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Tandem Prins/Wagner/Ritter process for the stereoselective synthesis of (3-oxabicyclo[4.2.0]octanyl)amide and (1-(5-aryltetrahydrofuran-3-yl)cyclobutyl)amide derivatives

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Three-component coupling of aldehyde, vinylcyclopropyl carbinol, and nitrile in the presence of 10 mol% TMSOTf at -40 to 0 °C in dichloromethane affords a novel class of (3-oxabicyclo[4.2.0]octanyl)amides in high yields with excellent selectivity, whereas (1-vinylcyclobutyl)methanol provides the corresponding (1-(5-aryltetrahydrofuran-3-yl)cyclobutyl)amides under similar conditions. This is the first report on the synthesis of oxabicycles through a sequential Prins/Wagner/Ritter process.

The cyclobutane ring is a structural motif in many natural and biologically active molecules.[1] It shows high reactivity because of ring strain that facilitates rearrangements, which makes it useful intermediate in the synthesis of complex natural products.[2] In particular, (+)-lineatin is an active pheromone, which was isolated from the female ambrosia beetle (Figure 1).[3] However, a few methods are reported for the stereoselective synthesis of cyclobutanes (Figure 1).[4]

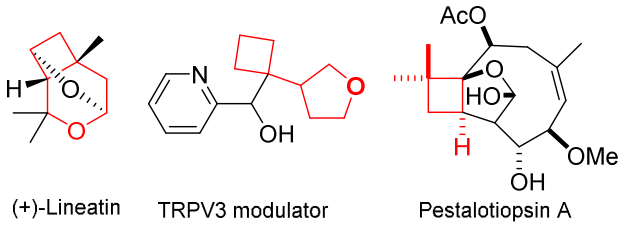

Figure 1. Biologically active natural products

'Prins cyclization' is one of the most elegant approaches for the stereoselective synthesis of tetrahydropyran and furan scaffolds.[5,6] In spite of its potential application in natural products synthesis,[7] there are no reports on the stereoselective synthesis of oxabicyclo[4.2.0]octane scaffolds, which are often present in natural products (Figure 1).

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#Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectrum of products. see DOI: 10.1039/b000000x/

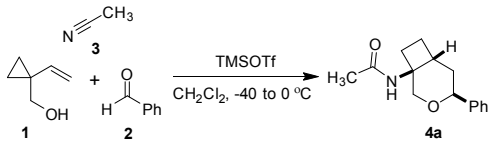
Following our interest on Prins and related cyclizations,[8] we herein report a novel cascade strategy for the stereoselective synthesis of 4-aryl-(3-oxabicyclo[4.2.0]octanyl)amide and (1-(5-aryltetrahydrofuran-3-yl)cyclobutyl)amide derivatives through a Prins/Wagner/Ritter reaction sequence. Therefore, the development of a novel cascade process for the synthesis of fused oxacycles with the creation of three stereogenic centers in a one-pot operation would expand the scope of this cascade process in natural product synthesis.

As a model reaction, we attempted the coupling of (1-vinylcyclopropyl)methanol (**1a**) and benzaldehyde (**2**) with acetonitrile (**3**) in dichloromethane in the presence of an acid catalyst. To optimize the reaction conditions, the above reaction was performed with different acid catalysts and the results are presented in Table 1. Of various catalysts screened, 10 mol% TMSOTf afforded the desired product **4a** in 82% yield (Table 1, entry a). The catalyst was added at -40 °C and the mixture was stirred at 0 °C. Under similar conditions, 10 mol% $BF_3.OEt_2$ also gave the product **4a** in good yield (Table 1, entry h). However, metal triflates such as $Sc(OTf)_3$ or $In(OTf)_3$ furnished the desired product **4a** in moderate yields (Table 1, entries f and g). To our surprise, no cyclization was observed with 10 mol% $InBr_3$ or $InCl_3$ under similar conditions (Table 1, entries i and j). Similarly, no desired product was isolated when the reaction was performed with 10 mol% molecular iodine or 10 mol% zinc chloride (Table 1, entries k and l). Under optimized conditions, the reaction proceeds smoothly in the presence of 10 mol% of TMSOTf at -40 to 0 ºC in dichloromethane. Under the above conditions, the product **4a** was obtained with *trans*-selectivity (Table 2, entry a). Though dihydropyran is known to form as a side product in Prins cyclization,[9] no such product was detected under the present conditions because 1,2-shift is favourable due to high ring strain. The starting material was recovered, wherein the yields are low (Table 1).

Next, we examined the role of solvents such as dichloromethane, acetonitrile, tetrahydrofuran, 1,2-dichloroethane and

nitromethane. Of various solvents, dichloromethane afforded the best results in terms of yields (Table 1).

Table 1. Screening of various catalysts and solvents in the formation of **4a**



Entry	Acid catalyst	Mol %	Solvent	Time (min)	Yield (%)
a	TMSOTf	10	DCM	15	82
b	TMSOTf	10	CH_3CN	15	70
c	TMSOTf	10	THF	35	45
d	TMSOTf	10	DCE	20	55
e	TMSOTf	10	CH_3NO_2	15	62
f	$Sc(OTf)_3$	10	DCM	20	60
g	$In(OTf)_3$	10	,,	20	50
h	$BF_3.OEt_2$	10	,,	15	73
i	$InBr_3$	10	,,	90	0
j	$InCl_3$	10	,,	90	0
k	I_2	10	,,	90	0
l	$ZnCl_2$	10	,,	90	0

The relative stereochemistry of **4b** was established by 1D and 2D NMR experiments. The two aromatic rings were distinguished based on characteristic nOe correlations between H13 and H16/H20 as well as NH and H2/H6. Also the presence of nOe correlations between NH/H11, H12/H20, H14/H9, H13/H10 indicates their conformation as shown in Figure 2.

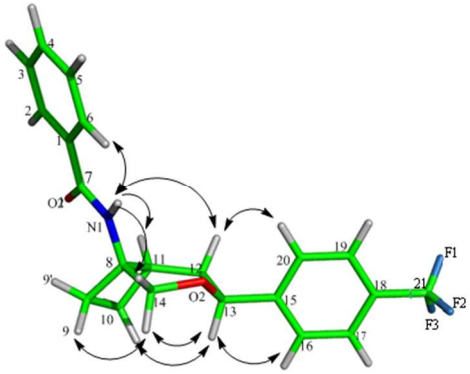


Figure 2. Characteristic nOe's of **4b**

The stereochemistry of **4b** was further confirmed by a single crystal X-ray crystallography (Figure 3).[10]

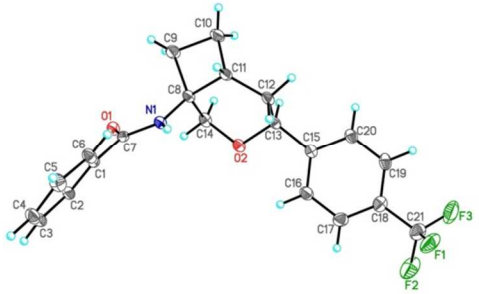
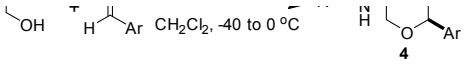
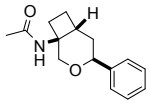
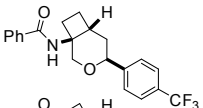
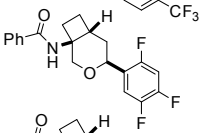
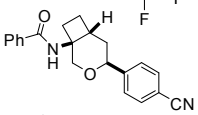
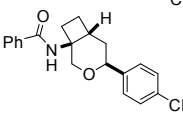
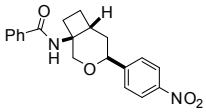
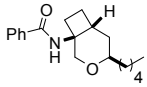
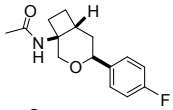
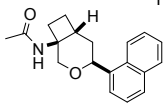
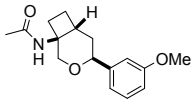
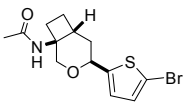
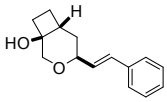


Figure 3. ORTEP diagram of **4b**

The scope of the reaction was further evaluated with respect to various aldehydes and nitriles. The results are presented in Table 2.

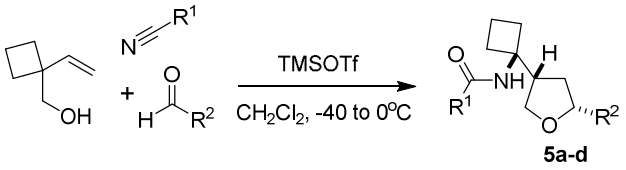
Table 2. Synthesis of (3-oxabicyclo[4.2.0]octanyl)amides



Entry	Ar	R	Product (**4**)[a]	Time (min)	Yield (%)[b]
a	C_6H_5	CH_3		15	82
b	p-$CF_3C_6H_4$	Ph		15	72
c	2,4,5-$F_3C_6H_2$	Ph		15	71
d	p-CNC_6H_4	Ph		15	70
e	p-ClC_6H_4	Ph		20	60
f	p-$NO_2C_6H_4$	Ph		15	75
g	*n*-Pentyl	Ph		15	52
h	p-FC_6H_4	CH_3		15	65
i	1-Naphthyl	CH_3		15	70
j	3-$MeOC_6H_4$	CH_3		25	50
k	5-Bromothienyl	CH_3		20	72
l	C_6H_5CH=CH-	CH_3		20	45

[a]Products were characterized by NMR, IR and mass spectroscopy.
[b]Isolated yields after chromatography

Interestingly, a diverse range of aldehydes underwent smooth Prins type cyclization with vinylcyclopropyl carbinol in the presence of nitrile under the influence of TMSOTf. A variety of 4-aryl-(3-oxabicyclo[4.2.0]octanyl)amide**s** were prepared using this protocol. Next, we studied the effect of substituent, which is present on the aromatic ring. In case of electron-deficient aldehydes, the yields were gradually increased with the increase of electron withdrawing ability of the substituent. For instance, *p*-cyano- and *p*-nitrobenzaldehydes gave the desired products relatively in high yields (Table 2, entries d and f). Furthermore, *p*-fluorobenzaldehyde is more effective than *p*-chlorobenzaldehyde (Table 2, entries h and e). In addition, *p*-CF_3-benzaldehyde is superior than *p*-fluorobenzaldehyde in terms of conversion (Table 2, entries b and h). Similarly, 2,4,5-trifluorobenzaldehyde afforded higher yield than mono-fluorobenzaldehyde (Table 2, entries c and h). However, aliphatic aldehyde, i.e. *n*-hexanal gave the product comparatively in low yield than aromatic counterpart (Table 2, entry g). Indeed, a sterically hindered 1-naphthaldehyde was also effective for this reaction (Table 2, entry i). In contrast, electron-rich substrate, i.e *m*-anisaldehyde gave the product in low yield than electron-deficient counterpart (Table 2, entry j). Nevertheless, heteroaromatic substrate, i.e. 5-bromothiophene-2-carboxaldehyde furnished the product in good yield (Table 2, entry k). Thus, the present method works not only with aromatic and heteroaromatic but also with aliphatic aldehydes. However, to our surprise, cinnamaldehyde furnished the corresponding hydroxy derivative **4l** instead of amide. This is due to the attack of hydroxyl group instead of nitrile. Inspired by the results obtained with vinylcyclopropyl carbinol (**1a**), we extended this process for (1-vinylcyclobutyl)methanol (**1b**). To our delight, the substrate **1b** also underwent a smooth rearrangement to give the corresponding (1-(5-aryltetrahydrofuran-3-yl)cyclobutyl)amide derivatives (**5a-d**) in good yields (Scheme 2, Table 3, entries a-d).



Scheme 2. Synthesis of (tetrahydrofuran-3-yl)cyclobutyl)amides

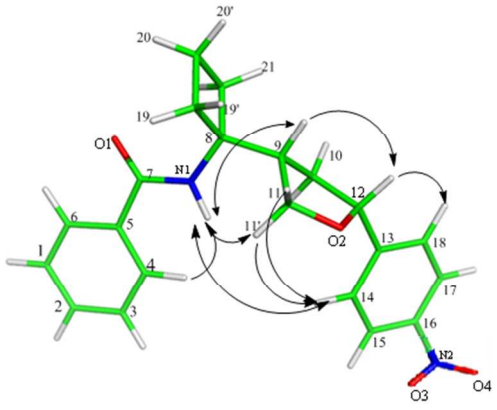
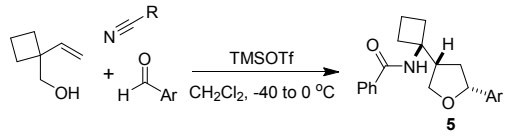
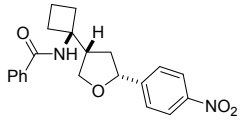
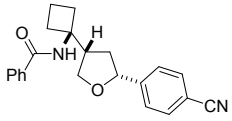
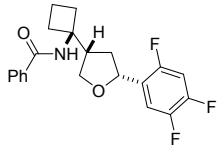
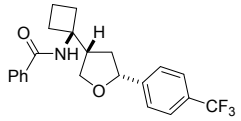


Figure 4. Characteristic nOe's of **5a**

In the case of **1b**, the desired product **5** was obtained with all *cis*-selectivity. The relative stereochemistry of **5a** was established by nOe correlations between amide proton and H4/H6 as well as H12 and H14/H18. The two aromatic rings were identified for compound 5a. The presence of nOe correlation between H9 and H12 indicates that these two protons are in cis orientation. This observation is supported by the absence of nOe between H9 and H14/H18 as well as the presence of nOe between amide proton and H14/H18. The presence of J-correlations H9/H11, H9/H10, H19/H20 and H20/H21 confirms the structure as shown in the figure, which is supported by the nOe correlations shown in Figure 4.

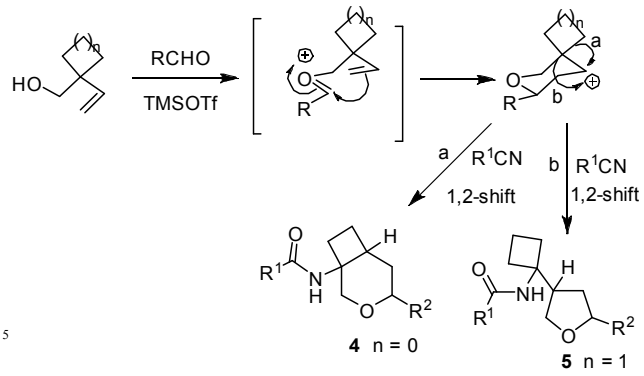
Table 3. Preparation of (1-(5-aryltetrahydrofuran-3-yl)cyclobutyl)amides



Entry	Ar	R	Product (**5**)[a]	Time (min)	Yield (%)[b]
a	*p*-$NO_2C_6H_4$	Ph		20	78
b	*p*-CNC_6H_4	Ph		20	70
c	2,4,5-$F_3C_6H_2$	Ph		20	68
d	*p*-$CF_3C_6H_4$	Ph		20	82

[a]Products were characterized by NMR, IR and mass spectroscopy.
[b]Isolated yields after chromatography

A plausible mechanism for the cascade process is proposed in Scheme 3. The reaction was assumed to proceed *via* the formation of oxocarbenium ion generated *in situ* from hemi-acetal, which is formed in situ by the reaction of vinylcyclopropyl carbinol with aldehyde under acidic conditions. Subsequent attack of the olefin on oxocarbenium ion with simultaneous 1,2-shift of the cyclopropane ring generates a more stable *tert*-carbocation. Thus formed *tert*-carbocation is trapped by a nitrile *via* Ritter amidation to give the desired product as shown in Scheme 3.



Scheme 3. A plausible reaction pathway

In summary, we have developed a novel cascade process for the synthesis of 4-aryl-(3-oxabicyclo[4.2.0]octanyl)amide and (1-(5-aryltetrahydrofuran-3-yl)cyclobutyl)amide derivatives. The reaction is a highly diastereoselective affording the products in good yields. This method provides a direct access to the synthesis of biologically relevant oxabicyclo[4.2.0]octane and (tetrahydrofuran-3-yl)cyclobutane derivatives in a single-step process (three reactions occur sequentially in one-pot).

Experimental

Dichloromethane was dried according to a standard literature procedure. Reactions were performed in an oven-dried round bottom flask, the flasks were fitted with rubber septa and the reactions were conducted under nitrogen atmosphere. Glass syringes were used to transfer the solvent. Crude products were purified by column chromatography on silica gel of 100-200 mesh. Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solvents were concentrated on rotary evaporator at 35–40 °C. IR spectra were recorded on FT-IR spectrometer. ^{1}H and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ on 300, 500 600, or 700 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (*J*) are quoted in hertz (Hz). Mass spectra were recorded on mass spectrometer by Electron impact-mass spectrometry (EI-MS).

Acknowledgements

MK thanks CSIR, New Delhi for the award of a fellowship.

Supporting Information

Spectral data and copies of ^{1}H and ^{13}C NMR spectra are available for all key intermediates and final products.

Notes and references

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10. CCDC 1009270 contains supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html