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Novel Domino Reactions for Diterpene Synthesis

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Abstract: New types of concerted domino acylation−cycloalkylation/alkylation−cycloacylation reactions have been described. These processes promoted by methanesulfonic acid−phosphorus pentoxide and concentrated H_2SO_4, respectively, provide efficient, elegant, and expeditious routes for biologically active naturally occurring diterpenoids, namely (±)-ferruginol (**1**), (±)-nimbidiol (**2**), (±)-nimbiol (**3**), (±)-totarol (**4**), and *ar*-abietatriene (**5**).

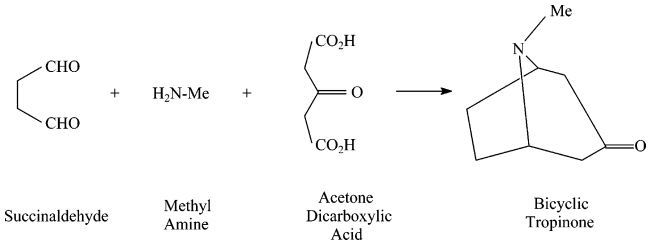
In recent years, the need to improve synthetic efficiency with the aim of generating diversified molecules has led to the development of domino processes.[1−3] The term domino reaction in organic chemistry was coined by Tietze[4] in 1990. The significant feature of domino processes is the formation of complex compounds starting from simple substrates in two or more steps which occur in succession in the same pot without isolation of intermediates. In nature domino reactions are rather common, although a direct comparison to the reactions in a flask is not possible because of the involvement of multienzymes.

The oldest known example of a domino type of reaction was performed by Robinson[5] in the synthesis of a natural product, a bicyclic tropinone, which is a structural component of several alkaloids such as cocaine and atropine (Scheme 1). The biosyntheses of fatty acids[6] and progesterone[7] are also characteristic examples of the domino type of reactions.

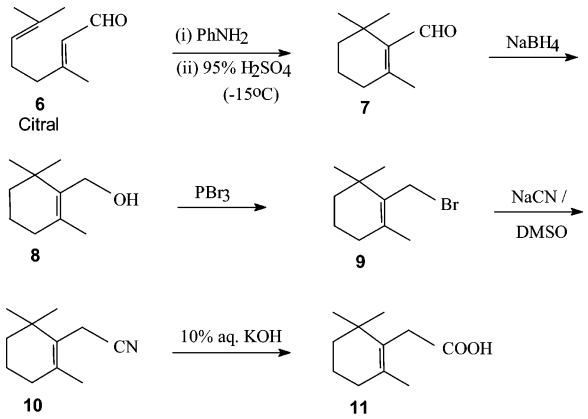
A domino reaction is therefore defined as a process involving two or more bond transformations (usually involving C−C bonds) which take place under the same reaction conditions without adding additional reagents and/or catalysts, and in which the second and any subsequent reactions result as a consequence of the functionality formed in the previous step.

In this Note, we disclose the strategy designed to achieve convenient, expeditious, stereocontrolled total syntheses of several naturally occurring diterpenoids, viz. (±)-ferruginol (**1**), (±)-nimbidiol (**2**), (±)-nimbiol (**3**), (±)-totarol (**4**), and *ar*-abietatriene (**5**), via a concerted mechanism of domino acylation−cycloalkylation/alkylation−cycloacylation as the principal step to construct the basic carbocyclic framework required for the trans-fused

SCHEME 1. Synthesis of Bicyclic Tropinone via Domino Reaction



SCHEME 2. The Common Synthon, 2,6,6-Trimethyl-1-cyclohexane-1-acetic Acid, Synthesized from the Acyclic Mooterpene Citral



octahydrophenanthrene nucleus, starting from the readily available acyclic monoterpene, citral (Scheme 2).

As depicted in Scheme 2, citral (**6**) was cyclized[8] to 2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde(*β*-cyclocitral) (**7**), which was then reduced to (2,6,6-trimethylcyclohex-1-enyl)methanol (**8**).[9] This was reacted with PBr_3 to give 2-(bromomethyl)-1,3,3-trimethylcyclohexene (**9**),[10] which was converted to (2,6,6-trimethylcyclohex-1-enyl)-acetonitrile (**10**).[11] Nitrile **10** was hydrolyzed with dilute alkali to give the important intermediate (2,6,6-trimethylcyclohex-1-enyl)acetic acid (**11**).[12]

Acid **11** was subjected to $CH_3SO_3H-P_2O_5$ (10:1) promoted domino acylation−cycloalkylation with anisole (**12**) to yield the tricyclic ketone (**13**), which was subsequently transformed, as depicted in Scheme 3, to the diterpene (±)-ferruginol (**1**), known to have antihepatomic, antitumour, antibacterial, and fungicidal[13] properties.

Similarly, the acid (**11**) was subjected to $CH_3SO_3H-P_2O_5$ promoted domino acylation−cycloalkylation with veratrole (**18**) to yield the tricyclic ketone (**19**), which was

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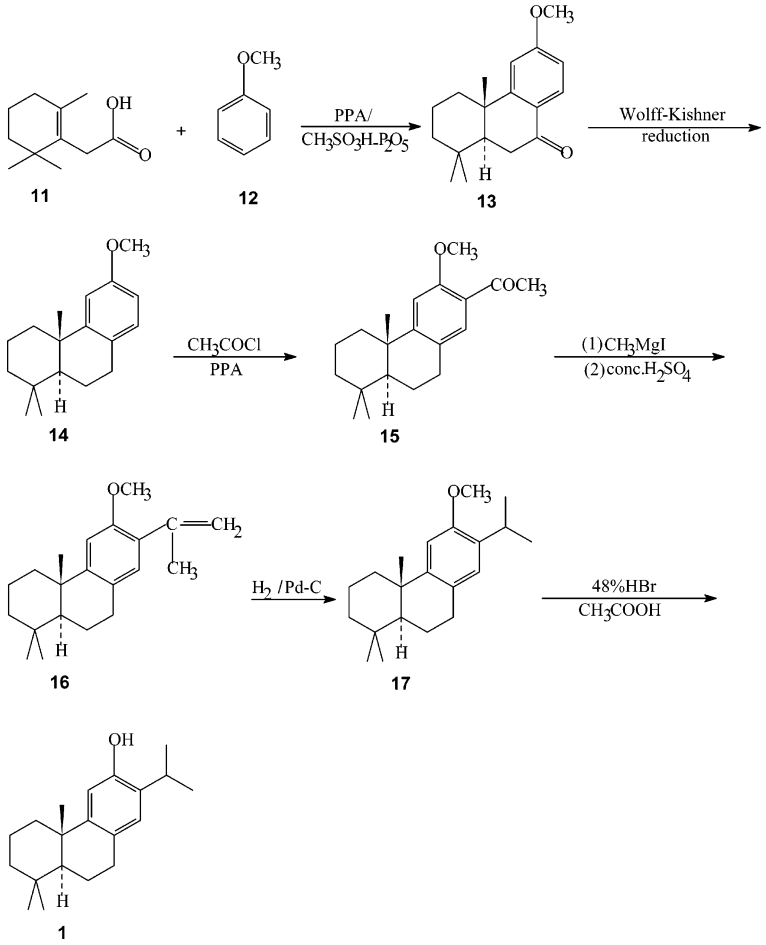
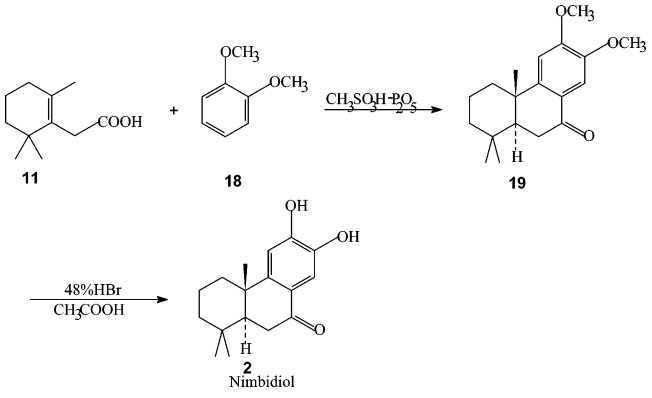
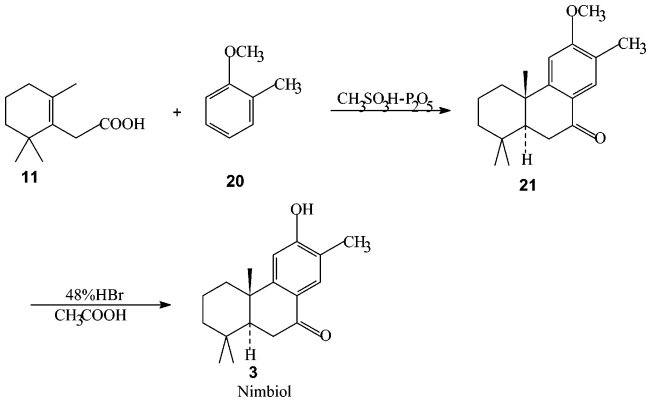
SCHEME 3. Total Synthesis of (±)-Ferruginol (1) via Domino Acylation−Cycloalkylation



SCHEME 4. Total Synthesis of Nimbidiol (2) via Domino Acylation−Cycloalkylation



SCHEME 5. Total Synthesis of (±)-Nimbiol (3) via Domino Acylation−Cycloalkylation



subsequently transformed, as depicted in Scheme 4, to the diterpene (±)-nimbidiol (**2**), which had been isolated from the root bark of *Azadirachta indica A. Juss*[14] (Indian neem) and used in the indigenous system of medicine in India.

Similarly, acid **11** was subjected to $CH_3SO_3H-P_2O_5$ promoted domino acylation−cycloalkylation with *o*-methylanisole (**20**) to yield the tricyclic ketone (**21**), which was subsequently transformed, as depicted in Scheme 5, to the diterpene, (±)-nimbiol (**3**), known to possess antimicrobial activity.[15]

A perusal of the structures of two other naturally occurring aromatic tricyclic diterpenes viz. (±)-totarol (**4**) and *ar*-abietatriene (**5**) revealed that they possess alkyl/alkoxy groups in the C_7 position. Such an orientation of groups is rather difficult to attain by conventional methods of diterpene synthesis. For this purpose, the methods reported above by us were modified by replacing $CH_3SO_3H-P_2O_5$ with concentrated H_2SO_4 at 0 °C. During

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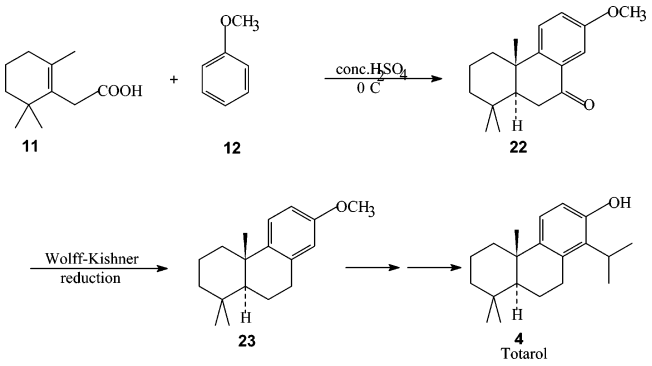
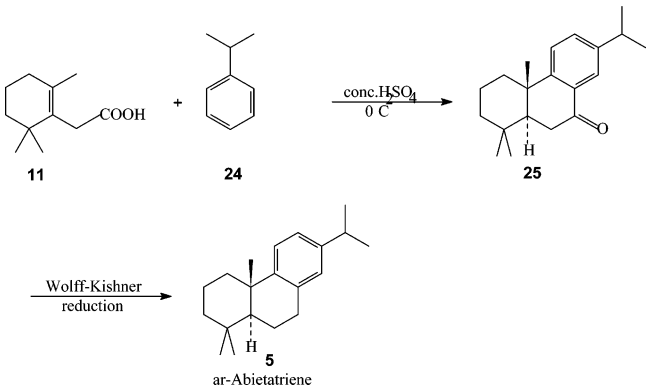
SCHEME 6. Total Formal Synthesis of Totarol (4) via Domino Alkylation-cycloacylation.



SCHEME 7. Total Synthesis of *ar*-Abietatriene (5) via Domino Alkylation−Cycloacylation.



tandem cyclization, it was observed that the former reagents preferred acylation first over alkylation whereas the use of concentrated H_2SO_4 led to a preference of alkylation over acylation thus changing the orientation of the substituent groups attached to the aromatic C-ring.

Acid **11** was then subjected to concentrated H_2SO_4 promoted domino alkylation−cycloacylation with anisole (**12**) to yield the tricyclic ketone (**22**), which was subsequently transformed, as depicted in Scheme 6, to the octahydrophenanthrene (**23**), which has been previously converted[16−33] to the antibacterial[16] diterpene, (±)-totarol (**4**).

Acid **11** was also subjected to concentrated H_2SO_4 promoted domino alkylation−cycloacylation with isopropylbenzene (**24**) to yield the tricyclic ketone (**25**), which was subsequently transformed, as depicted in Scheme 7, to the diterpene, *ar*-abietatriene (**5**), known to possess cytostatic, antibacterial properties.[17]

In previously reported references,[18] it has been well established that cycloalkylation yields more of the stable *trans*-trimethyloctahydrophenanthrene derivatives. Of the tricyclic ketonic compounds, the trans isomer, obtained by us in the pure state, is clearly the product of kinetic control as revealed by gas chromatographic studies of the cyclization products.

In conclusion, exceptionally short as well as stereoselective routes to the total synthesis of several tricyclic diterpenes have been designed by using novel types of domino processes, utilizing an acyclic monoterpene, citral, as the starting material. The literature methods[19−26] commonly used for the syntheses of these tricyclic diterpenes do not involve the one-pot construction of A/B trans-fused trimethyloctahydrophenanthrene nucleus, which represents the basic carbocyclic framework of a large number of naturally occurring tricyclic diterpenes.

Supporting Information Available: Experimental and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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