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Six-Membered Annulation Reaction by Sequential η^3-Allylpalladium Alkylation-Michael Addition

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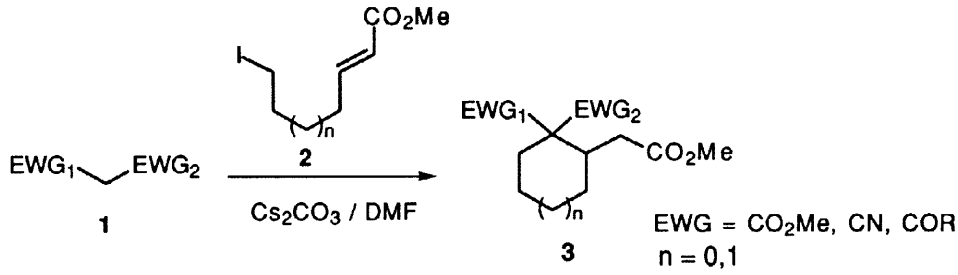
Abstract: Palladium catalyzed condensation of bisfunctional electrophile **16**, with 1,3 dione **17** or arylnitromethane derivative **7**, led to adducts **18** and **20** respectively, through a sequential process involving η^3-allylpalladium alkylation-Michael addition. Nitro ester **20** constitutes useful potential precursor for the synthesis of *Erythrina* alkaloids. © 1998 Elsevier Science Ltd. All rights reserved.

Sequential processes are very expeditious ways to construct highly functionalized polycyclic systems in only a few steps.[1] They are characterized by their great elegance, and by the simple manner in which they may be carried out. Moreover, the development of this type of synthetic method can lead to a reduction in the amount of solvents, eluents and undesired by-products, thereby contributing to the protection of the environment. Some time ago we reported a versatile annulation reaction base on a *tandem* alkylation-Michael addition exemplified in Scheme 1. Condensation of methyl 7-iodo-2-heptenoate **2** (n = 1) with a methylene active compound **1**, using cesium carbonate as base, afforded six membered annulated derivatives **3** (n = 1)[2] in good yields. This method was extended to prepare cyclopentannulated derivatives with the corresponding methyl 6-iodo-2-hexenoate **2** (n = 0) as starting material.[3] From a mechanistic point of view, we have established that most nucleophiles with pKa between 10 and 16 are potential substrates of this process, involving alkylation of the initially formed anion, followed by an additional deprotonation, and ring forming reaction through an intramolecular Michael addition (Scheme 1).[2]



Scheme 1

Although the sequential process has proven valuable for a number of substrates, we faced several limitations during our attempts to extend the scope of this reaction. For instance, cyclic 1,3-diketones did not afford annulated products because *O*-alkylation became the main pathway. Similar failure was found with

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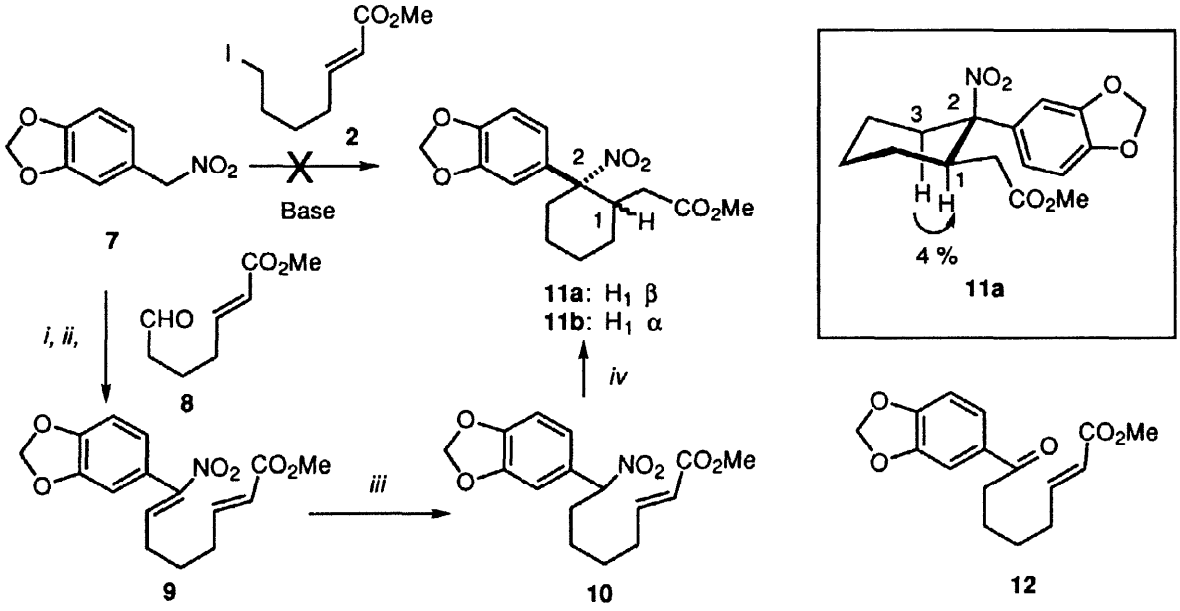
arylnitromethane **7**, a potentially useful substrate for the synthesis of alkaloids, due to the reluctance of such derivatives to give *C*-alkylated products.[5] In the latter case the involvement of the alkylation step in the failure of the tandem process was clearly established, since the base treatment of nitro derivative **10**, in which the crucial C-C bond is already established, afforded uneventfully the annulated products **11**. Thus, compound **10** was prepared by a three step-sequence involving first a nitroaldol condensation between arylnitromethane **7** and the known aldehyde **8**[6] (basic alumina[7], 20 °C, 12 h), followed by dehydratation according to the Seebach procedure[8] (DCC, CuCl, Et_2O, 25 °C, 48 h, 65 % overall yield from **7**), and finally chemoselective reduction of the double bond of nitro olefin **9** ($NaBH_3CN$[9], AcOH, 1 h, 88 % yield). Upon treatment with Cs_2CO_3, which had been successfully used in our earlier alkylation-Michael addition sequences,[2,4] nitro ester **10** did not cyclize. However, treatment of **10** with DBU[10] gave adduct **11a** in a modest 45 % yield, along with ketone **12**. The formation of the latter product was due to a competitive oxidation of the nitronate anion by oxygen, which could be minimized under carefully degassed conditions.[11] Replacement of DBU by *n*-Bu_4NF[12] (THF, 20 °C, 8 h) gave adducts **11a**[13] and **11b**[14] with 67 % yield, as a 1:1 mixture of isomers, in a more reproducible way. Relative stereochemistries of adducts were unambiguously determined by NOE experiments on isomer **11a**, revealing a 4 % enhancement at axial proton H-3 when H-1 was irradiated. The stereochemical outcome of the key Michael addition has been demonstrated to result from a kinetic control, since separated isomers were recovered unchanged when exposed to the reaction conditions (Scheme 2).

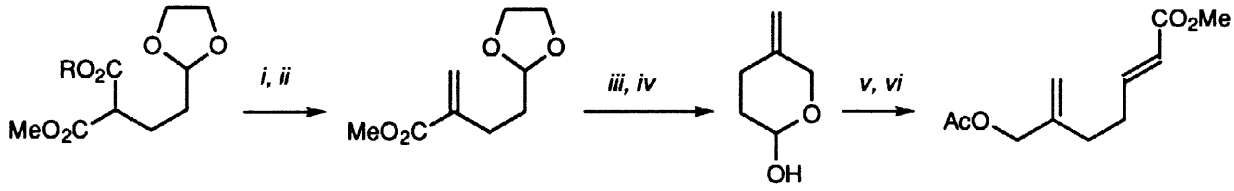


i: Al_2O_3, 20 °C, 12 h; *ii*: DCC, CuCl, Et_2O, 25 °C, 48 h; *iii*: $NaBH_3CN$, MeOH, AcOH; *iv*: n-Bu_4NF, THF, 20 °C.

Scheme 2

From a synthetic point of view, the failure of the domino process was highly frustrating, forcing us to a lengthy five step-sequence to obtain cyclized products. Assuming that the limiting step of our sequential annulation was the alkylation, we thought that replacing the SN_2 process by a η^3-allylpalladium complex alkylation might restore the carbocyclization reaction, since arylnitronate anions have been reported to react with π-allylpalladium derivatives to give *C*-alkylated products.[15] To test this idea, we prepared the unsaturated ester **16**, as bis-electrophilic partner, whose allylic acetate moiety should give rise to a η^3-allylpalladium with two

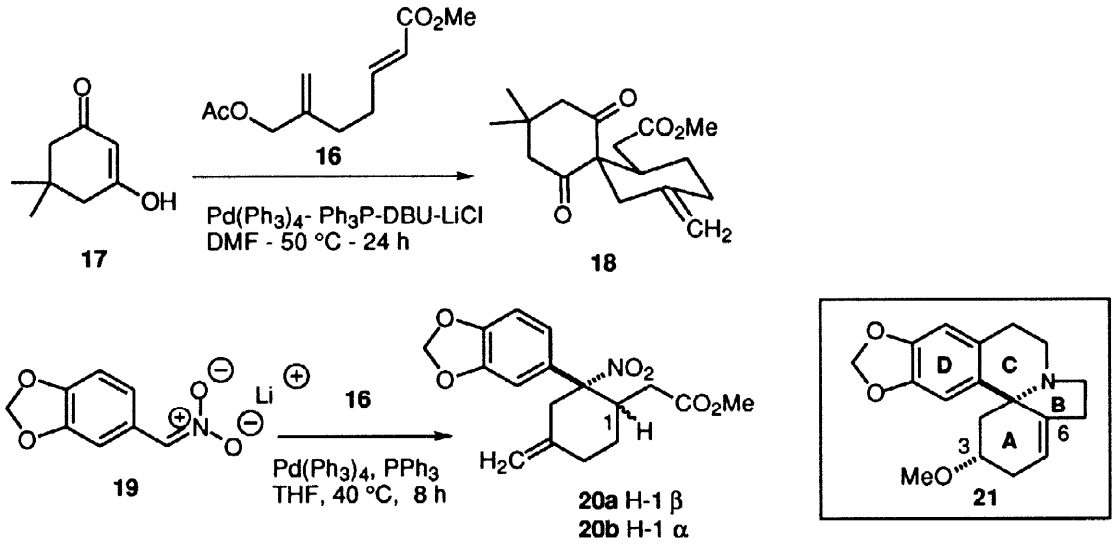
equivalent *C*-termini. Accordingly, the Michael adduct of dimethyl malonate and acrolein was protected as dioxolane and monosaponified as described by Vig.[16] The resulting acid **13b** was subjected to decarboxylative Mannich reaction affording unsaturated ester **14** in 90 % yield. DIBAL reduction,[17] followed by hydrolysis of the ketal protecting group gave the hemiketal **15** which was directly converted to the desired diester **16** by Wittig olefination and acetylation (Scheme 3).



i: NaOH, MeOH, 20 °C; *ii*: H_2CO, Et_2NH, DMSO, 80 °C; *iii*: DIBAL, CH_2Cl_2, -78 °C; *iv*: 2*N* HCl, THF, 20 °C ; *v*: $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 20 °C, 8 h ; *vi*: Ac_2O, DMAP, Et_3N, CH_2Cl_2, 20 °C.

Scheme 3

With the necessary bisfunctional electrophile in hand, we tested the crucial annulation reaction. Indeed, treatment of a mixture of dimedone **17** and diester **16**, in presence of a catalytic amount of palladium (0) with Cs_2CO_3 as base (3 eq Cs_2CO_3, 3 % $Pd(PPh_3)_4$, 12 % PPh_3, DMF, 50 °C, 24 h) gave spiroketone **18**,[18] but in a small 12 % yield, along with uncyclized products. However, changing to a mixture of DBU and LiCl[19] increased the yield to 48 %. Similar treatment of lithium nitronate **19**, gave in a one-pot reaction nitro esters **20a**[20] and **20b** in a *ca.* 2:1 mixture of diastereomers in 57 % yield. The stereochemistry of the major isomer **20a** bearing the acetate appendage *anti* to the aromatic nucleus, was established by NOE experiment, as in the case of adduct **11a** (Scheme 4).



Scheme 4

Nitro esters of type **20** seem suitable intermediates for the synthesis of *Erythrina* alkaloids, exemplified by erythramine **21**. Indeed, reduction of the nitro group should give rise to an amino group whose cyclization on

the ester group should close the five-membered B ring. Since, the C-6 center is usually a sp_2 carbon in most naturally occurring *Erythrina* alkaloids, both isomers of adduct **20** might be used for this transformation. The requisite C-3 methoxy group should easily be derived from the exocyclic double bond. Completion of this synthetic scheme is under investigation in our group.

In summary this study revealed that a sequential process involving η^3-allylpalladium alkylation-Michael addition provides a new route to obtain annulated derivatives from relatively acidic nucleophiles.

References and notes

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13. **11a**: white crystals, mp 90 °C; IR (film, cm^{-1}) 1732, 1540; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.81 (m, 3H), 5.92 (s, 2H), 3.58 (s, 3H), 2.75 (m, 1H), 2.49 (dd, *J* = 16.2, 9.0 Hz, 1H), 2,50 (m, 1H), 2.42 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.09 (m, 1H), 1.82-1.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.2 (C), 148.2 (C), 147.5 (C), 132.3 (C), 118.8 (CH_2), 108.2 (CH), 105.9 (CH), 101.3 (CH_2), 97.5(C), 51.5 (CH_3), 41.2 (CH), 36.8 (CH_2), 35.5 (CH_2), 27.9 (CH_2), 23.6 (CH_2), 22.5 (CH_2); Anal. Calcd. for $C_{16}H_{19}O_6N$: C, 59.80; H, 5.96; N, 4.35. Found: C, 59.62; H, 5.99; N, 4.26.
14. **11b**: white crystals, mp 115-116 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.99 (s, 1H), 6.98 (d, *J* = 9.5 Hz, 1H), 6.78 (d, *J* = 9.5 Hz, 1H), 5.97 (s, 2H), 3.61 (s, 3H), 2.97 (m, 1H), 2.35 (d, *J* = 12 Hz, 1H), 2.25 (d, *J* = 12 Hz, 1H), 2.00-1.80 (m, 2H), 1.60-1.20 (m, 6H).
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18. **18**: white crystals, mp 85 °C; IR (film, cm^{-1}) 1730, 1694, 1657; ^1H NMR ($CDCl_3$, 400 MHz, slow conformational exchange complicating the spectrum at 20 °C, it was recorded at 50 °C) δ 4.73 (s, 1H), 4.64 (s, 1H), 3.65 (s, 3H), 2.77-2.70 (m, 4H), 2.45 (dd, *J* = 15.1, 2.4 Hz, 1H), 2.43-2.31 (m, 2H), 2.27-2.23 (m, 2H), 2.12 (dd, *J* = 15.6, 2.9 Hz, 1H), 2.10-1.90 (m, 2H), 1.80 (m, 1H), 1.08 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.2 (C), 207.5 (C), 172.9 (C), 142.7 (C), 110.4 (CH_2), 70.1 (C), 51,7 (CH_2), 51.5 (CH_3), 50.7 (CH_2), 44.0 (CH_2), 36.0 (CH_2), 34.8 (CH), 32.8 (CH_2), 30.9 (C), 30.1 (CH_3), 28.2 (CH_2), 26.9 (CH_3); Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.68; H, 8.30.
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20. **20a**: colorless oil; IR (film, cm^{-1}) 1739, 1658, 1606, 1543; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.79-6.70 (m, 3H), 5.97 (s, 2H), 4.84 (m, 2H), 3.65 (s, 3H), 3.19 (d, *J* = 14.5, 1H), 2.98 (m, 1H), 2.86 (d, *J* = 14.5 Hz, 1H), 2.66 (dd, *J* = 17.0, 10.0 Hz, 1H), 2.48 (dd, *J* = 17.0, 2.3 Hz, 1H), 2.34 (dt, *J* = 14.2, 4.9 Hz, 1H), 2.20 (m, 1H), 1.85 (m, 1H), 1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5 (C), 148.7 (C), 148.1 (C), 141.8 (C), 131.8 (C), 119.2 (CH), 113.2 (CH_2), 108.4 (CH), 106.2 (C), 101.6 (CH_2), 98.4 (C), 51.8 (CH_3), 45.0 (CH_2), 41.4 (CH), 35.1 (CH_2), 32.4 (CH_2), 28.7 (CH_2).