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A New Synthesis of Rhein

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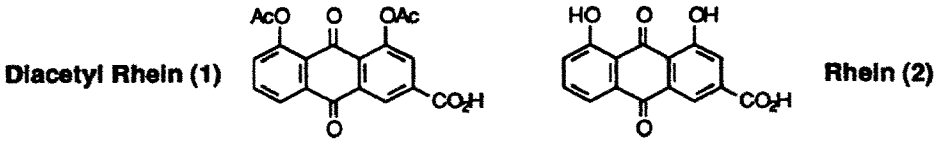
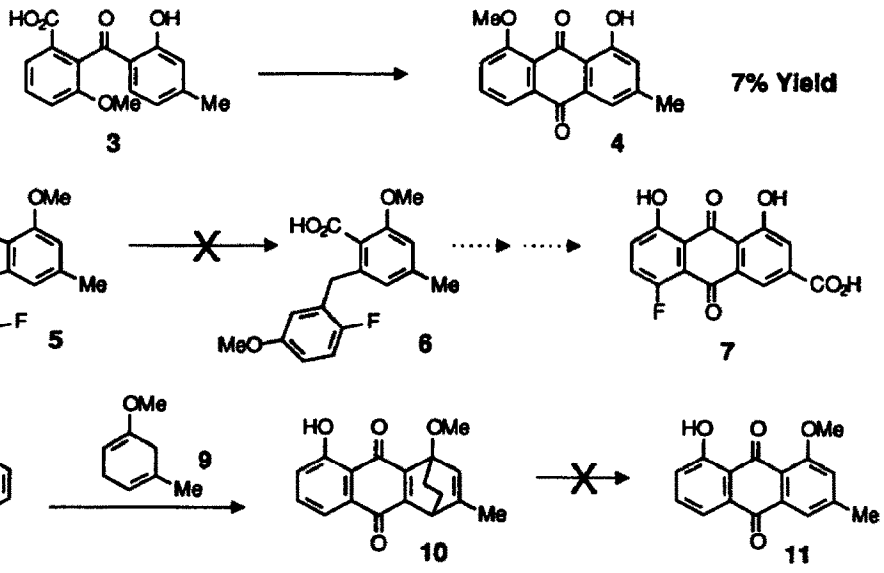
Abstract: A novel synthesis of Rhein (2), the active metabolite of the anti-osteoarthritic drug Diacetyl Rhein (1) has been achieved. Key steps include stereospecific olefination of aldehyde **21** with novel phosphonate **28** and the cyclisation of acid **31** to produce anthracene **32**.

The anthraquinone carboxylic acid Diacetyl Rhein (1) has been marketed for the treatment of osteoarthritis in Italy since 1986. The active metabolite of 1 is Rhein (2).[1a-d] However progress towards the development of newer analogues of 1 and 2 has been slow, due to the lack of facile syntheses.



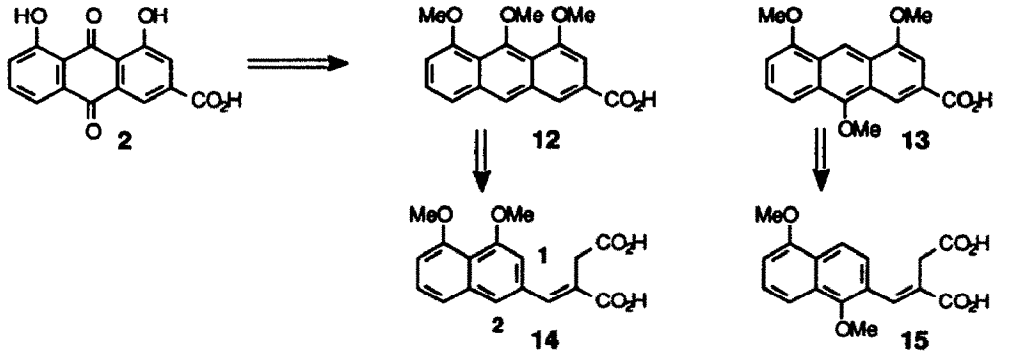
Several known approaches to 2 were tried, (Scheme 1) these included,[2a-c] the Bellaart synthesis, the general anthraquinone synthesis developed by Snieckus and a Diels-Alder route starting from Juglone (8). However we were unable to improve on the 7% yield of the cyclisation of 3 to 4 so this was not progressed.

Scheme 1



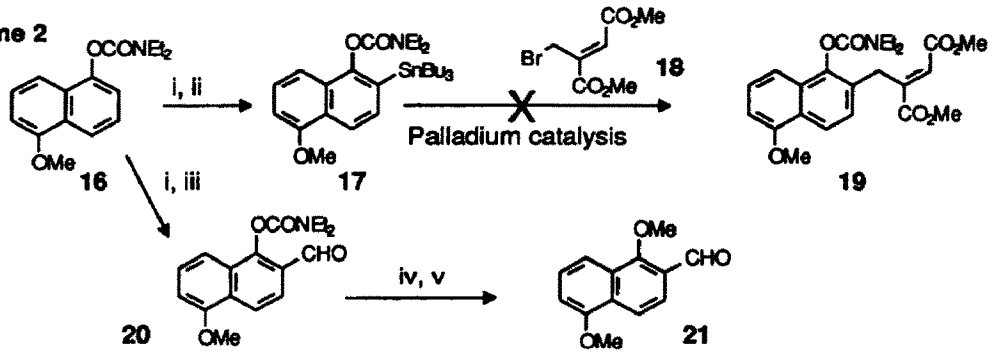
The Snieckus approach worked well for 4,5-dihydroxy-2-methylanthraquinone (Chrysophanol)[3]

but the presence of a fluorine substituent in **5** deleteriously affected a key reduction step in the production of **6**, thus preventing the synthesis of 8-fluororhein (**7**). The Diels-Alder route from **8** and 2-methoxy-4-methylcyclohexa-1,4-diene (**9**) was examined also, but after initial cycloaddition to give the benzoquinone (**10**), subsequent pyrolysis failed in our hands, to produce any **11**. Consequently because of these difficulties and the paucity of routes available to synthesise analogues of **2**, particularly with substituents in the 6,7 or 8 positions, we were prompted to consider new synthetic approaches to **2**.



Retrosynthetic analysis of **2** utilising the facile oxidation of 9-methoxyanthracenes to anthraquinones led to 2 potential intermediates, **12** and **13**. Further retrosynthetic analysis considering a ring disconnection on molecule **12**, revealed 2 possible sites for ring closure (1 & 2). Ring closure of **14** at position 1 would result in the formation of a utilisable anthracene, however if competing ring closure at position 2 was favoured then a phenanthrene would be formed. **13** was therefore selected as an intermediate target as only one position of the precursor naphthalene (**15**) was available for ring closure. With **15** identified, several attempts were made to synthesise a butenoic acid derivative (Scheme 2).

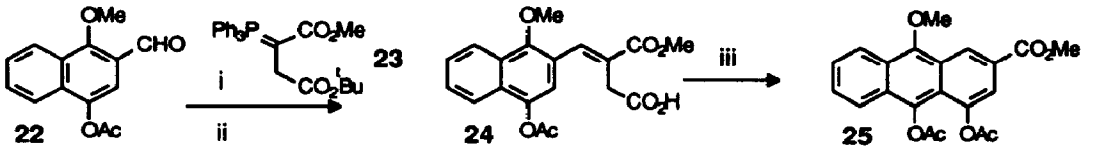
Scheme 2



i) s-BuLi, TMEDA, THF, ii) Bu_3SnCl, THF, iii) HCO_2Me, THF, iv) NaOH, H_2O
v) K_2CO_3, MeI, Acetone.

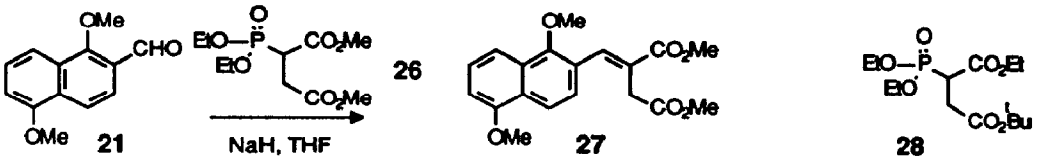
Starting from the readily available 1,5-dihydroxynaphthalene, bis-methylation of the phenols, followed by mono-deprotection[4] and carbamate formation provided carbamate (**16**) which was metallated and treated with tri-n-butyltin chloride.[5] The naphthyltin (**17**) was then subjected to palladium catalysed coupling reactions with diethyl 2-bromomethylfumarate (**18**) but a variety of

conditions failed to produce any coupled product (e.g. **19**). However when carbamate **16** was treated with *sec*-butyllithium and methyl formate, the naphthaldehyde (**20**) was produced; this aldehyde could be deprotected and re-methylated to give 1,5-dimethoxy-2-naphthaldehyde (**21**).



i) C_6H_6, 48h, 80C, ii) CF_3CO_2H, H_2O, (9:1), iii) KOAc, Ac_2O, 140C.

Examination of the literature for appropriate cyclisation strategies revealed that Stobbe condensation followed by ring closure of the resultant half acid ester could provide the necessary substitution pattern for Rhein.[6] However attempted Stobbe condensation with diethyl succinate produced double condensation and cinnamate by-products, so we next considered an approach such as Sargent's, who had converted **22** to **24** with stabilised ylide **23** and then converted **24** to **25** in 16 % yield.[7a-c]

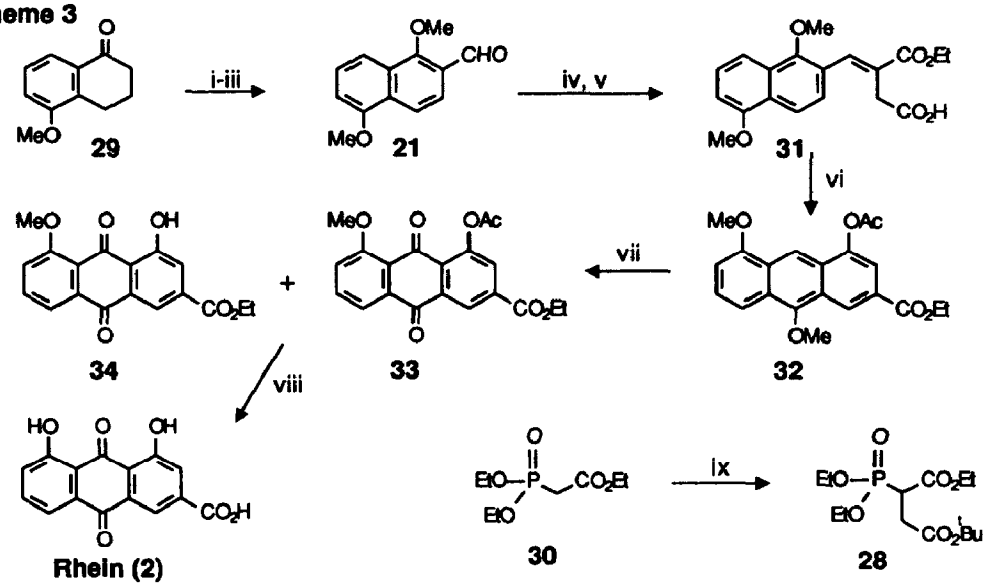


Sargent's findings prompted us to synthesise the known dimethyl diethylphosphonosuccinate (**26**)[8a,b] to react with aldehyde **21** under basic conditions. This produced methyl 3-carboxymethyl-4-(1,5-dimethoxynaphthalen-2-yl)but-3-enoate (**27**) in quantitative yield. At this point 2 intermediates were seen as key to the synthesis, the dimethoxyaldehyde **21** and the phosphonate **28**.

The synthesis of **21** in our hands was 6 steps but literature searching revealed that the 1-hydroxy-5-methoxy-2-naphthaldehyde was available in 2 steps from 5-methoxytetralone (**29**).[9,10] Methylation with iodomethane in acetonitrile (Scheme 3) containing potassium carbonate completed the synthesis of **21** in an overall yield of 82% from the commercially available tetralone.

The phosphonate **28** was synthesised by alkylation of triethyl phosphonoacetate (**30**) with *tert*-butyl bromoacetate under basic conditions in 64% yield.[11] Reaction of **28** in the presence of sodium hydride and THF with naphthaldehyde (**21**), followed by Sargent's conditions[7a-c] for selective deprotection of the *tert*-butyl ester function gave **31**[12] (38%, 2 steps), cyclisation of which with sodium acetate in acetic anhydride for 4h at 140°C provided the anthracene **32** in 85%.[13] The stereochemistry of the formed olefin was confirmed by n.O.e. experiments, on the acid-ester, to be the desired isomer. With the anthracene **32** in hand, oxidation with chromium trioxide in acetic acid[14] produced the anthraquinones **33** and **34** in a ratio of 11:9, partial cleavage of the acetate group occurring in the oxidation step. Finally 48% hydrobromic acid was used to demethylate and hydrolyse the ethyl esters and the remaining acetate of **33** to give Rhein (**2**)[15] (23%, 2 steps) in an overall yield of 6% from 5-methoxytetralone. This strategy has also been used for the synthesis of 8-fluororhein and this will be published shortly.

Scheme 3



i) NaH, THF, HCO_2Me, ii) DDQ, dioxan, iii) K_2CO_3, MeI, CH_3CN, iv) 28, NaH, THF, v) CF_3CO_2H, H_2O (9:1), vi) Ac_2O, NaOAc, 140C, 4h, vii) CrO_3, AcOH, viii) 48% HBr, ix) NaH, $BrCH_2CO_2{}^tBu$, THF.

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12 **31**, ^{1}H NMR ($(CD_3)_2SO$) δ 1.28 (t, 3H), 3.40 (s, 2H), 3.82 (s, 3H), 3.98 (s, 3H), 4.24 (q, 2H), 7.07 (d, 1H), 7.39 (d, 1H), 7.52 (dd, 1H), 7.67 (d, 1H), 7.95 (d, 1H), 7.96 (s, 1H). M^+ calculated 345.1338, M observed 354.1345, deviation +1.94ppm.

13 **32**, ^{1}H NMR ($CDCl_3$) δ 1.46 (t, 3H), 2.57 (s, 3H), 4.07 (s, 3H), 4.17 (s, 3H), 4.47 (q, 2H), 6.81 (d, 1H), 7.45 (d, 1H), 7.78 (d, 1H), 7.88 (d, 1H), 8.62 (s, 1H), 8.99 (d, 1H). M^+ calculated 369.1338, M observed 369.1368, deviation +8.1ppm.

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