$; **b**: m = n = 2, $R^1 = R^2 = H$ **c**: m = n = 2, $R^1 = CO_2Et$ $R^2 = CH_2$-CO_2Et

d: m = 2, n = 1, $R^1 = CO_2Me$, $R^2 = CH_2$-CO_2Et (throughout).

Scheme 2

Denitration of certain secondary or tertiary organic nitro compounds plays an important role in several synthetic schemes.[9] In these cases the nitro group acts only as an activator in the carbon-carbon bond forming reaction step and it is removed afterwards.[9,10] We envisioned that in our synthetic sequence instead of the Nef reaction that affords ketone **9** a radical denitration of intermediate **8** would provide suitable intermediates of type **11** for sorgolactone **1** (**Scheme 3**).



$R^1 = R^2 = H, CO_2R, (CH_2)_yCH_2CO_2R$ R = Me, Et; m,n = 1,2; y = 0, 1

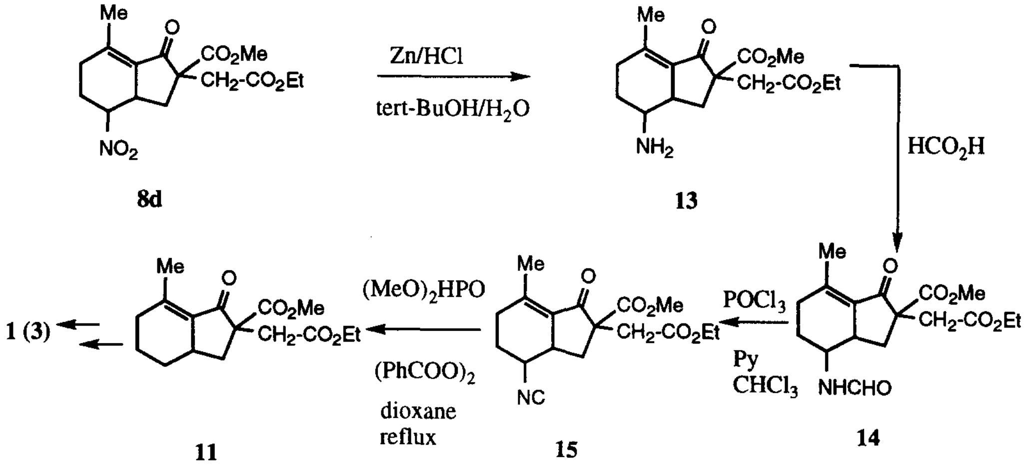
Scheme 3

Indeed, application of the Ono[11,12] method for the radical denitration of our bicyclic nitro compounds **8a-c** afforded bicyclic ketones **11a-c**. However, as expected, the tin hydride method suffered the known drawbacks of the radical denitration of secondary nitro compounds. Even the best versions (5 equivalents of tributyltin hydride, 1 equivalent of radical initiator, boiling toluene under nitrogen or argon)[9,10] furnished the corresponding denitrated compounds **11** in only 60-88% yields. Nonetheless, these yields still allowed the continuation of the planned synthesis toward sorgolactone analogs **3**.

The 6+5 annellated bicyclic nitro compound **8d**, however, resisted repeated attempts of tin hydride mediated denitration to **11**. In each run the nitro compound was recovered unchanged. It is noteworthy that this somewhat anomalous behaviour was more or less characteristic also in the case of the open A-chain congener **6d** that furnished the corresponding denitrated product in a yield of only about 30%. This was much less than the yields of the tin hydride mediated radical denitration reaction of related compounds in the series **6**. Molecular models for both **8d** and **6d** and their corresponding tributyltin adducts show that this finding cannot be related to steric hindrance caused by the cyclopentanone ring or its substituents.

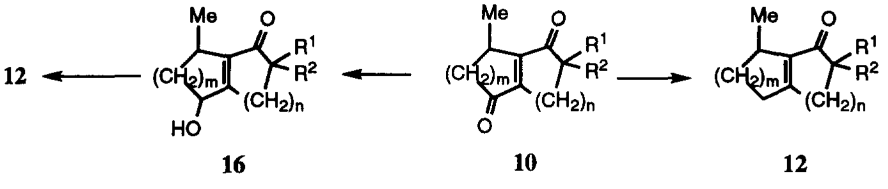
Alternatives of the direct denitration could be the transformation of the nitro group into either an amino or a hydroxyl functional group. The feasibility of such an approach would depend on the combined yield of the steps involved. Fortunately, most of the steps in the attempted 'denitration *via* deamination' process could be combined into a 'one-pot' procedure reducing potential losses. This could make the use of nitro compounds for carbon-carbon bond formation *ipso facto*, more attractive even in those cases when the subsequent direct removal of the nitro group by the tributyltin hydride based radical method from a secondary carbon would not be an advantageous process.

In order to test this assumption nitro ketone **8d** was reduced to the corresponding amine **13** (90% crude yield) with zinc and hydrochloric acid in tert-butanol/water.[13] After work-up but without isolation this amine was converted into a formamide **14**. The latter was then transformed[14] into isonitrile **15**. The isonitrile was deaminated by the method of Barton, Jang and Jaszberenyi[15,16] with dimethyl phosphite in a radical chain reaction initiated with benzoyl peroxide (**Scheme 4**). The unsubstituted ('denitrated') bicyclic ketone **11** thus obtained was identical in every respect to the compound obtained by us earlier *via* an independent synthetic sequence. Unfortunately, the combined yields (starting from the amine) need improvement.



Scheme 4

Another alternative could be the selective reduction of diketone **10** to the monohydroxy derivative **16** or directly to the corresponding monoketone **12**. The appropriate monohydroxy compound could then be deoxygenated (**Scheme 5**) by the Barton-McCombie reaction[8] or similar radical deoxygenations of more recent origin with silicon[17] or phosphorus compounds.[15,16,18]



$R^1 = R^2 = H, CO_2R, (CH_2)_yCH_2CO_2R \quad R = Me, Et; m,n = 1,2; y = 0, 1$

Scheme 5

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