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A general, norbornyl based approach to anti-Bredt alkenes *via* sequential RCM-fragmentation strategy

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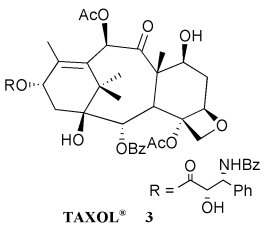
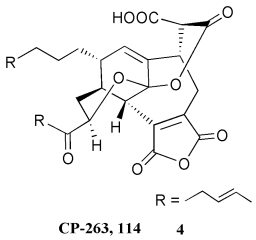
A general protocol for the synthesis of bicyclo[*n*.3.1]frameworks with bridgehead double bond (*anti*-Bredt alkenes), from a common, readily available norbornyl precursor, involving sequential ring closure metathesis (RCM) and Wharton fragmentation is outlined.

For several decades now, an assortment of bridgehead olefins (*anti*-Bredt alkenes)[1] of which bicyclo[3.3.1]non-1(2)-ene **1**[2a,b]and bicyclo[3.2.2]non-1(7)-ene **2**[2c] are prototypes, have been challenging targets of synthesis as these molecules provide insights into the strain induced distortions about the double bond and its manifestation in chemical reactivity.[1,2] More recently, many prominent natural products like taxol® **3** and CP-263,114 **4**, notable for structural complexity and biological


1


2

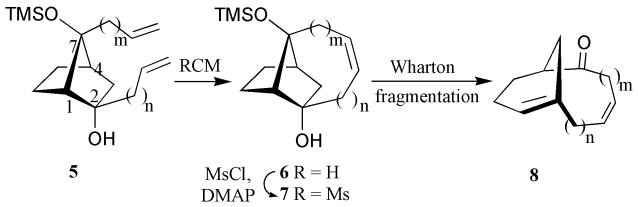

TAXOL® 3


CP-263, 114 4

activity, have been found to incorporate bridgehead double bonds in the form of a bicyclo[5.3.1]undec-1(10)-ene and a bicyclo[4.3.1]dec-1(9)-ene core, respectively, embedded within their structure. This has further stimulated widespread interest in the synthesis of bicyclo[*n*.3.1]frameworks embodying a bridgehead double bond.[3–6] Several strategies have been recently reported in the literature that provide access to bridgehead alkenes based on bicyclo[5.3.1]- and bicyclo-[4.3.1]frameworks, in the context of the synthesis of taxoids[3] and CP molecules[4] but general methodologies towards *anti*-Bredt alkenes are rather limited.[5a,c,6c] We have been enticed by this area and report a new, general approach to bicyclo[*n*-.3.1]framework based bridgehead olefins (*anti*-Bredt alkenes) which emanates from a norbornyl platform **5** and involves in sequential ring closure metathesis (RCM, **5**→**6**) and Wharton fragmentation (**7**→**8**) as the pivotal steps as shown in Scheme 1.

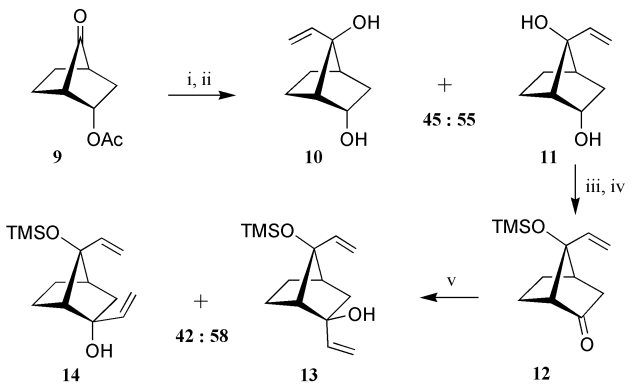
The key element of the approach delineated in Scheme 1 is the assembly of the norbornyl precursor **5** in which the two alkene arms at C2 and C7 are projected on the *exo*- and *syn*-face, respectively, in order to facilitate the RCM to the bridged tricyclic system **6**. When the unprotected hydroxy group in **6** is activated as in **7**, a facile fragmentation can be expected to deliver bridgehead alkene **8** with high level of functionalization. Successful execution of this scheme forms the subject matter of this communication.

Our synthetic approach emanated from the keto-acetate **9**, a readily available 2,7-disubstituted norbornyl derivative.[7] Addi-


Scheme 1

tion of vinyl magnesium bromide to **9** did not exhibit significant facial discrimination[8] and base hydrolysis furnished *anti*- and *syn*- addition products **10** and **11** (45:55), Scheme 2.[9] The secondary hydroxy group in *syn*-**11** was oxidised and the tertiary hydroxy group was protected to furnish **12**. Further vinylation of the C2 carbonyl in **12** led to a readily separable mixture of *endo*- and *exo*- addition products **13** and **14** (58:42).[9] The requisite *exo*-, *syn*-divinyl compound **14** on exposure to Grubbs' catalyst [benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium][10] underwent smooth RCM[11] to furnish the tricyclic olefin **15**[9] bearing the brexane framework, Scheme 3. Catalytic hydrogenation of **15** to **16** and mesylation furnished the tricyclic *endo*-mesylate **17**.[9] TMS- deprotection to **18** and exposure to base resulted in a smooth fragmentation, as contemplated, to deliver the *anti*-Bredt bicyclo[3.3.1]non-1(8)-en-4-one **19**[9] in good yield, Scheme 3.

In the backdrop of the successful acquisition of **19**, we looked for the generalization of this protocol. Accordingly, the keto-acetate **9** was subjected to allylation under Barbier conditions employing different metals to fine tune face-selectivity and obtain better access to the desired *syn* isomer **20**, Scheme 4. Allylation in the presence of zinc proved to be the best option with 68:32 ratio of **20** and **21**.[9] The *syn* isomer **20** was further elaborated to the TMS-protected ketone **22** through a series of straightforward transformations, Scheme 5. Further allylation of **22** proceeded cleanly but the steric factors dominated the addition to give **23** and **24** (3:1)[9] in which the required diastereomer formed through *exo*-addition was the minor product, Scheme 5. Nonetheless, **24** underwent smooth RCM in the presence of the Grubbs' catalyst[10] to furnish the tricycle **25**,[9]


Scheme 2 *Reagents and conditions*: (i) CH_2=CHMgBr, THF, 0 °C, 75%; (ii) K_2CO_3, MeOH, rt, 80%; (iii) TPAP, DCM, NMMO, 90%; (iv) TMSCl, Et_3N, DCM, 90%; (v) CH_2=CHMgBr, THF, 80%.

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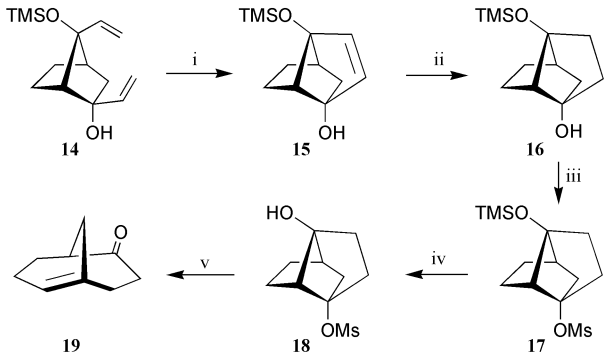
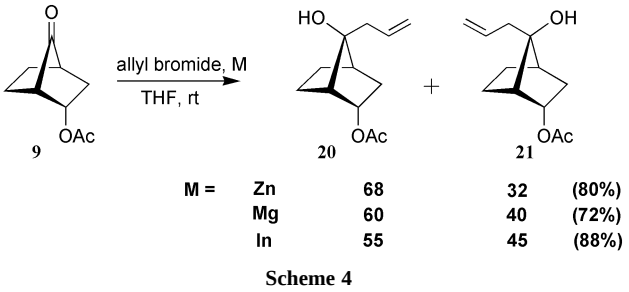


Scheme 3 *Reagents and conditions*: Grubb's catalyst (30 mol%), C_6H_6, reflux, 83%; (ii) 10% Pd/C, H_2, EtOAc, 95%; (iii) MsCl, Et_3N, DMAP, DCM, 0 °C, 85%; (iv) TBAF, THF, rt, 80%; (v) NaH, THF, 0 °C to rt, 87%.

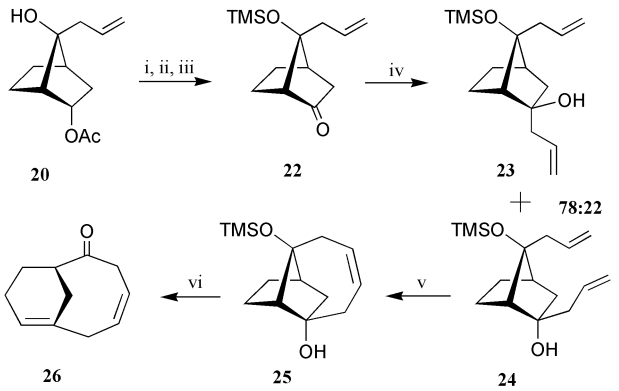


M =				
Zn	68	32	(80%)
Mg	60	40	(72%)
In	55	45	(88%)

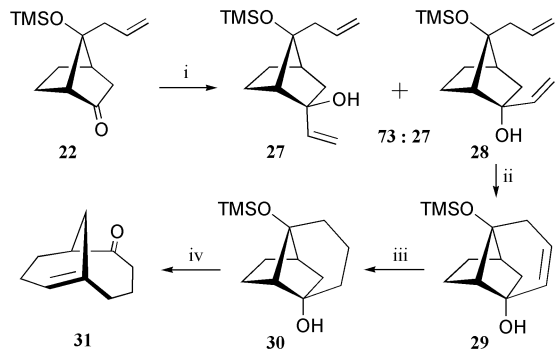
Scheme 4

Scheme 5. Under the conditions of mesylation, **25** underwent ready fragmentation to yield bicyclo[5.3.1]undeca-1(10),3-dien-6-one **26**, Scheme 5. The skeleton of the bridgehead alkene **26**[9] is reminiscent of the bicyclic AB ring core of taxoids.[3]

Our last example is of access to the bicyclo[4.3.1]dec-2(9)-ene framework present in the CP molecules[4] and originates from the *syn*-allyl ketone **22**.[9] Vinylation of **22** was again dominated by steric considerations and furnished *endo*- and *exo*- addition products **27** and **28** (73:27).[9] The *exo*, *syn*-**28** readily underwent RCM in the presence of Grubbs' catalyst[10] to furnish the tricyclic olefin **29**,[9] Scheme 6. As the direct fragmentation on **29** was unsuccessful, perhaps due to strain factors, the double bond in it was reduced to furnish **30**. Exposure of **30** to methanesulfonyl chloride in the presence of



Scheme 5 *Reactions and conditions*: (i) K_2CO_3, MeOH, rt,78%; (ii) PCC, DCM, rt, 80%; (iii) TMSCl, Et_3N, DCM, rt, 91%; (iv) allyl phenyl ether, Li, Et_2O–THF, 0 °C to rt, 76%; (v) Grubb's catalyst (30 mol%), C_6H_6, reflux, 90%; (vi) MsCl, Et_3N, DMAP, DCM, 0 °C, 75%.



Scheme 6 *Reactions and conditions*: (i) CH_2=CHMgBr, THF, rt, 30–35%; (ii) Grubb's catalyst (30 mol%), C_6H_6, reflux, 93%; (iii) 10% Pd/C, H_2, EtOAc, 95%; (iv) MsCl, Et_3N, DMAP, DCM, 0 °C, 85%.

base resulted in fragmentation to furnish bicyclo[4.3.1]dec-2(9)-en-5-one **31**[6c,9] in good yield, Scheme 6.

In summary, we have described a new, general approach to bicyclo[n.3.1]alk-1-enes with bridgehead double bond and additional functionalization on the framework from a single, readily available norbornyl precursor. We have employed ring closure metathesis (RCM) reaction on suitably crafted 2,7-disubstituted norbornyl derivatives, with *syn* disposed alkene arms, to generate the tricyclo[*n*.3.0.$0^{3,n+3}$]system which is tailored to orchestrate a Wharton fragmentation to deliver the *anti*-Bredt alkenes. The limiting factor at the moment to this otherwise promising sequence (Scheme 1) is the control of stereochemistry of the two alkene arms on the norbornyl framework and this issue is the object of our current attention.

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