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COMBINATION CLAISEN-NITRILE OXIDE ANNULATION. A STRATEGY FOR RING CONSTRUCTION WITH RIGID STEREOCONTROL DICTATED BY AN ALLYLIC HYDROXYL GROUP.

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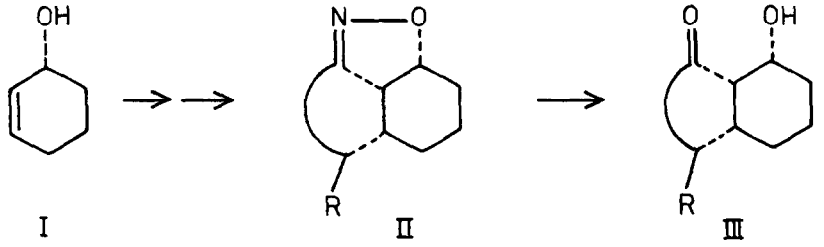
Summary: A new method for annulation of rings onto existing allylic alcohol derivatives is presented. The sequence involves Claisen rearrangement followed by nitrile oxide-olefin cycloaddition. Control of relevant stereochemistry is emphasized.

The utility of Δ^2-isoxazolines in organic synthesis has been greatly expanded by the development of a mild and general hydrogenolysis-hydrolysis procedure enabling the direct production of β-hydroxy ketones (cf. II → III).[2] We have emphasized the complementary nature of this cycloadditive strategy to the more traditional aldol approach and suggested that combination of this versatile cycloaddition-reduction sequence with other methods for carbon-carbon bond formation should provide useful annulation protocols.[2a,3] We now outline details of such an annulation method: the combination Claisen-nitrile oxide annulation.



I II III Eq. 1

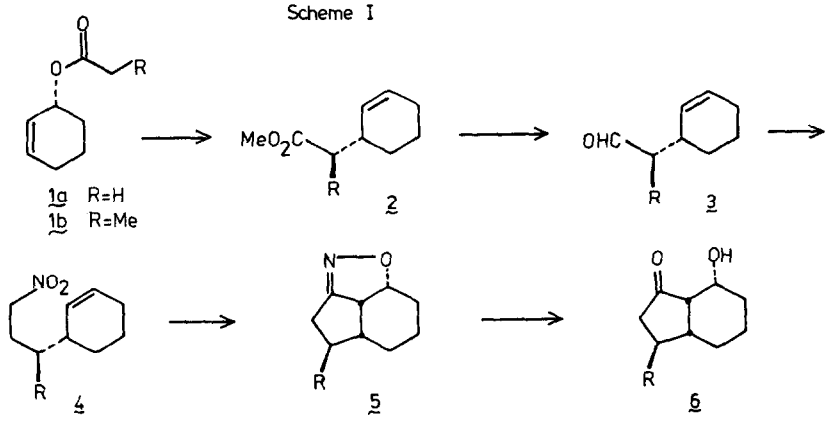
The overall transformation effected is outlined in equation 1. A new ring is annulated onto a readily available allylic alcohol derivative I to form β-hydroxy ketone III via the intermediacy of isoxazoline II. The two key steps involve stereocontrolled Ireland ester enolate Claisen rearrangement[4] and olefin-nitrile oxide [3+2]-dipolar cycloaddition. Central to the strategy is the ability to subsequently transpose the Δ^2-isoxazoline II to the β-hydroxy ketone III.[2a] Construction of bicyclic systems such as II (first illustrated by Wollenberg[5]) via nitrile oxide cycloaddition is now a common tactic. However, our strategy is designed to promote ring formation with complete stereocontrol which is dictated by the allylic hydroxyl group. Note that the new ring is

appended cis to the original hydroxy group in I and that this hydroxy group is ultimately returned to its original position with its original stereochemistry. The stereochemical control inherent in the Claisen rearrangement and the dipolar cycloaddition rigidly dictate these features. Finally, control of enolate geometry in the Claisen rearrangement[4] provides the ability for stereocontrolled introduction of a fourth asymmetric center (R) within the newly formed ring. While we will presently focus on the construction of five-membered rings, the overall strategy should permit the annulation of other ring sizes as well.

Scheme I outlines the sequence of reactions employed. Standard Ireland ester enolate Claisen rearrangement[4] of cyclohex-2-en-1-ol acetate (1a) (LDA/ TBSCl; 60°C) produced ester 2a in 87% yield after direct desilylation and methylation (KF, K_2CO_3, CH_3I, HMPA). This was reduced (DiBAl-H, pentane, -78°C) to produce aldehyde 3a in 60% yield after purification by flash chromatography. Homologation to the requisite nitro compound 4a was accomplished in 87% yield using the convenient one pot method of Wollenberg (CH_3NO_2/KF; Ac_2O; $NaBH_4$).[5a] Nitrile oxide generation and cycloaddition using the Mukaiyama conditions (PhNCO or p-ClC_6H_4NCO, ϕH, Et_3N)[6] then proceeded smoothly to generate the known isoxazoline 5a[5a] in 70% yield. Finally, reduction of 5a using our now standard conditions[2a] (Ra-Ni; H_2 gas, $B(OH)_3$, 5/1 MeOH/H_2O) gave β-hydroxy ketone 6a as a single "all cis" stereoisomer.

The ability to generate an additional stereocenter was demonstrated with the propionate ester 1b. Again using the Ireland method,[4] generation of the Z-ketene silyl acetal and rearrangement, followed by subsequent methylation, provided predominantly 2b (5/1; 91% yield) as described by Bartlett.[7a] This isomer arises via a chair-like transition state.[7a,b] After conversion to the aldehyde 3b by a reduction-oxidation sequence (LAH; PCC; 77%), Wollenberg homologation (41%) and cycloaddition provided 5b in 74% yield. At this stage, chromatographic separation to remove the minor endo isomer was possible. Usual reduction then provided 6b in 81% yield.

Scheme I



1a R=H
1b R=Me

2

3

4

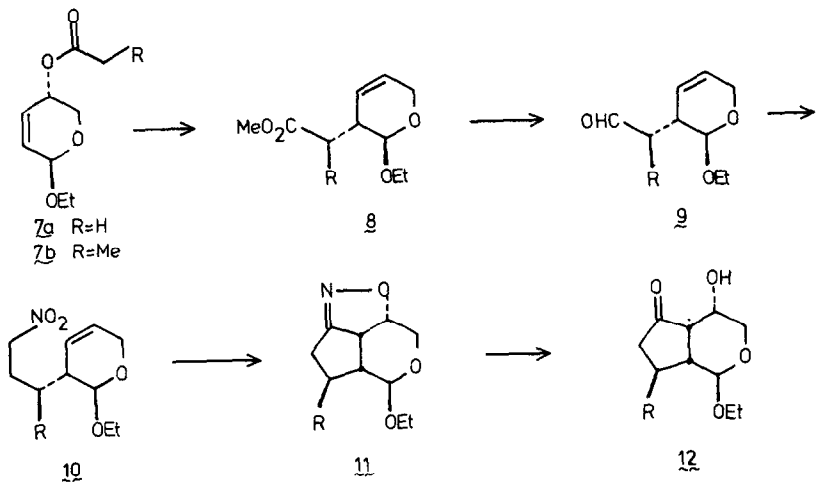
5

6

A particularly useful application of this sequence was envisioned to accomplish the task of annulation of a ring onto a pre-existing optically active sugar derived allylic alcohol. For example, such a transformation could permit economical use of sugars in the synthesis of members of iridoid family.[8] Accordingly, glycal 7a was prepared by Ferrier rearrangement of D-xylal as described by Fraser-Reid.[9] The minor isomer (α-OEt) was readily separable from 7a by preparative HPLC and could be equilibrated to the original 3/1 mixture by resubjection to the reaction conditions ($BF_3 \cdot Et_2O$, EtOH, RT). Claisen rearrangement and methylation provided a 66% yield of 8a as a single stereoisomer. DiBAl-H reduction (60%) and Wollenberg homologation (81%) provided nitro olefin 10a. After cycloaddition of 10a (47%), reduction provided β-hydroxy ketone 12 as a single stereoisomer in 90% yield.

Use of the propionate ester 7b allows for generation of a fifth stereocenter. Interestingly, in the dihydropyranyl case, the best selectivity was obtained by generation of the E-ketenesilyl acetal ($LiN(TMS)_2$, TBSCl)[10] and rearrangement. This proceeds with reasonable selectivity through a boat-like transition state[7] to give 8b and its diastereoisomer in a 5/1 ratio. In this series, rearrangement of the Z-ketenesilyl acetal also provided 8b as the major isomer (via chair TS) but the ratio was only 3/2. The crude acid (97%) produced by desilylation (K_2CO_3, MeOH/THF/H_2O) was directly reduced and oxidized as above to provide aldehyde 9 in 53% yield after chromatographic purification. The subsequent homologation (57%), cycloaddition (60%), and reduction (88%) proceeded as expected to give β-hydroxy ketone 12b. As before, separation of the minor diastereoisomer generated in the Claisen rearrangement was best accomplished at the isoxazoline stage (11b).

Scheme II



The combination Claisen-nitrile oxide annulation provides a useful sequence to annulate a ring onto an existing allylic alcohol under unusually mild conditions. Of particular note is the use of a readily available allylic alcohol to control the stereochemistry of four contiguous asymmetric centers. Since allylic alcohols are readily obtained from carbohydrates, a new method for formation of "annulated pyranosides"[11] is available. Application of this annulation to the synthesis of important iridoids in optically active form is a subject of current investigation.

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