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The Michael–Aldol condensation approach to the construction of key intermediates in the synthesis of terpenoid natural products

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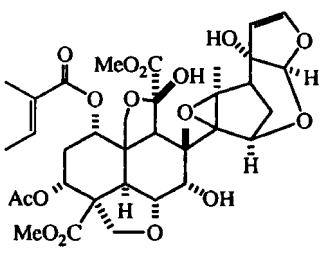
Abstract: Short routes for the preparation of highly oxygenated decalines, key intermediates for the synthesis of nimbolide (2a), by a sequence involving a Michael addition followed by an aldol condensation, are described.

Many terpenoid products possessing a variety of structures were isolated from *Azadirachta indica* Juss. (Meliaceae), the India's famed neem tree.[1] Of this large group of natural products, azadirachtin (1) has received increasing attention from a synthetic point of view due to its remarkable insecticidal properties.[2] More recently, two structurally less complex tetranortriterpenoids, nimbolide (2a) and 28-deoxonimbolide (2b), showing promising biological activity were also isolated from this interesting plant.[3]



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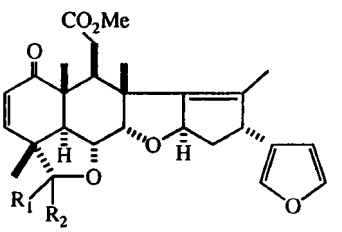
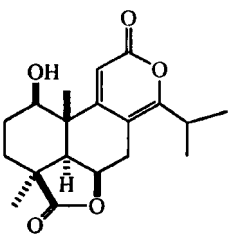


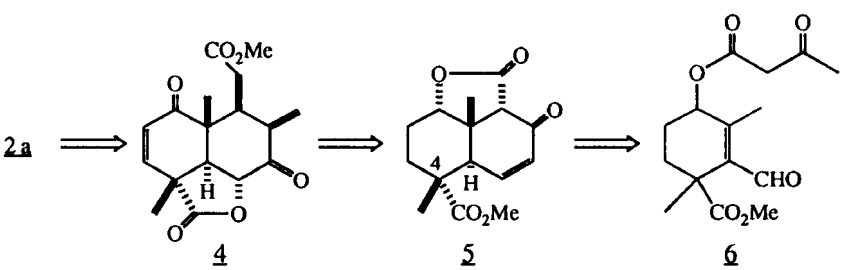
2a: $R_1 R_2 = O$
2b: $R_1 = R_2 = H$



3

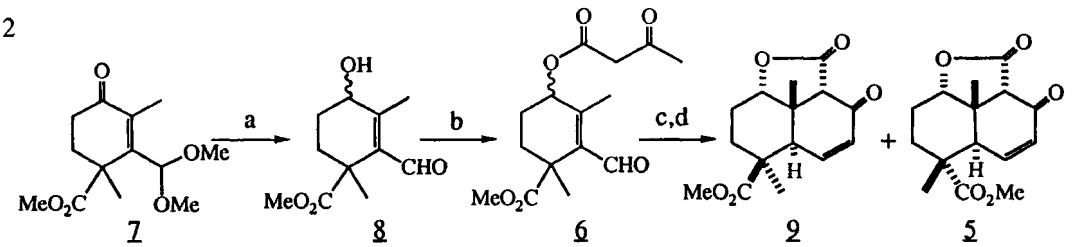
As an extension of our previous Michael addition-aldol condensation approach for the synthesis of highly oxygenated decalins,[4,5] we decided to study the development of short routes to compounds related to 4, resembling the decalin portion of nimbolide (2a), on the basis of the retrosynthetic analysis depicted in Scheme 1. The tricyclic enone 5 an adequate intermediate to be transformed into 4, was our first objective. This enone could be synthesized in turn, from the β-keto ester 6. For the synthesis of 6 we started with enone 7, readily prepared following a known procedure.[6] The analysis of the ^{1}H NMR spectrum of the reaction product of its reduction revealed the presence of a 2:1 mixture of allylic alcohols and also that the acetal moiety had been hydrolyzed, presumably during the work-up, giving directly 8.

Scheme 1



We have found no precedent in the literature for the hydrolysis of acetals under these conditions. Without separation the mixture of allylic alcohols 8 was transformed into the corresponding β-keto esters 6.

Scheme 2



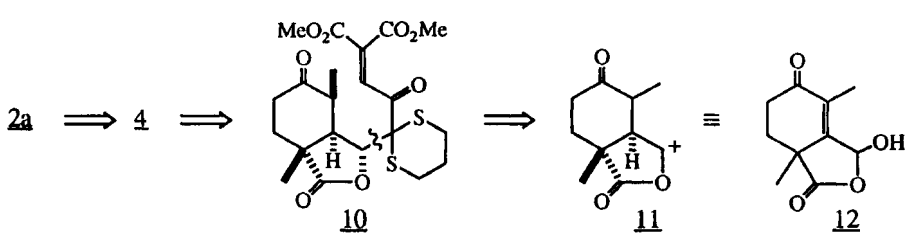
Reagentes and conditions: a) $NaBH_4$, $CeCl_3.7H_2O$, CH_2Cl_2, EtOH -78°C to rt; b) Acetyl derivative of Meldrum's acid, PhH, reflux; c) KO*t*-Bu, PhH, reflux; d) TsOH, $ClCH_2CH_2Cl$, reflux, 22% overall yield from 8.

The application of our previously described reaction conditions for the intramolecular Michael addition to 6 followed by the acid catalyzed intramolecular aldol condensation[7] gave a 2:1 mixture of tricyclic lactones 9 (mp 178°C) and 5 (mp 124-125°C) that were isolated in pure form by column chromatography (Scheme 2). For the determination of the stereochemistry of 9 and 5, an exhaustive analysis of their NMR spectral data was carried out, including also those of their corresponding dihydroderivatives.

Although the stereochemistry of the isomeric allylic alcohols 8 remained undetermined, it is reasonable to assume that both stereoisomers, through their corresponding β-keto esters, could undergo the intramolecular Michael addition at similar rates. If this is the case, the 2:1 ratio of the obtained stereoisomeric lactones, is simply a consequence of the ratio of allylic alcohols produced in the reduction of 7. Based on these arguments we hope that, through the stereospecific reduction of enone 7, we could direct the synthesis toward lactone 5 and/or to lactone 9 and, consequently, to our original targets or to some members of the large group of norditerpenoids represented by nagilactone A (3).[8]

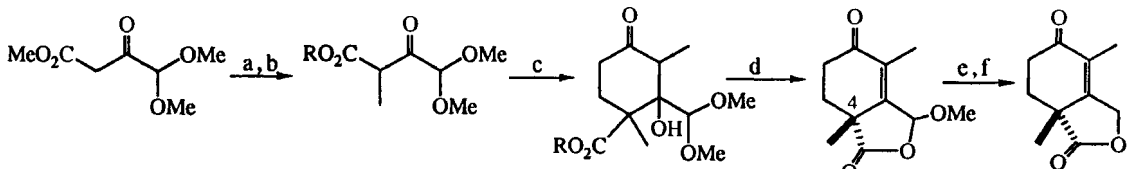
In spite of the fact that having established a simple route to key intermediates potentially useful for the preparation of 5 and/or related compounds in racemic form, it was attractive to investigate further the development of alternative synthetic routes in which the absolute stereochemistry at the quaternary carbon (C-4 in 5) could be under control, allowing the synthesis of intermediates in optically active form. With this idea in mind and using a sequence previously developed by Ley et al.[9] in attempt to the synthesis of azadirachtin (1) as analogy, we analyzed the structure of nimbolide 2a as shown in Scheme 3. Interestingly enough, compound 12, a synthetic equivalent of synthon 11, has been prepared by White et al. and used for the total synthesis of (±)-trisporic acids, a family of naturally occurring fungal pheromones derived from β-carotene.[10]

Scheme 3



We decided then to develop a synthetic sequence toward 12 in optically active form. As shown in the Scheme 4, starting with the known β-keto ester 13[6] and using 8-β-naphthylmenthol[11] as chiral auxiliary we prepared the crystalline acetal 16 in 20% overall yield, in more than 95% ee and with the same absolute configuration as that of nimbolide (2a). That the absolute configuration at the quaternary carbon of 16 (C-4) is R, was unambiguously shown by chemical correlation with the bicyclic lactone 17.[12]

Scheme 4

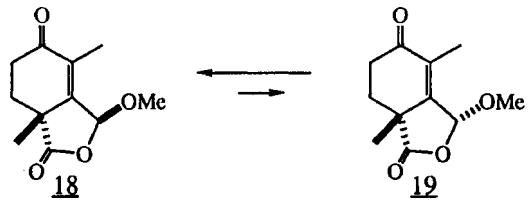


13 14, R= 8-β-naphthyl menthol 15, R= 8-β-naphthyl menthol 16 17

Reagents and conditions: a) 8-β-naphthylmenthol, DMAP, molecular sieves, PhMe, reflux; b) MeI, TlEtO; c) Ethyl vinyl ketone, K_2CO_3, MeOH, -25°C; d) $CuSO_4$, SiO_2, PhH, reflux; e) HCl, THF, H_2O, reflux, $NaBH_4$, $CeCl_3.7H_2O$, MeOH; f) H_2CrO_4, Me_2CO, 1h.

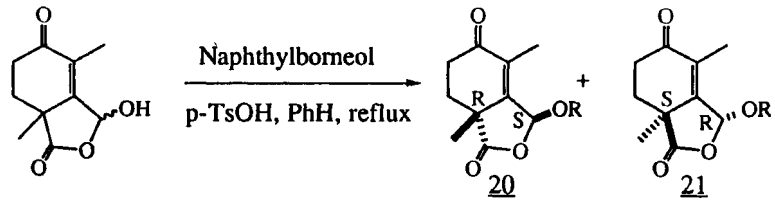
In order to have access to optically active 12 by a more efficient and direct methodology, we studied its optical resolution by transforming it into a mixture of diastereoisomeric acetals by reaction with an enantiomerically pure alcohol. After some experimentation we found that the acid catalyzed treatment of racemic 12[10] with naphthylborneol[13] afforded a mixture of only two diastereoisomeric acetals readily separable by column chromatography in very good yield. That indeed both diastereoisomeric acetals are the thermodynamic products, having the more stable configuration at the acetal moiety, was shown in the following way.

A careful analysis of the reaction mixture obtained in the last step of the preparation of 16 (Scheme 4) showed that a stereoisomeric minor acetal was also formed. The ^1H NMR analysis, including NOE experiments, of these compounds clearly showed that the major and minor products 18 and 19, respectively, differ only in the configuration of the acetal moiety. The acid catalyzed isomerization of 19 gave 18, indicating that the latter is the more stable isomer. This result was confirmed by semi-empirical calculations (PM3).



18 19

Based on the above results and on the ^1H NMR spectrum of both naphthylborneol acetals we concluded that the less and more polar derivatives showed structures 20 and 21, respectively. These structures were also confirmed by molecular mechanics calculations (MM+). The absolute configuration at the quaternary carbon center of both acetals was further confirmed by chemical correlation with the known lactone 17.



20 21

R= naphthylborneol

In conclusion, the sequences described in this communication, apart from providing short entries to precursors for the synthesis of complex natural products such as nimbolide (2a), show that the Michael addition-aldol condensation sequence is a valuable alternative to other cyclizations for the construction of highly functionalized molecules.[14]

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